Disease Recurrence After Liver Transplantation

Natural History, Treatment and Survival

Paul J. Thuluvath
Editor

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Contents

1 Overview: Disease Recurrence After Liver Transplantation 1
Paul J. Thuluvath

2 Hepatitis B Recurrence: Major Milestones and Current Status 13
Bruno Roche and Didier Samuel

3 HCV Recurrence: Predictors and Outcomes After Liver Transplantation 35
Angel Rubín and Marina Berenguer

4 Treatment of Recurrent Hepatitis C 55
Anantha K. Nuthalapati and Paul J. Thuluvath

5 Recurrence of Primary Biliary Cirrhosis Following Liver Transplantation 79
Russell H. Wiesner

6 Recurrence of Autoimmune Hepatitis After Liver Transplantation 91
James Neuberger

7 Alcoholic Cirrhosis, Transplantation, and Recurrence of Disease 105
Eric Siskind and Rolf N. Barth

8 Recurrence of Primary Sclerosing Cholangitis After Liver Transplantation 121
Phunchai Charatcharoenwitthaya and Keith D. Lindor

9 Recurrence of Metabolic Disorders After Liver Transplantation 135
Bijan Eghtesad and Charles Miller

10 Nonalcoholic Fatty Liver Disease Post-Liver Transplantation 145
Ibrahim Hanouneh and Bijan Eghtesad

11 Recurrence of Hepatocellular Carcinoma Following Liver Transplantation Within Milan Criteria 153
Anantha K. Nuthalapati, Steven I. Hanish, and Paul J. Thuluvath

12 Recurrence of HCC When Transplanted Outside Milan Criteria 165
Naveen Ganjoo and Thomas D. Schiano

13 Role of Neoadjuvant and Adjuvant Treatment in HCC Recurrence After Liver Transplantation 187
Masato Fujiki, Federico Aucejo, Minsig Choi, and Richard Kim

14 Cholangiocarcinoma 205
Nicholas Onaco and Göran B.G. Klintmalm

15 Recurrent Non-hepatic and De Novo Malignancies After Liver Transplantation 215
Ashokkumar Jain, Zakiyah Kadry, Stephanie L. Buchman, and Ali Riaz Shah

16 Recurrence of Disease After Liver Transplantation in the Pediatric Population 233
Elaine Y. Cheng, Robert S. Venick, and Ronald W. Busuttil

17 Disease Recurrence After Liver Transplantation: Quality of Life and Cost of Retransplantation 245
Vignan Manne and Sammy Saab

Erratum E1

Index 259

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Chapter 1
Overview: Disease Recurrence After Liver Transplantation

Paul J. Thuluvath

The short-term and long-term survival after liver transplantation (LT) improved significantly after the introduction of calcineurin inhibitors for immunosuppression. This improvement in outcomes and a better awareness resulted in an increasing demand for liver transplantation around the world. Transplant physicians have responded to this increased demand by developing several strategies including the use of older donors, grafts from hepatitis C virus (HCV)-positive donors or those with previous hepatitis B infection, graft from non-heart beating donors, domino transplantation, split-liver grafts, and live donor liver transplant (LDLT). Although there has been promising research in the fields of xenotransplantation, artificial liver support systems, hepatocyte transplantation and stem cell research, progress in these fields has been very slow. Currently, the only treatment that prolongs survival in those with end-stage acute or chronic liver failure is transplantation of either partial or full liver donor graft. Liver transplantation is also the treatment of choice for those with hepatocellular cancer (HCC)and cirrhosis. Because of the enormous disparity in supply and demand for donor organs, costs, and potential morbidity and mortality of live donors in LDLT, it has become incumbent on the transplant community to ration the available organs in a way that provides the best outcomes and in the process, serves the best interest of the population as a whole. When evaluating a potential candidate for LT, it is imperative to determine whether the recipient is going to benefit from the procedure immediately and in the long term.

The outcome of LT is dependent on many factors including graft quality, surgical techniques, postoperative care, immunosuppressive regimens and most importantly, careful pre-transplant recipient evaluation and selection. Currently, the expected 1-year and 5-year survival rates after LT are 85–95 % and 75–85 %, respectively [1].

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The most common causes of mortality after LT are infections, recurrence of primary liver disease or cancer for which LT was performed, cardiovascular events, de novo malignancy, and renal failure [2–6].

The immediate and late outcome of LT is dependent on many recipient factors including age, race, body mass index (BMI), presence of diabetes or coronary artery disease, pre-transplant serum creatinine, etiology, and severity (MELD score, ICU status, or on ventilation) of liver disease at the time of transplantation [7–13]. Cold ischemia time, ABO mismatch, donor age, graft quality, gender, and race are other predictive variables that are known only at the time of transplantation in deceased donor LT [14]. In addition, surgical expertise, ICU care, and immunosuppression regimen may also play a role in the outcome. There have been many attempts to develop models to predict survival, but those models lacked sufficient discriminating power needed for routine clinical care. Artificial neural network has been suggested as a possible alternative to traditional multivariate models, but to date, despite showing some promises, these models have not been used to reliably predict outcome after LT. As discussed earlier, one of the most common causes of mortality is recurrence of primary liver disease or cancer for which LT was initially performed. In this book, well-known authorities in LT review and critically analyze our current knowledge of the incidence and diagnosis of disease recurrence, natural history, and treatment options.

LT for hepatitis B virus (HBV)-related chronic liver failure is becoming less common in Western countries, and when done, it is mostly for HCC or fulminant liver failure [15]. In Chap. 2, Didier Samuel and colleagues review the progress that we have made in the past two decades in the management of transplant recipients with HBV infection. With a combination of pre-LT antiviral therapy and post-LT prophylaxis regimen containing hepatitis B immune globulin (HBIG) and nucleos(t)ide analogues, reinfection rates have come down from 80 % to less than 10 %. Moreover, these regimens have improved 5-year survival rates to over 80 % [16–20]. The authors make evidence-based recommendations on post-LT management of HBV in this section.

HCV-related liver disease and HCC remain the most common indication for LT in most countries [1]. Until recently, HCV reinfection was the Achilles heel of LT. The 5-year survival rate after LT for HCV-related liver disease is 61–75 %, compared with 76–85 % for other causes of liver diseases, including HBV infection [21, 22]. The predominant reason for the lower survival rate after LT in recipients with HCV infection is disease recurrence leading to cirrhosis and liver failure [21–27]. In LT recipients, fibrosis progresses at an accelerated rate, resulting in cirrhosis in 30 % of LT recipients within 5 years after transplantation. In less than 1 % of people with HCV infection, fibrosing cholestatic hepatitis may lead to rapid liver failure and graft loss [27, 28]. In Chap. 3, Marina Berenguer and colleagues discuss risk factors for progressive HCV disease after LT, and in Chap. 4, my colleague and I review the previous, current and future treatment options for HCV reinfection. Until recently, treatment of recurrent HCV was with interferon-based regimens, and these regimens were poorly tolerated and were associated with serious adverse events leading to very high drug discontinuation rates and lower cure rates. The recent approval of effective interferon-free regimens is likely to change the natural

history of recurrent hepatitis. Preliminary studies indicate that approximately 90 % of people with recurrent HCV could be cured with a combination of direct acting antiviral drugs with minimal side effects [29–32]. As with LT recipients with HBV infection, we are going to witness a remarkable improvement in the quality of life and long-term survival of HCV-positive LT recipients.

In Chap. 5, Russell Wiesner suggests that 10–40 % of patients develop clinical, biochemical, and histological changes consistent with recurrent primary biliary cirrhosis (PBC), but recurrence of PBC does not have an impact on 5-year graft and patient survival (~80 %) [33–38]. Diagnosis of recurrent PBC is a major challenge in LT recipients [39–42]. This review indicates that one potential risk factor for recurrence is the type of immunosuppression, with cyclosporine-based regimens, as compared to tacrolimus-based regimens, having a reduced incidence and prolonged time to recurrence [43–46]. The treatment with ursodeoxycholic acid does not appear to delay histological progression [47].

Similar to PBC, recurrent autoimmune hepatitis (AIH) may recur in a third of LT recipients after a median of 2–4 years post-LT [48–52]. James Neuberger (Chap. 6) eloquently discusses the challenges of making a diagnosis of recurrent AIH, and suggests that de novo AIH in LT recipients may indeed be a type of allograft rejection and better termed plasma cell hepatitis [53–55]. Many studies suggest that long-term use of steroids may reduce the risk of recurrent AIH. While most cases of recurrent AIH respond to increased immunosuppression and increased dose or introduction of corticosteroids, some may progress to graft cirrhosis and failure. Plasma cell hepatitis is also treated with increased immunosuppression [56].

A significant proportion of LT recipients have a history of obvious or occult alcohol or drug use. These recipients are at significant risk of resuming this behavior if it is not appropriately addressed prior to LT. Alcoholic liver disease is the second leading indication for liver transplantation in North American and Europe, and recidivism has been reported in a third of these patients [57]. Rolf Barth and colleagues (Chap. 7) discuss the complexity and controversies in this field including the defined periods of pre-transplant sobriety and appropriateness of LT in those who present with alcoholic hepatitis [58–61]. Although recidivism is common, recurrent alcoholic liver disease (8–19 %) leading to graft failure is less common [62]. The authors point out that alcoholic liver transplant recipients are at greater risk for mortality from cardiovascular disease and aero digestive malignancy, associated with alcohol and tobacco, and reinforce the importance of screening for malignancy and treatment of cardiac disease in these subjects [63–67].

Keith Lindor and colleague discuss the recurrence rates in primary sclerosing cholangitis (PSC), difficulty in distinguishing recurrence from ischemic strictures or chronic rejection, potential risk factors for recurrence and prognosis in a scholarly manner in Chap. 8. It appears that PSC recurs in about ~20 % of patients, and has a negative effect on long-term graft survival and patient survival [68–73]. However, 5-year survival is still around 80 %, but compared to PBC, retransplantation rates are higher (12.4 % vs. 8.5 %) in PSC [73].

In Chaps. 9 and 10, Drs. Bijan Eghtesad, Charles Miller and colleagues discuss the long-term outcomes of patients transplanted for metabolic disorders such as

familial amyloidal polyneuropathy (FAP), hemochromatosis, Wilson's disease, homozygous familial hypercholesterolemia, primary hyperoxaluria type 1 and non-alcoholic fatty liver disease (NAFLD). For metabolic disorders, except NAFLD, the metabolic defect is cured by LT, but the outcomes of end organ damage are unpredictable. FAP is a metabolic disorder for which LT is performed mostly to prevent neurological complications of FAP. According to the FAP registry, to date, over 2060 patients with FAP have been transplanted [74–80]. The estimated 10-year survival probability after LT for common variant amyloid is above 90 % compared to 56 % for non-transplant patients [74]. The result of 5-year survival for LT in non-V30M patients is far inferior (59 %) [75]. The outcomes of neurological and cardiovascular complications following LT for FAP is variable, and in some recipients, it may continue to progress. Similarly, cardiovascular complication is a common cause for mortality after LT for hemochromatosis [81]. NAFLD has become a common indication for LT, but the metabolic derangements that led to NAFLD persist or even get worse after LT resulting in significant cardiovascular morbidity and mortality [82–84]. Moreover, NAFLD recur in majority of patients, as reported in studies where protocol biopsies are performed, and in some it may progress to cirrhosis.

About 20 % of LT is performed for hepatocellular carcinoma (HCC), and the recurrence rates of HCC depend on patient selection [85–90]. Prior to the introduction of Milan criteria, the long-term results of liver transplantation in patients with HCC have been variable and disappointing, with an overall 5-year survival rate ranging from 30 to 40 %. Application of Milan criteria has reduced tumor recurrence rates to ~10 % and has improved 5-year tumor-free survival (~70 %). The UNOS data also suggest that the survival rates have improved after the publication of Milan criteria in the United States. In Chap. 11, my colleagues and I review the Milan criteria, recurrence rates when transplanted within Milan criteria and long-term recurrence-free survival rates. One of the major criticisms of Milan criteria is that it is based on pre-LT imaging findings, and only 70 % of explant pathology findings correlate with imaging. Moreover, imaging techniques, protocols, and interpretations of images are not uniform, and additionally, Milan criteria do not take into consideration the variability of tumor biology. There is an ongoing debate whether Milan criteria could be expanded without having an adverse effect on tumor-free survival. In Chap. 12, Thomas Schiano and colleague examine the expanded criteria by various authors, recurrence rates, predictors of recurrence, the role of down-staging, and the role of expanded criteria in living donor LT in a critical manner. The authors suggest that there will be an increasing demand for LT in those with HCC, and conclude that ongoing evaluation of the different pre-LT staging systems is necessary along with refinement of prognostic tools based on clinical parameters, treatment response, and molecular biologic/genetic markers in order to meet this anticipated transplant need. In Chap. 13, Richard Kim and colleagues examine the role of adjuvant and neoadjuvant treatment in HCC recurrence, and its role in down-staging liver tumors that are outside Milan criteria. Published studies suggest that HCC patients transplanted outside the Milan criteria have 5-year survival rates between 46 and 60 %. Use of multimodality approach, taking advantage

of the benefits of different loco-regional therapy for HCC has been adopted as down-staging and bridging therapies for LT. However, the value of adjuvant therapy using systemic cytotoxic chemotherapy after LT has been disappointing, and similarly, the role of sorafenib in this situation has not been well defined; these issues are discussed in detail in Chap. 13.

LT for cholangiocarcinoma has been a controversial area because of high recurrence rates and early experience showed that 1-year survival was as low as 36 %, and the 5-year survival varying between 5 and 38 % [91–94]. Recent data, however, suggest that multimodal therapies, with neoadjuvant chemotherapy and/or radiation, and surgical exploration followed by LT may offer patients acceptable long-term tumor-free survival rates [95–98]. In Chap. 14, Groan Klintmalm and colleague review the literature and suggest that LT for cholangiocarcinoma should be performed using strict multimodal protocols in order to ensure good outcomes.

As discussed earlier, malignancy is a common cause of long-term mortality after LT. Ashokkumar Jain and colleagues discuss the common recurrent non-hepatic and de novo malignancyrates in LT recipients in Chap. 15 [99–107]. Rates of de novo malignancy increase in proportion to age at transplant and length of follow-up with skin cancer being the most common malignancy. The risk factors for other de novo cancers include history of alcoholic cirrhosis, smoking, Barrett's esophagus, and PSC with inflammatory bowel disease. Authors point out that the rates of gynecological and breast cancers are lower than general population in most studies, and there may be geographical differences in de novo cancer rates after LT. In those with pre-LT non-hepatic malignancies, recurrence of neuroendocrine tumors and skin cancers are high. In this section, authors remind us of the importance of surveillance of LT recipients for recurrence as well as de novo malignancies.

The indications for LT in children are different from adult, and as per UNOS registry, the common indications are biliary atresia (47 %) followed by metabolic disorders (14 %), primary liver malignancy (13 %), and acute liver failure (11 %). In Chap. 16, Ronald Busuttil and colleagues review disease recurrence patterns in children transplanted for primary liver malignancy and metabolic disorders [108–111]. The authors show that disease recurrence is uncommon in children, and the spectrum of recurrent conditions is different from adults. Even in the presence of locally advanced hepatoblastoma, recurrence rates are low when children are transplanted after neoadjuvant chemotherapy followed by liver transplantation. In this chapter, authors discuss recurrence rates of other conditions including AIH, GCH-AIHA, and PSC. Another interesting observation is the recurrence of bile salt export pump deficiency in children [112].

In Chap. 17, Sammy Saab and colleague analyze the literature on quality of life in liver transplant recipients, and discuss potential reasons for poor quality of life and estimate the costs and outcomes associated with retransplantation. Most studies have shown that health-related quality of life improves significantly after LT, and this improvement is sustained for the first decade after LT when compared to the same patients in the pre-transplant period or an equivalent waiting list group of patients with chronic liver disease. Most studies, however, have shown that LT recipients have poorer performance in physical function when compared to the

general population. Additionally, the quality of life measurements are poorer in those (transplanted for alcoholic cirrhosis) who resume drinking and in those with recurrent HCV [113]. The difficulty in assessing the quality of life in LT recipients in the absence of a validated, disease-specific measurements tool, and the complexity of patients with confounding variables are well described in this section.

In summary, in this book, eminent authors have described and analyzed all aspects of disease recurrence in great detail based on evidence. I sincerely hope that liver transplant community involved with patients care will find it a useful reference book.

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Chapter 2
Hepatitis B Recurrence: Major Milestones and Current Status

Bruno Roche and Didier Samuel

2.1 Introduction

Five to 10 and 80 % of patients undergoing liver transplantation (LT) have hepatitis B virus (HBV)-associated chronic or fulminant liver disease in the USA, Europe, and Asia, respectively [1, 2]. Historically, the spontaneous risk for HBV reinfection was about 80 % related to the initial liver disease and to the presence of HBV replication at the time of transplantation [3, 4]. Since 1990, the impact of recurrent HBV infection has been greatly diminished due to the effectiveness of pre-transplant antiviral therapy, post-transplant prophylaxis regimens, and antiviral therapy for treating HBV infection of the graft. Using a combination prophylaxis with hepatitis B immune globulin (HBIG) and nucleos(t)ide analogs, LT in patients with hepatitis B produces survival rates at 5 years in over 80 % and recurrence rates below 10 % even in patients with preoperative viral replication [5–7]. There is a consensus regarding the use of a life-long HBV prophylactic therapy supported by the detection of low levels of HBV DNA in serum, liver, and peripheral blood mononuclear cells or the presence of total and covalently closed circular HBV DNA in liver tissue transiently post-LT in the absence of a positive HBsAg [8, 9]. However, the long-term prophylaxis is expensive and inconvenient for patients. This has led to the development of alternative strategies aimed to reduce the dose and duration of HBIG or to avoid the use of HBIG.

In this chapter, we will describe the significant improvements in the prevention and the management of HBV recurrence after LT.

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2.2 Indications and Results of Transplantation

Pre-transplant antiviral treatment using nucleos(t)ides analogs to suppress HBV replication may induce clinical improvement in a subset of patients and has lead to a major decrease in the rate of LT for HBV cirrhosis. Actually, the main indications for LT in the setting of HBV cirrhosis are hepatitis flares related to viral resistance or noncompliance to antiviral therapy and hepatocellular carcinoma (HCC) [1]. Kim et al. reports an overall reduction of the number of LT for HBV-related end-stage liver disease over time in the USA, along with a persistent increase in LT for HCC [1]. The impact of antiviral therapy on the incidence of HCC is less well established and delayed compared with that on end-stage liver disease.

Historically, in the absence of prophylaxis of HBV reinfection, the 5-year survival rate was between 40 and 60 % and HBV-related deaths are frequent [3, 4]. Major advances in prophylaxis and treatment of HBV recurrence have resulted in overall survival rates as high as 80–90 % at 5 years [2, 5–7]. In 206 European patients using prevention of HBV recurrence with HBIG and lamivudine (LAM), the 2-year patient survival increased from 85 % in 1988–1993 to 94 % after 1997 ($P<0.05$) and the 2-year recurrence rates decreased from 42 to 8 % ($P<0.05$), respectively [5]. In the multivariate analysis for patient survival, only the covariates HCC and HBV recurrence were statistically significant. The 5-year survival of HBV-infected transplant recipients has increased from 53 % in the period 1987–1991 to 69 % in the period 1992–1996, to 76 % in the period 1997–2002 in a study from the USA [6].

2.3 Diagnosis, Mechanisms, and Risk Factors for HBV Recurrence After Liver Transplantation

Recurrence of HBV infection after LT iscommonly defined as the reappearance of circulating hepatitis B surface antigen (HBsAg) with or without detectable HBV DNA. However, only patients who develop persistently detectable HBV DNA are shown to be at risk for clinical disease and graft loss [10]. HBV reinfection is the consequence of an immediate reinfection of the graft by circulating HBV particles, a later reinfection from HBV particles coming from extra-hepatic sites, such as peripheral blood mononuclear cells [11, 12], or both.

Whatever the prophylaxis used, there is a direct relationship between HBV viral load at transplantation (i.e., >20,000 IU/mL) and the rate of recurrence [7, 13–17]. Other factors associated with low rates of recurrence are surrogate markers for low levels of viral replication and include negative hepatitis B e antigen (HBeAg) status at listing, fulminant HBV and HDV coinfection [7, 15]. Thus, the use of antivirals before transplantation to achieve undetectable HBV DNA levels is a consensus. Several studies have recently reported that HCC at LT, HCC recurrence or chemotherapy used for HCC are independently associated with an increased risk of HBV

recurrence [18–21]. The detection of cccDNA in HCC cells suggests the possibility of viral replication in tumor cells, which would then act as a viral reservoir [18].

In patients receiving antiviral monoprophylaxis with low genetic barrier agents, HBsAg remains positive, progressively declining over a period of a few months after transplantation to become undetectable. In compliant patients, recurrence is most often associated with HBV polymerase mutations [14, 22–26]. In patients without overt recurrence, persistence or reappearance of HBsAg positivity without detection of HBV DNA can be observed [24, 27].

After the removal of the major viral reservoir, the use of HBIG at the anhepatic phase is aiming at inhibiting entry by neutralizing viral determinants of attachment. In patients receiving HBIG, HBV reinfection may be the consequence of the incomplete neutralization of viral particles at the anhepatic phase due to high viral load or HBV overproduction coming from extrahepatic sites. Recurrence is often, but not exclusively, associated with the emergence of escape variants with mutations in the S domain of HBV, and particularly in the antigenic loop ("a" determinant) [28, 29].

Reinfection in patients on combined prophylaxis are associated with mutations in both the surface and the polymerase genes [30].

Whatever theprophylaxis used, measurable low levels of HBV DNA have been reported after LT in a significant proportion of patients without detectable HBsAg and without evidence of chronic hepatitis on the liver graft. HBV DNA has been reported in serum, peripheral blood mononuclear cells, and liver, both total and cccDNA [8, 9, 12, 31–34]. These findings suggest that occult HBV reinfection occurs in some HBV recipients and implies a risk of overt HBV recurrence if prophylaxis is stopped. Conversely, for the few patients who are negative for HBV DNAand cccDNA in all compartments, the discontinuation of HBV prophylaxis could be discussed [9].

2.4 Prevention of HBV Recurrence

2.4.1 Pre-transplantation Antiviral Therapy

The goals of antiviral treatment for patients with end-stage HBV liver disease are to improve liver function, thereby obviating the need for liver transplant and in patients who require a transplant to decrease the risk of HBV recurrence. The major factor to achieve these goals is to obtain sustained viral suppression. LAM, adefovir (ADV), and Telbivudine are no longer considered as an optimal first-line therapy related to a high rate of resistance development and latest recommendations suggest using entecavir (ETV) or tenofovir (TDV) as primary antiviral agents [35, 36].

ETV, a nucleoside analog, is more potent than LAM in both HBeAg-positive and HBeAg-negative patients [37, 38] and exhibits a very low resistance rate (i.e., near 1 %) in LAM naive patients, even after 5 years of therapy [39]. In contrast, ETV resistance occurred in more than 35 % of patients after 4 years of therapy in LAM-resistant patients [40].

TDF, a nucleotide analog, is more potent than ADV against the wild type and nucleosides analogs-resistance HBV strains [41]. No drug-resistant variants have been reported with 6 years of continuous treatment [42]. TDV could be prescribed in combination with emtricitabine, a nucleoside analog with an antiviral activity profile similar to that of LAM (Truvada®).

Patients with decompensated cirrhosis should be treated in specialized liver units, as the application of antiviral therapy is complex [43]. Most studies have shown a biphasic survival pattern with most deaths occurring within the first 6 months of treatment [44–46]. Patients with higher pretreatment bilirubin levels, creatinine levels, and HBV DNA levels were at greatest risk for early death while early suppression of HBV replication was not associated with more favorable outcomes [44]. Transplantation should not be delayed in patients with CTP class C or a MELD score $\geq$15 at baseline, or be urgently considered in patients displaying suboptimal improvement in hepatic reserves after 3 months of antiviral treatment, due to our inability to identify those patients with a poor short-term prognosis. Conversely, long-term antiviral treatment could be done in patients who can be stabilized with antiviral therapy. These patients must undergo frequent clinical and laboratory assessment to insure medication compliance and surveillance for virological and clinical response as well as drug side effects, drug resistance, and HCC.

2.4.2 Post-transplant Prevention of HBV Recurrence

2.4.2.1 Combination Prophylaxis

Since the study by Samuel et al., HBIG has been the cornerstone of prophylaxis against HBV recurrence post-LT [15]. This study demonstrated a dramatic reduction in the rate of HBV recurrence from 75 % in patients receiving no or short-term therapy with HBIG to 33 % in those receiving long-term IV HBIG treatment ($p<0.001$) and was associated with improved graft and patient survival. Recurrence of HBV occurred in 67 %, 32 %, and 17 % of patients who underwent transplantation for HBV cirrhosis, HDV cirrhosis, and fulminant hepatitis B, respectively. Whatever the mechanism involved, there is evidence for a dose-dependent response to HBIG treatment [47, 48]. These results were confirmed by other clinical trials in the USA, Europe, and Asia and sustained efforts to reduce HBV replication in patients with HBV cirrhosis while waiting for LT [8, 49–51]. The advent of antiviral therapy further changed the landscape of post-LT prophylaxis and the standard of care now is to combine HBIG with a nucleos(t)ide analog. Reduction of the pretransplant viral load with antivirals may decrease the risk that high levels of HBsAg saturate the binding capacity of HBIG and the immune pressure that triggers the selection of mutation of the "a" determinant of the HBV surface protein. Antivirals may inhibit HBV replication allowing a dose reduction of HBIG [52]. Binding of HBV particles by HBIG may reduce the viral substrate available to antivirals and may thus decrease the risk for the development of resistant mutants.

In conventional protocols, HBIG were used at high doses during the anhepatic phase and the first postoperative week (i.e., generally 10,000 IU/day) (Table 2.1) [5, 14, 16, 18–20, 53–65]. In the medium and long-term follow-up, IV HBIG has been administered in two different ways: at a frequency dictated by the maintenance of specific anti-HBs levels (i.e., 100 IU/L) and on a fixed schedule. The latter approach is simpler and requires less monitoring but is more expensive [49, 66]. The optimal anti-HBs titre needed to prevent recurrence in the medium and long-term follow-up is unknown, probably reduced if potent antiviral therapy is associated with HBIG.

In an effort to find less costly ways of providing HBIG prophylaxis long-term, alternative approaches have been studied including the use of low-dose intramuscular (IM) HBIG [14, 53, 55, 59–61, 64], subcutaneous HBIG [62, 67, 68], withdrawal of HBIG after a finite period or prophylaxis regimens without HBIG.

Combination prophylaxis with low-dose IM HBIG (400–800 IU IM) decreases costs by more than 90 % as compared with an IV regimen, with a recurrence rate as low as 4 % at 4 years [53, 56, 69]. More recently, subcutaneous HBIG initiated 6 months after LT have proven effective as well, with some advantage regarding tolerability and the possibility of self-administration by patients [62, 67, 68]. Degertekin et al. analysed data from 183 patients who had undergone LT between 2001 and 2007 [7]. Patients received combination prophylaxis with antiviral therapy (mostly LAM monotherapy) plus HBIG given either IV high dose (25 %, 10,000 IU monthly), IV low dose (21.5 %, 3000–6000 IU monthly), IM low dose (39 %, 1000–1500 IU every 1–2 months), or for a finite duration (14.5 %, median duration 12 months). Cumulative rates of HBV recurrence at 1, 3, and 5 years were 3 %, 7 %, and 9 %, respectively. A multivariate analysis showed that positivity for HBeAg and a high viral load at transplant, but not the post-transplant HBIG regimen, were associated with HBV recurrence.

Several meta-analyses have compared the use of HBIG, antivirals, or both (Table 2.2) [48, 70–73]. Despite methodological limitations, combination prophylaxis was significantly superior to antivirals or HBIG alone in preventing HBV recurrence, irrespective of the HBV DNA level at transplantation and in reducing overall and HBV-related mortality in some studies. A high HBIG dose ($\geq$10,000 IU/day) vs. a low HBIG dose (<10,000 IU/day) during the first week after LT was associated with a lower frequency of HBV recurrence (3.2 % vs. 6.5 %, $p=0.016$).

The role and the safety of newer nucleos(t)ide analogs (i.e., ETV or TDV) have not yet been adequately evaluated [60, 73–75]. In a recent systematic review, the combination of HBIG and a newer nucleos(t)ide analogwas superior to the combination of HBIG and LAM in reducing the risk of HBV recurrence (1 % vs. 6.1 %, $p=0.0004$) [73].

The use of IV HBIG has limitations, namely the high cost, parenteral administration, limited supply, need for frequent clinic visits and laboratory monitoring, lower effectiveness in patients with high levels of HBV replication before LT (HBIG monoprophylaxis), and the potential selection of HBsAg escape mutants (HBIG monoprophylaxis). The intramuscular (IM) route of administration is a cost-effective alternative to IV HBIG. Subcutaneous injections improve quality of life by offering greater independence and home self-administration may contribute to decrease

Table 2.1 Prevention of HBV recurrence after liver transplantation with antiviral drugs and HBIG

Authors (references)	No. of patients	HBV DNA positive at LT (%)	Prevention of HBV recurrence		Follow-up (months)	HBV recurrence *N* (%)	Risk factors for HBV recurrence
			HBIG regimen	Antiviral			
Indefinite high-dose IV HBIG							
Markowitz [57]	14	1 (7 %)	HBIG IV 10,000 IU/month	LAM	13	0 %	
Marzano [54]	26	0	HBIG IV 5000 IU/month	LAM	31	1 (4 %)	
						LAM-R $n=1$	
Rosenau [58]	21	5 (24 %)	2000 IU IV until anti-HBs >100 IU/L	LAM	20	2 (9.5 %)	
						LAM-R $n=2$	
Steinmuller [5]	51	NA	1500–2000 IU IV until anti-HBs >100 IU/L	LAM	35	8 %	
Faria [18]	51	21 (41 %)	10,000 IU IV until anti-HBs >150 IU/L (HBV DNA negative at transplant) or >500 IU/L (HBV DNA positive at transplant)	LAM ± ADV or TDV	43	3 (6 %)	HCC pre-LT
							Pre-LT HBV DNA $>10^5$ copies/mL
							HBIG monoprophylaxis
Han [56]	59	16 (27 %)	HBIG IV 10,000 IU/month	LAM	15	0 %	
Chun [20]	186	70/167 (32 %)	10,000 IU IV until anti-HBs >350 IU/L	LAM	35	22 (12 %)	Recurrent HCC
							Pre-LT HBV DNA $>10^5$ copies/mL
							Lamivudine therapy for >1.5 years
Yi [19]	108	43 (40 %)	10,000 IU IV until anti-HBs >350 IU/L	LAM	31	15 (14 %)	Cumulative dose corticoids
							Systemic therapy against HCC
Woo [63]	165	95 (58 %)	HBIG IV 10,000 IU/month during 5 months, HBIG IM 2000 IU biweekly	LAM	40	7 (4 %)	Pre-transplant Lamivudine therapy for >6 months
						LAM-R $n=5$	

Authors (ref.)	No. of patients	HBV DNA positive at LT (%)	Prevention of HBV recurrence		Follow-up (months)	HBV recurrence *N* (%)	Risk factors for HBV recurrence
			HBIG regimen	Antiviral			
Indefinite low-dose IM or IV HBIG							
Gane [53]	147	125 (85 %)	HBIG IM 800 IU/month	LAM	62	5 (1 % 1 years, 4 % 5 years)	Pre-LT HBV DNA $>10^6$ copies/mL
						LAM-R $n=5$	
Zheng [26]	114	$\geq 10^5$ c/mL (32 %)	HBIG IM 800 IU/month	LAM	20	16 (13.5 % 1 years, 15.2 % 2 years)	Pre-LT HBV DNA $>10^5$ copies/mL
						LAM-R $n=11$	
Anselmo [59]	89	NA	HBIG IM 1560 IU according to anti-HBs titers	LAM	29	10 (11 %)	
Xi [60]	ETV 30	18 (60 %)	HBIG IM 800 IU until anti-HBs >500 IU/L month 3, >300 IU/L month 3–6, > 200 IU/L month 6–12	ETV	NA	0 %	
	LAM 90	52 (58 %)		LAM		10 (11 %)	
						LAM-R $n=2/4$	
Jiang [55]	254	53 (21 %)	HBIG IM 8–1200 IU/2–4 week	LAM	41	14 (2.3 % 1 years, 6.2 % 3 years, 8.2 % 5 years)	Pre-LT HBV DNA $>10^5$ copies/mL
						LAM-R $n=5$	Prednisone withdrawal time >3 months
Akyildiz [61]	209	NA	HBIG IM 200–1000 IU/1–4 weeks until anti-HBs >50 IU/L	LAM	18	11 (5.2 %)	
						LAM-R $n=5$	

(continued)

Table 2.1 (continued)

Authors (ref.)	No. of patients	HBV DNA positive at LT (%)	Prevention of HBV recurrence		Follow-up (months)	HBV recurrence *N* (%)	Risk factors for HBV recurrence
			HBIG regimen	Antiviral			
Cai [64]	ETV 63	NA	HBIG IM 400 IU until anti-HBs >250 IU/L month 3, >100 IU/L >month 3	ETV	ETV 41.2	0 %	
	LAM 189			LAM	LAM 38.5	18 (9.5 %)	
						LAM-R *n* = 15	
Iacob [65]	42 HDV + 69 %	1 (2 %)	HBIG IV 2500 IU until anti-HBs <50 IU/L	LAM	21	2 (4.8 %)	
Subcutaneous HBIG							
Di Costanzo [62]	135	NA	HBIG IV 6000 IU/month >12 months post-LT	LAM 87	12	0 %	
			HBIG S/C/week 500 IU body weight <75 kg, 1000 IU body weight ≥75 kg	Other 17			

NA not available, *LT* liver transplantation, *HBIG* hepatitis B immune globulin, *LAM* lamivudine, *ADV* adefovir, *TDV* tenofovir, *ETV* entecavir, *LAM-R* resistance mutation(s) to lamivudine, *HCC* hepatocellular carcinoma, *IM* intramuscular, *IV* intravenous

Table 2.2 Results of meta-analyses comparing combination prophylaxis to HBIG or antiviral monoprophylaxis

Authors (ref.)	Studies	Patients	Results: HBV recurrence, HBV-related mortality
Loomba [72]	6 studies	HBIG + LAM $n=193$	*HBIG + LAM vs. HBIG*:
	1999–2003	HBIG $n=124$	– Decrease risk of HBV recurrence 4.1 % vs. 36.1 %
			– Decrease HBV-related mortality: RR = 0.08; 95 % CI (0.02, 0.33)
Rao [70]	6 studies	HBIG + LAM $n=306$	*HBIG + LAM vs. LAM*
	2003–2007	LAM $n=245$	– Decrease risk of HBV recurrence: RR = 0.38; 95 % CI (0.25, 0.58)
Katz [71]	20 studies	LAM $n=249$	*HBIG + LAM vs. HBIG*
	(3 RCT)	HBIG $n=351$	– Decrease risk of HBV recurrence: RR = 0.28; 95 % CI (0.12, 0.66)
	1999–2007	LAM + ADV = 23	– Decrease HBV-related mortality: RR = 0.12; 95 % CI (0.05, 0.30)
		HBIG + antiviral $n=712$	*HBIG + LAM and/or ADV vs. LAM and/or ADV*
			– Decrease risk of HBV recurrence: RR = 0.31; 95 % CI (0.22, 0.44)
			– Decrease HBV-related mortality: RR = 0.31; 95 % CI (0.09, 1.10)
			HBIG vs. LAM[a]: no statistically significant difference in HBV recurrence and HBV-related mortality
Cholongitas [48]	46 studies	HBIG + LAM and/or ADV $n=2162$	*HBIG + LAM and/or ADV*: HBV recurrence 6.6 %
	(3 RCT)	HBIG + ADV $n=154$	*HBIG + LAM and/or ADV vs. HBIG*: HBV recurrence 6.6 % vs. 26.2 %
	1998–2010	HBIG $n=260$	*HBIG + LAM and/or ADV vs. LAM and/or ADV*: HBV recurrence 6.6 % vs. 19 %
		LAM and/or ADV $n=189$	*HBIG + LAM vs. HBIG + ADV and/or LAM*: HBV recurrence 6.1 % vs. 2 %
Cholongitas [73]	17 studies	ETV or TDV or TDV + FTC and HBIG $n=304$	*ETV or TDV or TDV + FTC and HBIG*: HBV recurrence 1.3 %
	(1 RCT)	ETV or TDV or TDV + FTC and HBIG discontinuation $n=102$	*ETV or TDV or TDV + FTC and HBIG discontinuation*: HBV recurrence 3.9 %
	2009–2012	ETV or TDV or TDV + FTC without HBIG $n=112$	*ETV or TDV or TDV + FTC without HBIG*: HBV recurrence
			– HBsAg + 26 %
			– HBV DNA + 0.9%

[a]In two out of three studies, LAM was given after pretreatment with HBIG (1 week or 6 months)
RCT randomized-controlled trial, *HBIG* hepatitis B immune globulin, *LAM* lamivudine, *ADV* adefovir, *ETV* entecavir, *TDV* tenofovir, *FTC* emtricitabine

costs by avoiding the need for day hospitals. HBIG has a satisfactory safety record and adverse events observed have usually been minor. Hypersensitivity reactions or even anaphylaxis rarely occur following HBIG administration and can be controlled with antihistamines or steroids.

HBIG Discontinuation

Indefinite combination therapy with HBIG plus a nucleos(t)ide analog may not be required in all liver transplant recipients. The replication status of the patient prior to the initiation of antiviral therapy and at the time of LT should guide prophylaxis. Alternative strategies to consider, especially in patients without detectable HBV DNA prior to transplantation, are the discontinuation of HBIG after a defined period of time and continuing treatment with antivirals alone.

Studies of hepatitis B vaccination as an alternative to long-term HBIG in LT recipients showed that successful hepatitis B vaccination and discontinuation of HBIG are feasible only in a small group of selected patients but the optimal vaccine protocol has not been established [76–84].

Another strategy is HBIG withdrawal after a defined period of combination prophylaxis (Table 2.3) [9, 10, 85–93]. In a study of 29 patients, high-dose HBIG and LAM were used in the first month, and patients were then randomized to receive either LAM monotherapy or LAM plus IM HBIG at 2000 IU monthly [85]. None of the patients developed HBV recurrence during the first 18 months but later recurrences developed in 4 patients after 5 years of follow-up related with poor LAM compliance [86]. An alternative approach is to switch from HBIG/LAM to a combination of antiviral agents. In a randomized prospective study, 16 of 34 patients receiving low-dose IM HBIG/LAM prophylaxis were switched to ADV/LAM combination therapy, whereas the remaining patients continued HBIG/LAM [88]. At a median follow-up of 21 months post-switch, no patient had disease recurrence, although one patient in the ADV/LAMgroup had a low titre of HBsAg in serum but was repeatedly HBV DNA negative. The same group has recently reported the outcome of 20 patients receiving LAM + ADV initiated at the time of listing and continued after LT [92]. Eight hundred IU of IM HBIG were given immediately after LT and daily during 7 days. After a median follow-up of 57 months post-LT, only one patient became HBsAg positive (HBV DNA negative) at the time of HCC recurrence. Recently, Teperman et al. evaluated the use of a combination of TDV with Emtricitabine after HBIG discontinuation [91]. In this study, subjects were treated with a combination of Emtricitabine/TDV and HBIG for 24 weeks and then randomized to continue this regimen ($n = 19$) or to discontinue HBIG ($n = 18$). At 72 weeks post-randomization, only one patient in the Emtricitabine/TDV group had a transient detectability of HBV DNA related to poor compliance. Several studies demonstrated cases of seroconversion to positive HBsAg associated with undetectable HBV DNA (Table 2.3) [87–89, 92]. A proposed mechanism for this is that HBsAg was being produced at low levels during HBIG therapy and became detectable after HBIG cessation. Longer follow-up of these patients is necessary to deter-

Table 2.3 Prevention of HBV recurrence after liver transplantation with HBIG discontinuation and long-term antiviral therapy

Authors (references)	No. of patients	HBV DNA positive at LT (%)	Prevention of HBV recurrence	Duration of HBIG	Follow-up (months)	HBV recurrence *N* (%)
Buti [85, 86]	29	0	Randomized trial	1 months	83	1/9 (11 %) in the LAM + HBIG group
			HBIG + LAM then LAM ($n=20$) vs. LAM + HBIG IM 2000 IU/ month ($n=9$)			3/20 (15 %) in the LAM group (poor compliance to LAM)
						Transient detection of HBV DNA $n=6$
Wong [87]	21	20 %	HBIG ± LAM then LAM or ADV	median 26 months	40	HBV DNA+, HBsAg + (LAM-R) $n=1$ (5 %) (poor compliance to LAM)
		HBV DNA >5 log copies/mL				HBV DNA +, HBsAg—(LAM-R) $n=1$
						Transient detection of HBV DNA $n=3$
						Transient detection of HBsAg $n=1$
Neff [90]	10	0	HBIG + LAM, then LAM + ADV	6 months	31	0
Angus [88]	34	20 %	Randomized trial	>12 months	21	0/18 in HBIG + LAM group
			IM HBIG + LAM then HBIG + LAM ($n=18$) vs. ADV + LAM ($n=16$)			1/16 (6 %) in ADV + LAM group (HBsAg+, HBV DNA−)

(continued)

Table 2.3 (continued)

Authors (references)	No. of patients	HBV DNA positive at LT (%)	Prevention of HBV recurrence	Duration of HBIG	Follow-up (months)	HBV recurrence *N* (%)
Saab [89]	61	21 %	IM HBIG + LAM then LAM or ETV + ADV or TDV (3 months of overlap therapy)	>12 months	15	2/61 (3.3 %) (HBsAg+, HBV DNA−)
Teperman [91]	37	47 %	Randomized trial At a median of 3.4 years post-LT, HBIG + TDV-emtricitabine 24 weeks then HBIG + TDV-emtricitabine vs. TDV-emtricitabine	Median 3.4 years + 24 weeks	22	0
Gane [92]	20 + 10	65 %	IM HBIG + LAM + ADV then LAM + ADV	7 days	57	0 Transient detection of HBsAg in a patient with concomitant HCC recurrence
Nath [93]	14	79 %	IV HBIG + LAM then LAM + ADV	7 days	14.1	1 (7 %)
Lenci [9]	30	0	HBIG + LAM ± ADV were withdrawn after liver biopsy specimens were negative for total and cccDNA	NA	29	5/30 (17 %) HBV DNA+, HBsAg + $n = 1$ Transient detection of HBsAg $n = 4$

NA not available, *LT* liver transplantation, *HBIG* hepatitis B immune globulin, *LAM* lamivudine, *ADV* adefovir, *ETV* entecavir, *TDV* tenofovir, *LAM-R* resistance mutation(s) to lamivudine, *IM* intramuscular, *IV* intravenous

mine whether they will clear HBsAg or whether they are at future risk of viral breakthrough. Duration of HBIG in HBIG withdrawal strategies is variable across centers and has not yet been established (Table 2.3). Drug compliance during long-term antiviral therapy may be a very important issue for transplant patients who have a lifelong risk of HBV recurrence.

An ultimate approach was to evaluate the safety of complete and sustained prophylaxis withdrawal in LT recipients at a low risk of HBV recurrence. Lenci et al. evaluated a cohort of 30 patients treated with a combination of HBIG and LAM (± ADV) for at least 3 years [9]. Using the absence of intrahepatic total HBV DNAand cccDNA as a guide, HBIG and then antiviral therapy was withdrawn. After a median of 28.7 months off all prophylactic therapy, 83 % of the cohort remained without serologic recurrence of HBV infection. Five patients developed HBsAg recurrence but only one patient was HBV DNA positive. In the other patients, HBsAg positivity was transient. The ability to measure total HBV DNA and cccDNA in a liver biopsy has limitations: this strategy requires sequential liver biopsies and assays for quantification of total HBV DNA and cccDNA are not standardized.

The studies available to date highlight several key issues to consider prior to the discontinuation of HBIG: First, the risk of HBV recurrence after cessation of HBIG may increase with time off HBIG either due to the development of viral resistance or due to noncompliance to antiviral therapy. Second, the patients with high levels of HBV DNA at the time of transplantation appear to be a higher risk group for recurrence when HBIG is discontinued; Third, we currently lack the ability to identify patients who may have cleared HBV post-transplantation.

HBIG-Free Prophylactic Regimens

LAM has been evaluated as a prophylactic monotherapy, pre- and post-transplantation without HBIG. The outcome at 1 year showed a 10 % recurrence rate [22]. However, with longer follow-up, rates of recurrence reached 22–41 % at 3 years post-LT (Table 2.4) [14, 22–26]. Recurrence was due to the emergence of escape mutations in the polymerase gene and was observed mainly in patients with a high level of HBV replication prior to drug exposure. Schiff et al. reported 61 LAM-resistant patients treated with ADV on the waiting list [45]. Sixty percent of these patients received HBIG and ADV combination prophylaxis post-LT and 40 % ADV ± LAM prophylaxis. Interestingly, no patient in either group had recurrent HBV infection. Recently, Gane et al. reported the results of a combination prophylaxis using LAM and ADV without HBIG in 18 patients who had documented suppression of HBV DNA below 3 $\log_{10}$ IU/mL before LT [92]. No case of HBV recurrence was observed after a median follow-up of 22 months. The combination of LAM and ADV is cost-effective as compared to low-dose IM HBIG and LAM. The availability of more potent antivirals with a higher barrier to resistance could increase the proportion of patients with undetectable HBV DNA pre-transplantation and decrease the risk of recurrent disease post-transplantation [10]. Fung et al. investigated the efficacy of ETV as monoprophylaxis in 80 patients with chronic hepatitis B who received a liver transplant [27].

Table 2.4 Prevention of HBV recurrence with antiviral(s) before and after liver transplantation

Authors (ref.)	No. of patients	Patients HBV DNA positive at time of treatment	Patients HBeAg positive at time of treatment	Duration of treatment before LT months	Patients HBV DNA positive at time of LT	No. of LT	No. of HBV recurrences (%)	Follow-up (months)	Deaths related to HBV recurrence
LAMIVUDINE									
Mutimer [26]	17	9	11	2 (1.2–5.6)	0	12	5 (29 %) LAM-R $n=4$	32 (16–51)	2
Lo [24]	31	11	18	1.6 (0.03–20.4)	6	31	7[a] (22.6 %) LAM-R $n=1$	16 (6–47)	0
Perillo [23]	77	26	24	2.1 (0.03–20.9)	6	47	17 (36 %) LAM-R $n=15$	38 (2.7–48.5)	1
Zheng [14]	51	51	NA	0	51	51	21 (41 %) LAM-R $n=14$	30 (6.5–60)	3
LAMIVUDINE + ADEFOVIR									
Lo [80]	8	8	NA	LAM 30 (16.8–59.9) ADV 2.9 (0–9)	7	8	2[b] (25 %)	11.5 (4.4–26)	0
Schiff [45]	23	23	NA	LAM (NA) ADV 5 (NA)	NA	23	3[c] (13 %)	9 (NA)	0
Gane [92]	18	79 %	18 %	LAM 15 (1–89) ADV (NA)	64 %	18	0	22	0
ENTECAVIR									
Fung [27]	80	NA	NA	5 (0–44) Forty seven treated patients (LAM, ADV, ETV)	59	80	18[d] (22.5 %)	26 (5–40)	0

[a]Six of these patients were HBsAg positive, HBV DNA negative by PCR
[b]These two patients were HBsAg positive, HBV DNA negative by PCR
[c]Two of these patients were HBsAg positive and three HBV DNA positive
[d]Seventeen of these patients were HBsAg positive, HBV DNA negative by PCR
HBeAg hepatitis B e antigen, *HBV* hepatitis B virus, *NA* not available, *LT* liver transplantation, *LAM* lamivudine, *ADV* adefovir, *ETV* entecavir

A total of 18 patients (22.5 %) had persistent HBsAg positivity after transplant without seroclearance ($n=8$) or reappearance of HBsAg after initial seroclearance ($n=10$). One out of 18 patients had a very low HBV DNA level of 217 copies/mL at 36 months post-LT. The pre-LT HBsAg level was significantly higher in those who had HBV recurrence/persistence compared with those who did not. Whether other antivirals such as TDV or a combination of antivirals without HBIG would provide effective prophylaxis is unknown.

2.4.2.2 Guidelines and Future Prospects for Prevention of HBV Reinfection

The principles guiding strategies to prevent HBV recurrence should be to maximize antiviral potency while minimizing the risk of viral resistance, costs, side effects, and inconvenience for patients.

Viral suppression is the goal for all patients on a waiting list. For those patients with viral replication, ETV, TDV, or a nucleoside/nucleotide combination should be used.

There is a consensus regarding the need for a life-long prophylactic therapy. In the early post-transplant period, some studies reported that a high IV HBIG dose (≥10,000 IU/day) vs. a low HBIG dose (<10,000 IU/day) was associated with a lower frequency of HBV recurrence. At long-term, low-dose IM (or subcutaneous) HBIG in combination with a potent nucleos(t)ide analog is the most cost-effective prophylaxis. Patients with an undetectable HBV DNA level at the time of transplant are eligible for protocols using short-term low-dose IV or IM HBIG and antiviral therapy, followed by antiviral mono- or combination therapy (Fig. 2.1). A more cautious approach to this prophylactic regimen is necessary for those patients with high pre-transplant HBV DNA levels, those with limited antiviral options if HBV recurrence occurred (i.e., HIV or HDV coinfection, preexisting drug resistance or intolerance), those with a high risk of HCC recurrence, and those with a risk of noncompliance with antiviral therapy. In this group, HBIG-free prophylaxis cannot be recommended.

2.5 HBV Recurrence

Most cases of HBV reinfection occur during the first 2–3 years after transplantation. HBV reinfection is characterized by the appearance of HBsAg in serum. The HBV replication level is usually high, and large amounts of HBV particles are present in the graft. Historically, before the advent of antivirals, HBV reinfection had a major impact on graft and patient survival because almost all patients with HBV reinfection developed graft disease [3, 4]. This severe evolution was probably related to the high amount of HBsAg, HBeAg, and hepatitis B core antigen present in the nuclei and the cytoplasm of the hepatocytes, suggesting that liver injury is caused by a

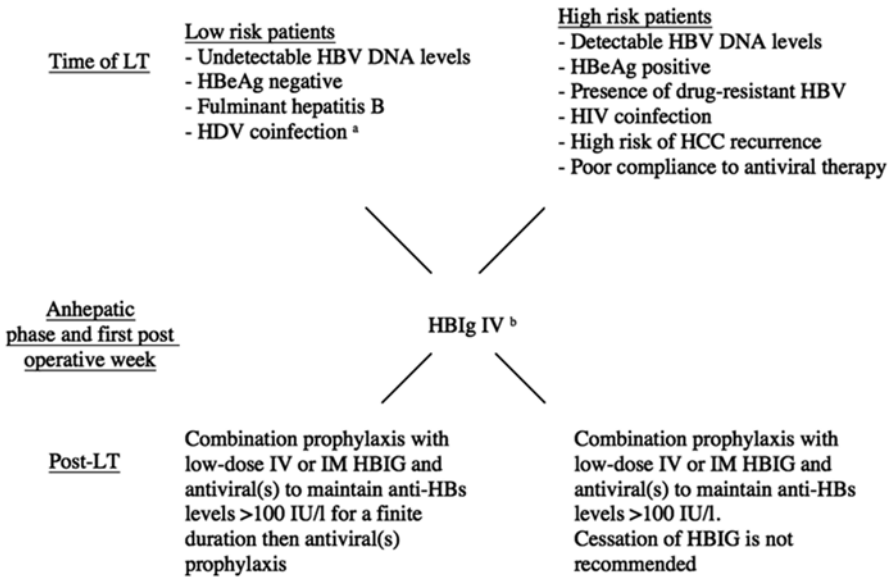

Fig. 2.1 Prophylaxis for prevention of HBV graft recurrence following LT. Proposal for guideline. [a]Shortening the duration of HBIG administration in HDV/HBV patients could have detrimental consequences as reinfection in the case of HDV latency may lead to chronic hepatitis B and delta. [b]High-dose IV HBIG during the first postoperative week could be associated with a lower frequency of HBV recurrence. *HCC* hepatocellular carcinoma, *LT* liver transplantation, *HBIG* hepatitis B immune globulin

direct cytopathic effect of the virus. A particular form of virus recurrence was called fibrosing cholestatic hepatitis. Antiviral treatments have dramatically improved the prognosis of HBV graft reinfection. HBV infection after LT is usually the result of failed prophylaxis, either due to noncompliance or the development of drug-resistant HBV infection. The availability of safe and effective antivirals allows the majority of patients with recurrent infection to survive without graft loss from recurrent disease. Selection of therapy for HBV infection depends on treatments previously received by patients (i.e., no therapy, HBIG alone, antiviral alone, or HBIG and antiviral in combination). The optimal management strategy to ensure long-term HBV suppression is predicted to be the use of an antiviral with high genetic barrier to the development of resistance such as ETV or TDV or the use of combinations of antivirals. A close monitoring for initial response and for subsequent virological breakthrough is essential to prevent disease progression and flares of hepatitis. Patients with a suboptimal response warrant a change of therapy. In patients who are naïve to treatment or with S gene mutants, ETV or TDV are drug of choice as single agents but combination therapy could be considered. In those patients with LAM-resistant HBV, TDV in combination with LAM has been shown to be effective [45, 94]. In those patients with ADV-resistant HBV, ETV in combination with ADV has been shown to be effective [95]. In summary, long-term

suppression of HBV replication is essential to prevent disease progression, prior drug exposures and achieved resistances mutations is important in guiding drug choices and combination antiviral therapy is recommended over sequential antiviral use to minimize the risk of treatment failure.

2.6 Conclusion

During the past two decades, major advances have been made in the management of HBV transplant candidates. The advent of long-term HBIG administration and efficient antiviral drugs used pre- and post-transplant, as a prophylaxis of HBV recurrence were major breakthroughs in the management of patients. The combination of long-term antiviral and low-dose HBIG can effectively prevent HBV recurrence in >90 % of transplant recipients. Some form of HBV prophylaxis needs to be continued indefinitely post-transplant. However, in patients with low HBV DNA levels pre-transplantation, discontinuation of HBIg, with continued long-term nucleos(t)ide analog(s) treatment is possible.

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Chapter 3
HCV Recurrence: Predictors and Outcomes After Liver Transplantation

Angel Rubín and Marina Berenguer

3.1 Introduction

Despite the fact that very effective antiviral treatments against HCV are going to certainly change the panorama of hepatitis C both in the general population but especially in the setting of LT, there will remain patients at need of transplantation in coming years. In a meta-analysis of 129 studies assessing long-term outcome of 34,563 interferon (IFN)-treated patients, sustained viral response (SVR) was associated with a significant decrease in the need for LT as soon as 5 years following therapy, so that the risk was reduced from 7.3 to 0.2 % in the cirrhotic patient and from 2.2 to 0 % in the general HCV-infected population [1]. Indeed, HCV eradication modifies the natural history of hepatitis C so that the deposition of fibrosis is halted with regression of fibrosis even in cases of recently developed cirrhosis. SVR rates with the newest antiviral combinations are excellent but not universal; indeed, in certain difficult-to-treat subgroups, such as advanced cirrhotic prior null responder patients, SVR rates are only achieved by 70–80 %. Furthermore, while many studies have demonstrated that successful antiviral therapy is associated with a significant decrease of the risk of hepatocellular carcinoma (HCC), the risk is not fully eliminated with a cumulative probability of about 8 % at 5 years, increasing to 12 % in those aged greater than 60 years [2, 3]. In summary, although HCV can be eradicated in the vast majority of treated patients, HCV-related complications will remain

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an indication for liver transplantation in the next years. Most patients will reach surgery being HCV RNA negative, but there will remain some undergoing transplantation with positive viremia, either because they have failed new antivirals or alternatively because there hasn't been time to treat them while in the waiting list.

Reinfection occurs invariably in those who are viremic at transplantation resulting in recurring disease with uncertain outcome. Several factors, in particular, donor age, have repeatedly proven their influence on the natural history of HCV post-transplantation. Understanding which factors determine disease and patient outcomes, which modifications can be implemented to improve results, the feasibility of use and diagnostic reliability of available tools for monitoring disease evolution, and the place of retransplantation are still essential aspects in the setting of limited access to new antiviral drugs as well as for those failing new antiviral regimes.

3.2 Natural History of HCV Recurrence After Liver Transplantation

Liver allograft reinfection is universal, occurring at reperfusion [4]. In the anhepatic phase, HCV RNA levels drop and become undetectable; in just a few hours, they quickly rise, peaking by the fourth postoperative month. At 1 year, HCV RNA levels are 1–2 log higher than before LT. The diagnosis of recurrent disease requires histologic confirmation. Most lesions develop after 3–6 months, and are similar to those viewed in the non-transplanted graft. Clinical presentation, severity of recurrent disease, and outcome are extremely heterogeneous [5]. The commonest recurrence pattern is the gradual progression to chronic hepatitis and cirrhosis as observed in immune competent patients but occurring at greater levels of viremia and faster fibrosis progression. In this setting, progression to cirrhosis takes place after only a median of 9–12 years from LT [5, 6]. Fibrosis can progress linearly [6], present a delayed onset of rapid progression or a rapid and exponential increase during the first 3 years followed by a slower progression in the long-term [7, 8]. A recent non-Markov analysis created using 901 fibrosis measurements in 401 patients has demonstrated a decreasing risk of progression as the duration in a given stage increases [9]. A rarer, but very severe form of recurrence (<10 %) termed fibrosing cholestatic hepatitis (FCH), is thought to be mediated by a direct cytopathic mechanism in the context of very high viral burdens and limited immune response [5]. It is characterized by a lack of lobular inflammation and lymphoid aggregates in addition to severe centrizonal hepatocyte ballooning, and intense cholestasis. In 50 % of patients, graft failure occurs within a few months of onset. In 2003, during a consensus conference, diagnostic criteria were proposed [10]. However, a systematic reappraisal recently proved that just 3 out of 12 studies, published after 2003, actually used this definition, preventing an accurate analysis of this entity [11]. Recently Verna et al. reviewed 179 post-LT biopsies that were initially categorized as cholestatic hepatitis C and refined the classification of FCH so as to only include patients

meeting a minimum of three out of four pathologic criteria: (1) ductular reaction; (2) cholestasis; (3) hepatocyte ballooning with lobular disarray; and (4) periportal sinusoidal/pericellular fibrosis [12]. Finally, in a small number of infected recipients, progression is not witnessed, at least not for 10 years, and liver damage remains mild or absent, despite high viral burden.

Regardless of the pattern of recurrence, cirrhosis is present in around 25 % of recipients (range: 8–44 %) after 5–10 years from LT and this percentage typically rises with increased follow-up [6]. Once cirrhosis is established, survival drops to 41 and 10 % at 1 and 3 years, respectively. The first episode of decompensation normally occurs after a median of 8 months since the diagnosis of cirrhosis. The risk of decompensation is indeed very high in the transplant setting with 42 and 63 % cumulative rates at 1 and 3 years. A short duration (<1 year) from LT to cirrhosis, a Child-Pugh score >*A*, low albumin levels (<3.5 mg/dL), and relatively high meld score at time of cirrhosis diagnosis predict the risk of decompensation and death [13]. Graft failure secondary to recurrent HCV is presently the most common cause of death, graft failure, and need of retransplantation (RT) in HCV-infected recipients [14, 15]. Survival rates are significantly impaired in comparison to other indications with an overall 10 % difference at 10 years reported in recent large series. Thus, in a recent study based on the OPTN/UNOS registry, the 3-year survival was 78 % among 7459 anti-HCV-positive recipients compared with 82 % in 20,734 anti-HCV-negative patients ($P<0.0001$) (www.unos.org). Similar data was reported by the Spanish National Registry of adult elective transplant patients transplanted between 1984 and 2013, where the 15-year survival rate of 5968 non-HCV patients was 49 % but only 35 % of the 4097 anti-HCV-positive patients (www.ont.es).

3.3 Post-transplant Monitoring

The frequent incidence of abnormal histological findings, in particular, the gradual rise in those designated as severe, supports the need for frequent disease monitoring. Progression to advanced fibrosis may happen in the presence of normal liver function tests. Furthermore, disease severity is helpful in predicting outcome and, hence, providing a basis for early antiviral therapy. Several studies have shown that necroinflammatory activity and fibrosis stage in early biopsies are excellent predictive factors of subsequent progression to cirrhosis at 5 years [16–18]. Moreover, significant disease progression rarely occurs in those without fibrosis at 12 months [6, 16, 18]. Lastly, improved SVR has been demonstrated if treatment with IFN-based therapies and possibly also IFN-free regimes are begun before reaching the stage of advanced cirrhosis [19–21]. The gold standard for monitoring disease progression has traditionally been the liver biopsy. The inclusion of the hepatic venous pressure gradient measurement (HVPG) may lead to increased diagnostic accuracy, especially identifying those at increased risk of hepatic decompensation. One study found that HVPG ≥ 6 mmHg at 1 year post-LT identified 12 (80 %) out of 15 patients with severe recurrence while just 9 (60 %) of these had significant

fibrosis (F ≥ 2) in the first year biopsy [22]. Noninvasive assessment of liver fibrosis with elastography in addition to serum and molecular fibrosis markers have been appraised in a small number of transplant studies. Elastography (Fibroscan®) has proven to have the most satisfactory diagnostic performance, especially if repeated at different time points. In one study, elastography was used to differentiate slow and rapid "fibrosers" at an early stage. Median liver stiffness measurements (in kilopascal) at months 6, 9, and 12 were significantly higher in rapid fibrosers (9.9, 9.5, 12.1) compared to slow fibrosers (6.9, 7.5, 6.6) ($P < 0.01$ all time points) [23]. Noninvasive tools such as elastography are extremely useful in the transplant setting but should be used as complement tools to liver biopsy. Recently, Burroughs et al. developed a quantitative method of measuring fibrous tissue using digital image analysis of the proportion of collagen in liver tissue, namely collagen proportionate area (CPA) [24, 25]. This method has been validated both against HVPG and clinical outcomes, including recurrent HCV after LT. A study showed that CPA predicts decompensation in patients with recurrent hepatitis C virus (HCV) cirrhosis: in 62 transplanted patients with Ishak stages 5 and 6, CPA correlated with HVPG, but had a wider range of values, suggesting a greater sensitivity for distinguishing "early" from "late" severe fibrosis/cirrhosis. CPA was a unique, independent predictor of HVPG ≥ 10 mmHg, and hence can be used to subclassify cirrhosis and for prognostic stratification [26].

3.4 Risk Factors for Severe Post-transplant HCV Recurrence (Table 3.1)

Numerous pre- and post-transplant variables have been linked to progressive disease and increased mortality. There is robust evidence pointing to a negative effect of old donor age, over-immunosuppression as a result of rejection treatment, post-transplant diabetes or metabolic syndrome and HIV coinfection [5, 10, 27–31].

Old *donor age* is independently linked to greater disease severity and progression in addition to poorer graft and patient survival [10, 28, 32], both when using deceased and living donors and when using anti-HCV-positive donors. In the Spanish Liver Transplant Registry, the 5-year survival was only 41 and 52 % for HCV patients using grafts from donors older than 74 or 50 to 74 compared to 63 % in those transplanted with grafts from younger donors (www.ont.es). The effect is nonlinear, with donor age greater than 65 years linked to the poorest results. In a retrospective analysis of more than 20,000 transplants performed between 1998 and 2000 in the USA, donor age >40 years (and particularly over 60 years) was significantly associated with high risk of graft failure [33]. More recent data has further suggested that the use of allografts from old donors is also a risk factor for the development of FCH. Applying the more rigorous diagnostic of FCH from Verna et al., donor age (OR = 1.37, 95 % CI: 1.02–1.84, $P = 0.04$) and previous history of acute cellular rejection (OR = 4.19, 95 % CI: 1.69–10.4, $P = 0.002$) were the most

Table 3.1 Factors associated with post-transplantation outcome

Factor	Effect on recurrent HCV	References
Donor		
Donor age	Worse evolution	[10, 12, 28, 32, 33]
Donor steatosis	Unclear	[28, 34]
Anti-HCV donors	No influence with grafts with little or no fibrosis and only minimal inflammation	[10, 27, 35, 36]
IL28B "CC" genotype	Unclear	[37, 38]
Virus		
Pre-LT HCV RNA levels	Unclear	[10, 27]
HCV genotype 1 or 4	Worse evolution	[5, 40–46]
Post-LT HCV RNA levels	Unclear, a peak viral load ≥ 107 IU/mL within 1 year post-LT could be a risk factor	[39]
Operative factors		
Prolonged ischemia times	Worse evolution (≥ 12 h of ischemia)	[27, 28]
Living donor vs. deceased	No differences	[47, 48]
Donation after cardiac death vs. brain death	No differences	[49–51]
Recipient		
IL28B non "CC" genotype	Better evolution	[37, 38]
Female sex	Worse evolution	[52–54]
Post-LT diabetes mellitus	Unclear, synergistic effect with donor age	[30]
Post-LT metabolic syndrome	Worse evolution	[55–57]
African american D/R mismatch	Worse evolution	[58, 59]
HIV coinfection	Worse evolution	[31, 60–62]
CMV infection	Unclear	[63–65]
Immunosuppression		
Over-Immunosuppression (triple-quadruple therapies at full doses)	Worse evolution	[67–69]
Steroid bolus	Worse evolution	[5, 27, 28, 81–83]
Monoclonal CD3-antibodies (OKT3)	Worse evolution	[5, 8, 27, 28, 69, 81, 98]
IL-2 receptor blockers	Unclear	[84, 94–96]
Cyclosporine vs. tacrolimus	No differences in graft-patient survival	[70–80]
Steroids on induction and maintenance	Unclear	[67, 84–86]
Mycophenolate mofetil	Unclear	[84, 87, 88]
Azathioprine	Unclear	[25, 69, 87, 89]
mTOR inhibitors	Unclear	[90–93]

reliable predictors of developing FCH on multivariate analysis. In summary, the transplantation of older allografts into HCV recipients results in worse outcomes due to recurrent HCV in the short as in the long-term [12], and hence the recommendation to avoid the allocation of "elderly donors" to HCV(+) recipients. Unfortunately, donor age has increased dramatically in recent years so that allocating only young donors to HCV(+) recipients remains a near impossible task in most centers. Reasons that explain the negative effect of increased donor age are incompletely understood. Telomere shortening, impaired proliferative response to insults, increased fibrogenesis, and reduced fibrinolysis, in conjunction with immunological changes, may contribute to the "lower quality" of advanced donor-aged grafts. It's likely that the increased use of elderly donors might explain the worse outcomes observed in some centers in recent years, as well as the discrepant results in terms of fibrosis progression post-transplantation between centers. Importantly, the donor age effect can be heightened by other cofactors such as diabetes, ischemic time, preservation injury, recipient age, or over-immunosuppression. Decreasing ischemic times, using donor-recipient models such as the D-MELD (donor age × MELD score) for organ allocation, promoting immunosuppressive protocols that avoid over-immunosuppression and also diabetes, should always be tried, but particularly when using old donors.

Donor liver steatosis has also been described as a risk factor for increased disease severity. The degree of steatosis that would define a specific risk is however still unclear [28, 34].

Anti-HCV(+) *donors* can be an additional source of organ donors in an era of organ scarcity. These grafts can be safely used if extracted from young donors <46 years of age when fibrosis is absent or minimal and only slight inflammation is present. In the era before new direct antiviral agents were available, these grafts could only be used in genotype 1 HCV recipients [10, 27, 35]. This restriction is likely to disappear with the advent of highly effective anti-HCV therapies [36].

While *IL28B polymorphism*, particularly that of the donor, was found to have a substantial impact on IFN responsiveness to post-transplant IFN-based therapy, the effect of both donor and recipient IL28B genotype on the natural history of recurrent hepatitis C is less evident [37, 38].

High *pre-transplantation levels of viremia* have been described in those with severe recurrent hepatitis C and high mortality [10, 27]. An association between *post-transplant levels of viremia* and long-term outcome has also been shown in some but not all studies. In one interesting retrospective analysis of 118 HCV LT recipients, a peak viral load $\geq 10^7$ IU/mL post-transplantation was found to be an independent predictor of reduced patient and graft survival and HCV-allograft failure. A peak viral load in the first year after transplant of $>10^8$, 10^7 to 10^8, and $<10^7$ IU/mL was associated with a mean survival of 11.8, 70.6, and 89.1 months, respectively ($P \leq 0.03$) [39]. In turn, the impact of HCV genotype on outcome is controversial [5, 40–46].

While early studies suggested that living donor LT was a risk factor for developing aggressive recurrent disease, more recent and larger studies have proven otherwise. In the large retrospective study of HCV-infected transplant recipients

from the 9-center Adult to Adult Living Donor Liver Transplantation Cohort Study, patient and graft survival as well as incidence of advanced fibrosis were compared between 195 living donor liver transplant (LDLT) recipients and 180 deceased donor liver transplant (DDLT) recipients, monitored for a median of 4.7 years. The 5-year cumulative risk of advanced fibrosis (Ishak stage ≥ 3) was 44 and 37 % in LDLT and DDLT patients ($p = 0.16$), respectively. The 5-year unadjusted patient and graft survival probabilities were 79 and 78 % in LDLT, and 77 and 75 % in DDLT ($p = 0.43$ and 0.32), with 27 and 20 % of LDLT and DDLT graft losses due to HCV ($p = 0.45$). Biliary strictures (HR = 2.25, $p = 0.0006$), creatinine at LT (HR = 1.74 for doubling of creatinine, $p = 0.0004$), and AST at LT (HR = 1.36 for doubling of AST, $p = 0.004$) were found to be independent predictors of graft loss, but LDLT was not (HR = 0.76, 95 % CI: 0.49–1.18, $p = 0.23$). Importantly, first analyses of these series demonstrated lower graft and patient survival among the first 20 LDLT cases at each center (LDLT ≤ 20) compared to later cases (LDLT ≥ 20; $P = 0.002$ and $P = 0.002$, respectively) and DDLT recipients ($P < 0.001$ and $P = 0.008$, respectively) [47]. Therefore a learning curve is necessary to avoid worst results in LDLT recipients with HCV [48].

Given the expansion in the use of organs retrieved from cardiac death donors (DCD), there has been a significant interest in assessing whether HCV is more aggressive in that setting. While initial studies showed conflicting results, more recent data suggest that the severity of HCV disease over the first 3–5 years following LT is comparable to that seen following DDLT [49, 50]. In a recent meta-analysis the authors evaluated the clinical outcomes of DCD vs. DBD organs in HCV(+) patients ($n = 324$). The use of DCD livers was associated with a significantly higher risk of primary nonfunction but not with a significantly different patient or graft survival, rate of recurrence of severe HCV infection, retransplantation or liver disease-related death, and biliary complications [51].

Whether outcome differs based on gender is a matter of debate. An Italian study highlighted that women were at greater risk of developing severe recurrent HCV disease [52]. A recent multicenter study (CRUSH-C), involving 1264 patients (24 % women), reported similar findings. In their multivariate analysis, female sex was found to be an independent predictor of advanced disease (HR = 1.31, 95 % CI: 1.02–1.70, $P = 0.04$), death (HR = 1.30, 95 % CI: 1.01–1.67, $P = 0.04$), and graft loss (HR = 1.31; 95 % CI: 1.02–1.67; $p = 0.04$) [53]. Interestingly, a large retrospective study of the UNOS/OPTN cohort, including 18,159 HCV(−) LT recipients and 9,403 HCV(+) recipients, found an increased risk of graft loss only among HCV(+) recipients transplanted with organs from male donors with an HR of 1.23 (1.10–1,38). In contrast, this increased gender mismatch-related risk was not observed in the HCV(−) recipients [54].

Metabolic syndrome (MS) post-LT is associated with worse HCV outcomes after LT, similar to that observed in the non-transplant setting, and could represent a significant modifiable risk factor [55–57].

Afro-American HCV+ recipients of a racially mismatched allograft are at risk of graft failure and mortality. Two recently published investigations added further weight to the survival data by establishing that racial mismatch was a significant independent predictor of advanced fibrosis [58, 59].

3.4.1 HIV Coinfection

Recent prospective data from a consortium of US human immunodeficiency virus (HIV)/HCV researchers has strongly highlighted that HIV coinfection is a significant risk factor for graft failure in HCV(+) recipients. Old donor age, combined kidney-liver transplantation, anti-HCV(+) donor, and BMI <21 were linked to poor outcome [60]. Other series that have also attempted to identify factors leading to poor outcome in the coinfected population have found similar results. Other factors linked to outcome in these series have been MELD at LT, HCV genotype 1, centers with less than 1 coinfected LT per year, treated rejection, and recipient female [31, 61]. In summary, LT in HIV-HCV coinfected patients is characterized when compared to HCV mono-infected ones as follows: (a) younger recipient age; (b) greater disease severity with higher incidence of cholestatic forms; (c) very poor results using IFN-based treatments; and (d) low survival rates. New antiviral agents against HCV, given pre- or post-transplantation will likely result in significantly better outcome in this population [62].

Cytomegalovirus (CMV) has been varyingly linked to recurrent HCV disease severity following LT. Herpesviruses, and in particular CMV, have been shown to have immunomodulatory effects, that could promote HCV replication and thereby result in accelerated HCV disease progression [63]. Viral reactivation may merely be a marker of a more profound immunosuppressed state promoting both HCV and herpesvirus replication. Alternatively, more specific interactions as well as cross-reactive immunologic responses may exist [64, 65].

3.5 Immunosuppression

The adequate use of immunosuppressive agents is especially important to avoid aggressive recurrence. The results of an international survey of 81 transplant centers published in 2008 [66] revealed that a third had specific immunosuppression protocols for positive HCV recipients. Less than 10 % used protocols without steroids and 98 % of those using steroid withdrew them within the first year (over half in the first 3 months). The duration of steroid treatment was significantly shorter in the USA than in the rest of the world (10.8 vs. 29.4 weeks, $p<0.001$). Overall, it is accepted that, in these patients, excessive immunosuppression should be avoided, particularly sudden changes in the net immune status. A prospective study confirmed the benefits of this strategy [67]. Indeed, the rate of severe recurrence dropped from 54 to 33 % after establishing an immunosuppression protocol where steroid boluses, triple/quadruple therapies at full doses and rapid steroid withdrawal were avoided. While there is a certainty on the effect of immunosuppression, the role played by each one of the immunosuppressive agents on HCV replication and the course of recurrent HCV disease is still controversial [68, 69].

3.5.1 Calcineurin Inhibitors

There is ongoing debate about whether there is any advantage of using CsA as opposed to Tac with respect to the evolution of graft hepatitis C. Studies based on in vitro models (replicon and cultivated hepatocytes) have demonstrated that CsA but not Tac inhibits HCV replication. However, most retrospective and prospective studies were not able to confirm these results in clinical practice [70–77] (Table 3.2). Furthermore, discrepant results were also reported in several systematic reviews [77–80] so that no firm recommendations regarding a specific Calcineurin Inhibitors (CNI) can be made.

3.5.2 Steroids

There is consensus that the use of bolus steroids for the treatment of cellular rejection is detrimental for HCV(+) recipient [5, 27, 28, 81–83] and is associated with a marked increase in viral replication, aggressive recurrence, and early mortality [5, 27–29].

With regards to maintenance steroids, the data are less robust [84, 85]. If steroids are used, some data favor a gradual steroid taper over time [67, 84, 86]. In conclusion, the use of bolus steroids in mild-moderate rejections should be avoided. Steroid-free regimens are safe. If steroids are used, an abrupt discontinuation should be avoided.

3.5.3 Mycophenolate Mofetil

Although in one study [87] Mycophenolate Mofetil (MMF) was associated with increased viremia, two large studies have failed to find differences in outcome in those randomized to MMF compared to those treated without [84, 88].

3.5.4 Azathioprine

A systematic review as well as a recent prospective study suggests that Azathioprine (AZA) might be beneficial for HCV recipients by reducing the rate of aggressive recurrence [25, 69, 87, 89].

Table 3.2 Studies assessing the association between calcineurin inhibitors and HCV recurrence[a]

Authors/year	Design	HCV(+) recipients (n)	Outcome	Results
Samonakis et al. 2005 [70]	Retrospective	Tac (96)	Graft/patient survival	No differences
		CyA (92)	Progression to HCV fibrosis	No differences
O'Leary et al. 2011 [71]	Retrospective	Tac (246)	Graft/patient survival at 5 years	75 % Tac vs. 67 % CsA (p 0.002)
		CyA (246)	Progression to HCV fibrosis	No differences
Irish et al. 2011 [72]	Retrospective	8.809	Graft/patient survival at 1 years	CyA vs. Tac
		(CyA, $n=717$/Tac, $n=8.092$)	Graft/patient survival at 3 years	– HR of death = 1.3 (95 % CI 1.07–1.58)
				– HR of graft failure = 1.26 (95 % CI 1.06–1.5)
Martin et al. 2004 [73]	Prospective	Tac (38)	Histological HCV recurrence	No differences
		CyA (41)	Change in viral load	Higher viremia in CsA ($p=0.032$)
			Graft/patient survival	No differences
Levy G et al. 2006 [74]	Prospective	Tac (85)	Mortality or graft loss at 1 year	16 % Tac (14/85) vs. 6 % CyA (5/88) ($p<0.03$).
	(LIS2T)	CyA (88)	Mild fibrosis	(18/19 RIP < 6 months post LT)
			Change in viral load	No differences
			Time to recurrence	No differences
				70 ± 40 days Tac vs. 100 ± 50 days CyA ($p<0.05$)
Berenguer et al. 2006 [75]	Prospective	Tac (46)	Severe recurrence Death	27 % CyA vs. 32 % Tac ($p=$ ns)
		CyA (44)		No differences
Berenguer et al. 2010 [76]	Prospective	Tac (117)	Severe recurrence	27 % CyA vs. 26 % Tac ($p=$ ns)
		CyA (136)	Patient survival at 1 year	83 % CyA vs. 78 % Tac ($p=$ ns)
			Patient survival at 7 years	67 % CyA vs. 64 % Tac ($p=$ ns)
Berenguer 2007 [77]	Systematic review	Tac (183)	Fibrosing cholestatic hepatitis	No differences
		CyA (183)	Graft/patient survival	No differences

CyA cyclosporine, *Tac* tacrolimus, *RR* relative risk, *ns* not significant

[a]Adapted from Rubin et al. Gastroenterol Hepatol. 2013;36(1):48–57

3.5.5 mTor Inhibitors

Results are also controversial. Patsenker et al. analyzed the likelihood of several immunosuppressive agents to halt the progression of experimental hepatic fibrosis, noting that treatment with inhibitor of mTor was associated with a significant reduced fibrosis progression compared to that observed with CNI therapy [90].

SRTR data from 26,414 liver transplants (12,589 for HCV) were analyzed to determine risk factors for patient and graft survival. 6.5 % (795/12,269) of HCV+ transplant recipients were prescribed sirolimus at hospital discharge and 3.5 % of these were still taking the drug 1 year following transplant. On multivariate analysis, sirolimus was associated with higher 3-year mortality in HCV+ recipients (HR = 1.26, 95 % CI: 1.08–1.48, $P = 0.0044$), but not in the non-HCV patients. In a propensity analysis to compensate for confounding baseline factors (renal function, MELD score, HCC rate) sirolimus still proved to be an independent risk factor for higher 3-year mortality (HR = 1.29, 95 % CI: 1.08–1.55, $P = 0.0053$) [91]. More extensive studies have been recently performed with everolimus. Although none showed a detrimental effect of this drug on HCV recurrence, they were mostly designed to determine the efficacy, safety, and renal protective benefits and not the impact on HCV recurrence [92, 93]. In summary, no definitive conclusions can be made regarding the effect of mTor inhibitors on the natural course of HCV recurrence.

3.5.6 IL-2 Recipient Blockers (Basiliximab, Daclizumab)

The information on induction through monoclonal anti-interleukin 2 (IL-2) antibodies are equally contradictory. While retrospective data suggest a detrimental effect [94], 3 controlled randomized studies [84, 95, 96] and a large retrospective study [97] failed to demonstrate an effect on survival, and in HCV recurrence.

3.5.7 Antilymphocyte Agents

The use of monoclonal antibodies OKT3 is associated with increased viremia [98], severe recurrence, and graft loss [5, 8, 27, 28, 81]. As such, antilymphocyte agents that are used for treating rejection should be used with caution [69]. In conclusion, except for rejection treatment using OKT3 or bolus steroids, no immunosuppressive agent seems to determine by itself the course of recurrent hepatitis C. As such, no firm recommendation can be given regarding the optimal immunosuppressive regime in HCV(+) recipients. The only recommendation would be to avoid sudden changes in immunosuppression and avoid over-immunosuppression.

3.6 Retransplantation (RT) for HVC(+) Recipients

RT in HCV patients continues to be controversial. Previously, HCV infection was thought to be an independent predictor of mortality post-RT, most likely as a result of a late indication of RT. Certainly, increased scrutiny during donor and recipient selection for RT using prognostic scores as screening tools have demonstrated that outcomes can resemble those achieved by non-HCV RT patients. These mathematical models can be used in clinical practice to identify the most adequate RT candidates, and particularly to define the best timing for RT [99–104] (Table 3.3). Independent predictors of RT mortality in HCV patients include higher recipient age, hyperbilirubinemia, renal dysfunction, MELD >25, RT within 1 year of the first transplant, extended warm ischemia time, and donor age ≥60 years [10, 15, 27].

Overall though [105, 106], RT is associated with poorer graft and patient survival in comparison to primary transplantations (approximately 20 % reduction in survival) [107, 108]. With primary LT survival benefit is obtained with MELD scores greater than 15. For RT though, higher cutoffs (MELD 21) are needed to achieve a benefit from the RT procedure, particularly in the HCV population where a MELD of 27 is required to obtain a transplant benefit [109]. The introduction of highly active antiviral drugs is likely to change this panorama and equate HCV-positive patients to HCV-negative ones.

To conclude, the decision to indicate RT in patients with HCV recurrence is likely influenced by a number of conditions, some depending on the patient characteristics and disease severity, and others on transplant center policies, experience, and geographic donor organ availability. New antiviral treatments using direct antiviral agents will significantly reduce the need for RT. If, in patients in whom HCV has been successfully eradicated, RT is still needed, general and not specific HCV donor-recipients models should be applied to achieve the best outcomes [110].

3.7 Conclusions

HCV-related liver diseases are the primary indication for LT in most centers. While highly effective antiviral therapies are likely to change this panorama in the future, there will still remain patients infected with HCV requiring LT, particularly those failing consecutive antiviral treatments or those with HCC. If viremia is present at time of transplantation, reinfection is the rule and recurrent disease is among the most pertinent problems that face transplant physicians. In the absence of effective post-transplant therapy, the outcome of LT is impaired in HCV-infected patients due to the aggressive course of recurrent hepatitis C. The natural history of recurrent hepatitis C though is determined by the presence of donor, host, surgical, immunosuppression, and environmental factors. A number of these factors (in particular the

Table 3.3 Predictive models used in Re-LT in HCV graft cirrhosis

Predictive model	Model	Cutoffs associated with different survival rates	Survival in low risk-groups	Survival in high risks
Rosen model (1999) [99]	0.024 × recipient age (years) + (0.112 $\sqrt{}$bilirubin) (mg/dL) + (0.23 × $\log_e$ creatinine (mg/dL)) − (0.974 × cause of graft failure (1 for PNF, 0 for non PNF)) + UNOS status (0.261 for status 1, 0.463 for status 2, and 1.07 for status 3)	<0.75: low risk	$R < 0.75$	$R \geq 1.47$
		0.75–1.47: medium risk	5-year survival: >60 %	5-year survival:<40 %
		>1.47: high risk		
Rosen model (2003) [100]	$R = 10 \times$ [(0.0236(recipient age) + 0.125 $\sqrt{}$bilirubin + 0.483($\log_e$ creatinine)) − 0.234(RI)]. [0 for 15–60 and 1 for >60 days]	<16: low risk	1 year survival: 75 %	1 year survival: 42 %
		16–20.49: medium risk		
		>20.5: high risk		
MELD score [101]	9.57 × $\log_e$ creatinine (mg/dL) + (3.78 × $\log_e$ bilirubine (mg/dL) + 1.120 × $\log_e$ INR) + 6.43	<18: low risk	<18: 5 year survival >70 %	>25: 5 year survival <40 %
		>25: high risk		
		>30: very high risk		
RT-DRI [102]	exp[(0.154 if 40 ≤ age < 50) + (0.274 if 50 ≤ age < 60) + (0.424 if 60 ≤ age < 70) + 0.501 if 70 ≤ age] + (0.079 if COD = anoxia) + (0.145 if COD = CVA) + (0.184 if COD = other) + (0.176 if race = African American) + (0.126 if race = other) + (0.411 if DCD) + (0.422 if partial/spli) + (0.066((170-height)/10)) + (0.105 if regional share) + (0.244 if national share) + (0.010 × cold time) + (0.119 if graft failure: biliary) + (0.094 if graft failure: recurrent disease) + (0.063 if graft failure: rejection) + (0.187 if graft failure: vascular thrombosis) + (0.017 if graft failure: all others)	<1.30: low risk	Overall survival: 93 %	Overall survival: 53 %
		1.30–2.59: medium risk		
		>2.5: high risk		

(continued)

Table 3.2 (continued)

Predictive model	Model	Cutoffs associated with different survival rates	Survival in low risk-groups	Survival in high risks
Markman model [103]	$R = (0.726 \times \text{cold ischemia} + 0.561 \times \text{ventilator status} + 0.0292 \times \text{bilirubin} + 0.202 \times \text{creatinine} + 0.526 \times \text{age})$	Based on number of risk factors	Based on number of RF	if $R > 2.3$: <40 %
	[Cold ischemia = 1 if >12 and 0 if < 12, ventilator status = 1 if ventilation is required and 0 if not, age = 1 if >8 and 0 if <18]	0–2: low risk	1 RF: 83 %	Based on number of RF
		3–5: high risk	2 RF: 67–72 %	3 RF: 43–53 %
				4 RF: 20–27 %
				5 RF: 6 %
Andres model [104]	$0.23 \times \text{DnAge} + 4.86 \times \log \text{Creat} - 2.45 \times \log \text{Int} + 2.69 \times \text{INR} + 0.10 \times \text{RecAge} - 3.27 \times \text{Alb} + 40$	<30: low risk	<30	>40
		30–40: medium risk	3 year survival 71 %	3 year survival 37 %
		>40: high risk		

DRI donor risk index, *COD* cause of death, *CVA* cerebrovascular accident, *RI* retransplant interval, *RF* risk factor, *DnAge* donor age, *RecAge* recipient age, *Alb* albumin

use of extended donor criteria) are growing in frequency, likely accounting for low long-term transplant improvement over the last 20 years in this indication. Antiviral treatment remains the unique convincing factor that has demonstrated to modify the natural history of recurrent HCV.

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Chapter 4
Treatment of Recurrent Hepatitis C

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Recurrence of HCV infection is universal in all patients who are HCV RNA PCR positive at the time of transplantation, and cirrhosis from recurrent HCV occurs in about 30 % of recipients within 5 years after transplantation [1–3]. The early recognition and treatment of recipients with progressive, recurrent HCV after liver transplant (LT) is the most important step in improving the clinical outcomes of these patients. In the past few years, there has been tremendous progress in the treatment of hepatitis C, including the introduction of direct acting antiviral (DAA) drugs, in the non-transplant population. However, there are only limited data with DAA in liver transplant recipients with HCV. In this chapter, we will examine the historical data and emerging treatment outcomes of liver transplant recipients with HCV.

There are two approaches for the management of hepatitis Cin liver transplant recipients. First approach is to prevent the recurrence by treating potential recipients before liver transplantation. This strategy has many limitations since most of these patients, excluding some with liver cancer, have advanced liver failure or renal impairment making it difficult to treat them with either interferon or DAA-based regimens. The second approach is to treat them after liver transplantation, and this could be done soon after LT before the histological evidence of recurrent hepatitis (also known as preemptive strategy) or after the development of significant inflammation or fibrosis on liver biopsy.

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4.1 Antiviral Therapy Prior to Liver Transplantation

Presence of HCV RNA prior to LT will result in universal infection and inflammation of the graft within hours or days after LT [4]. In contrast, it has been shown that sustained viral response (SVR) with interferon or DAA-based regimen prior to LT is associated with lack of HCV recurrence after LT [5]. The optimal duration of undetectable HCV-RNA with DAA prior to LT is unknown, but it has been shown that 4 weeks of undetectable HCV-RNA, by a sensitive assay, prior to LT is associated with very low probability of recurrence after LT. Although the primary objective of treatment in patients awaiting LT is to prevent disease recurrence, it is also possible that successful treatment may stabilize the liver disease and delay or avoid LT in those who achieve SVR.

In addition to curative options, other modalities to reduce infection of the graft have been attempted with minimal long-term benefits. Anti-HCV antibodies to neutralize HCV viremia prior to transplant have been studied, based on the success of anti-hepatitis B immunoglobulin in those with hepatitis B. One study had reported the use of human monoclonal antibodies against the HCV E2 glycoprotein in patients undergoing LT. Treatment with this antibody using a regimen of pre- and post-LT dosing significantly delayed time to viral rebound compared with placebo treatment [6]. However, the experimental treatment with antibody did not prevent HCV recurrence.

4.1.1 Interferon-Based Regimen

To date, a total of 12 randomized studies, in 500 patients awaiting LT, have been published using various antiviral regimens including monotherapy with interferon, Peg-interferon (Peg IFN), or combination therapy with Peg IFN + ribavirin (RBV) (Table 4.1). These studies did not show a significant difference in 90-day mortality between the treatment regimens and control arms [7]. In the above studies, a short course prophylactic treatment with pegylated (Peg) and RBV had shown moderate benefit in preventing HCV recurrence after LT in patients with genotype 2 and 3 patients [8]. However, majority of patients in those studies had genotype 1, and in those patients, a combination treatment with interferon and RBV prevented HCV recurrence in only 20–28 % of patients, and moreover, the treatment was associated with significant and often life-threatening adverse events [9–12]. Interferon-based treatments were poorly tolerated mostly due to severe hematologic toxicity (anemia, neutropenia, and thrombocytopenia) and life-threatening infections, and a third of patients discontinued interferon-based treatment because of these adverse events [12–14]. In one dose accelerating regimen (starting with a smaller than usual dose and titrating the dose up) containing interferon and RBV, lower adverse events and a higher SVR, compared to the conventional regimen, was found in non-genotype 1 patients (SVR 50 %), but only 13 % of genotype 1 patients achieved SVR [5].

Table 4.1 Pre-transplant antiviral therapy to prevent HCV recurrence after liver transplantation

First author	Total *n*; % of male	% of Genotype 1	Treatment regimen	Virologic response	Adverse events
Forns 2003 [9]	30, 83	83	Interferon alfa-2b + ribavirin for 12 weeks	9 Patients (30 %) were negative for HCV RNA at the time of transplantation; of these, 20 % remained negative after transplantation	Hepatic encephalopathy (n = 3), ascites (n = 2), and variceal bleeding (n = 1), neutropenia (n = 18)
Crippin 2002 [10]	15, n/a	n/a	Interferon alfa-2b daily or interferon alfa-2b three times weekly or interferon alfa-2b daily + ribavirin	No patient had sustained response, 2 who underwent transplantation had recurrence of HCV, and the study was halted because of serious side effects	Thrombocytopenia was the most common adverse event. Two infectious complications occurred; one of these had a fatal outcome.
Everson 2005 [5]	124, 65	70	Low accelerating dose regimen of interferon alfa-2b or PEGIFN alfa-2b + ribavirin for 6 months for genotypes 2 and 3 or 12 months for genotypes 1, 4, and 6	46 % were HCV RNA–negative at ETR and 22 % achieved SVR. 12/15 patients (80 %) who were HCV RNA–negative pre-LT had no post-transplantation recurrence. All 32 patients who were HCV RNA–positive pre-LT recurred after transplantation 2 weeks after LT	Infection (n = 5), worsening ascites (n = 5), encephalopathy (n = 6), gastrointestinal bleeding (n = 2), diabetes mellitus, severe thrombocytopenia
Carrión 2009 [11]	51 Treatment and 51 controls, n/a	n/a	PEGIFN—alfa-2a and ribavirin	29 % had undetectable HCV-RNA at the time of transplantation and 20 % achieved SVR	Higher incidence of bacterial infections in treated patients vs. controls

(continued)

Table 4.1 (continued)

First author	Total *n*; % of male	% of Genotype 1	Treatment regimen	Virologic response	Adverse events
Everson 2013 [12], LADR-A2ALL trial	79, 75	56	Low accelerating dose regimen with PEGIFN alfa-2b and RBV	None of the 13 controls but 26/44 (59 %) treated patients achieved undetectable HCV RNA by the time of transplantation ($p<0.0001$). 11/44 (25 %) had undetectable HCV RNA at week 12 post-LT	Infections (12 %) and cytopenias (19 %) were more common in treated patients
Lin 2014 [8]	48, n/a	60	Peg-IFN—alfa-2a + RBV for 4 weeks	HCV RNA was undetectable at transplantation in 26/48 (54 %) patients. 13 /48 (26 %) patients remained free of HCV infection 6 months after transplant	Most patients experienced cytopenias during treatment, but no mortality was noted

HCV hepatitis C virus, *LT* liver transplantation, *IFN* interferon, *PEGIFN* pegylated interferon, *n/a* not available, *ETR* end of treatment response defined as undetectable HCV RNA at the end of treatment, *SVR* sustained virological response

This regimen also was also poorly tolerated and drug discontinuation rates were unacceptably high. Interferon and RBV in combination with first generation protease inhibitors, telaprevir (TVR) or boceprevir (BOC), was also associated with severe adverse events including severe infections, clinical decompensation, and sometimes death [15]. Based on the above studies, one could conclude that interferon-based regimens should not be used in patients with decompensated liver disease awaiting liver transplantation.

4.1.2 Interferon-Free Regimens (Combination of DAA)

Interferon-free DAA combination is currently being tested in patients awaiting liver transplantation. In an open label single arm study, 61 patients awaiting LT with HCV cirrhosis, but with CTP score 7 or less, were treated with sofosbuvir (SOF), an

NS5B nucleotide polymerase inhibitor, in combination with RBV [16]. Of the 43 patients who achieved pre-transplant viral levels of HCV RNA <25 IU/mL, 30 (70 %) were able to maintain a post-transplant virologic response at 12 weeks. Notably, recurrence of HCV was inversely related to the number of consecutive days of undetectable HCV RNA before transplantation. The main adverse reactions noted with this combination were fatigue, headache, and anemia due to RBV, but the drug discontinuation rates due to adverse events were low. In addition to treating patients before LT, there is anecdotal evidence of benefit by extending the therapy to immediate post-LT period if HCV RNA undetectability prior to LT is less than 30 days [17]. These anecdotal observations require further corroboration before such a strategy is recommended.

The cure rates in patients with well-compensated cirrhosis, whether treatment naïve or treatment experienced, with recently approved DAA regimens (Harvoni or Viekira Pak with or without RBV) is over 90 % with 12–24 weeks of treatment. Those with HCC and compensated HCV cirrhosis (Child A) could be treated with above regimens if there are no obvious contraindications. While SOF/ledipasvir (Harvoni) is contraindicated in people with renal failure, Viekira Pak could be used in the presence of renal failure, except those on dialysis. The side effect profile of these regimens is excellent with fatigue and headache being the most common side effects. When RBV is used, hemoglobin should be monitored closely especially in those with renal impairment. Use of these regimens in the pre-LT setting is preliminary in nature and requires further evaluation in larger studies. Moreover, the current studies comprised patients with compensated or mildly decompensated liver disease undergoing transplantation and studies involving patients with more advanced disease are currently in progress. The cure rates with DAA regimens in well-compensated cirrhosis (Child A) are shown in Table 4.2.

4.2 Antiviral Therapy Immediately After Liver Transplantation

Another approach to chronic HCV patients who undergo LT is to treat them with antiviral agents immediately after LT before histological evidence of inflammation or fibrosis is established (i.e., begin treatment within 4 weeks after LT; this is also known as preemptive strategy). The rationale for such treatment is that fibrosis is absent in the early period after LT, and therefore these patients are more likely to respond antiviral therapy. The experience with interferon-based regimens immediately after LT showed that interferon-based regimens are poorly tolerated in the immediate postoperative period, and it is not very practical to treat these patients in the immediate postoperative period with interferon-based regimes (Table 4.3) when they have many other issues related to the transplant surgery. There is only anecdotal experience with DAA regimens in this setting, but we are likely to see more studies in this area in the near future.

Table 4.2 Clinical trials with IFN-free regimens in patients with HCV cirrhosis

Therapeutic regimen	Treatment duration in weeks in specific arms	Predominant genotype	Prior treatment experience	% of cirrhosis in the study	Virological response in cirrhosis
LDV/SOF ± RBV (ion-1)	12, 24	1	Treatment naive	16	SVR12 97 and 100 % ± RBV in 12 and 24 wks
LDV/SOF ± RBV (ion-2)	12, 24	1	Treatment experienced	20	SVR12 82–86 % in the 12 wk arm (± RBV) and 100 % 24 wk arm
DCV + ASV (hallmark-dual)	24	1b	Treatment naïve, IFN intolerant, ineligible and nonresponders	30	SVR12—91 %,87 %, and 81 % in the naïve, nonresponders, and intolerant/ineligible, respectively
ABT-450/r + ombitasvir + dasabuvir + RBV (turquoise II)	12, 24	1	Treatment naïve and experienced	100	SVR12 92 and 96 % in 12 and 24 wks
SOF + RBV (fusion)	12,16	2, 3	IFN nonresponders	35 %—12 wk arm and 33 %—16 wk arm	SVR 12—60 and 78 % in G2, 19 and 61 % in G3 (12 and 16 wk, respectively)
SOF + RBV (valence)	12 G2 24 G3	2, 3	Treatment naïve and experienced	14 %—12 wk arm and 22 %—24 wk arm	SVR 12—100 and 88 % in G2, 92 and 60 % in G3 (12 and 16 wk, respectively)

SOF + RBV (positron)	12	2, 3	IFN intolerant	15	SVR 12—94 % in G2 and 21 %in G3
SOF + RBV (fission)	12	2, 3	Treatment naive	20	SVR 12—47 %
SOF + LDV ± RBV (Cohort B) (Lonestar)	12	1 (85 % G1a)	Nonresponder to protease inhibitor regimen	55	SVR 12—100 % and 95 % with and without ribavirin, respectively
SMV + SOF ± RBV (Cohort 2) (cosmos)	12, 24	1 (78 % G1a)	Naïve and null responders	25	SVR 12—91 % and 94 % in null responders and naïve, respectively
SOF + RBV or GS-0938 or GS-0938 + SOF (± RBV) (quantum)	12, 24	1–4	Treatment naive	9	SVR 12—50 % in the SOF + RBV arm, 24 wk

Wk weeks, *G* genotype, *SVR12* sustained virologic response 12 weeks after the end of treatment, *SVR24* sustained virologic response 24 weeks after the end of treatment, *SMV* simeprevir, *DCV* daclatasvir, *SOF* sofosbuvir, *LDV* ledipasvir, *ASV* asunaprevir, *ABT-267* ombitasvir, *ABT-333 dasabuvir*, *RBV* ribavirin

Table 4.3 Preemptive treatment with IFN-based antiviral therapy: prospective and randomized studies

First author	Total (*N*)	Predominant genotype	Antiviral therapy	Transplantation treatment interval	Virological response	Histological results	Adverse events
Singh [19]	24	1a	IFN vs. no treatment for 24 weeks	<2 weeks	0 in both groups	HCV recurrence: 50 % in the IFN group vs. 42 % in the control group, *P* = NS	IFN group: Leucopenia (17 %) Headache, asthenia (33 %)
Sheiner [20]	71	1a and 1b	IFI IFN vs. no treatment for 48 weeks	<2 weeks	ETR: IFN—17 % control—5 %; *P* = NS	No difference in severity of recurrence; incidence of early recurrence reduced in IFN group: 26 % vs. 54 % in control group (*P* = 0.017)	Thrombocytopenia (17 %) in IFN group
Shergill [21]	44	n/a	IFN or Peg-IFN vs. IFN + Ribavirin for 48 weeks	<6 weeks	SVR: IFN—5 % IFN + RIB—18 %; *P* = NS	n/a	IFN—cytopenias, headache; hemolytic anemia with ribavirin

Chalasani [18]	54	n/a	Peg-IFN vs. no treatment for 48 weeks	<3 weeks	SVR: IFN—8 %, no treatment—0; P = NS	HAI score and increase in fibrosis are lower in IFN group, however not statistically significant	IFN group: headache, pyrexia, thrombocytopenia, and anemia
Bzowej [22] (PHOENIX Study Group)	115	80 % genotype 1	Escalating-dose regimen of Peg-IFN alfa-2a + RBV for 48 weeks to prophylaxis patients upon enrollment and Observation patients received the same regimen only upon significant HCV recurrence	10–26 weeks	SVR—22.2 % in prophylaxis patients and 21.4 % in the observation arm (SVR rates—18.6 % and 33.3 % for HCV genotype 1 and non-type 1 prophylaxis patients, respectively)	Similar rates of histological HCV recurrence at 120 weeks in the prophylaxis arm (61.8 %) and the observation arm (65), P = 0.725	Anemia, fatigue, headache, and neutropenia were noted in 100 % of the prophylaxis patients and 97 % of all observation patients

N number of patients, *IFN* interferon, *Peg* pegylated, *Rib* ribavirin, *HCV* hepatitis C virus, *ETR* end of treatment response defined as undetectable HCV RNA at the end of treatment, *SVR* sustained virological response, *NS* not statistically significant, *n/a* not available

Treatment with standard interferon, as a part of preemptive strategy, has been largely unsuccessful in reducing recurrence of HCV [18–20]. Peg IFN and RBV combination regimen for preemptive therapy after LT has shown better efficacy than interferon monotherapy, but the SVR rates for genotypes 1, 2, and 3 were not encouraging. In one study, only 51 of 124 patients were eligible for preemptive therapy suggesting that this therapy is difficult to administer in the immediate post-operative period [21]. Additionally, 27 % of patients had serious adverse events, 85 % required dose reductions, and 37 % required discontinuation of treatment [20]. The large PHOENIX study [22] evaluated the preemptive strategy using Peg IFN/RBV and concluded that rates of histological recurrence, graft loss, and death were similar in the active and control groups. Although adding TVR/BOC to conventional dual therapy (interferon/RBV) improved SVR rates [23], there are only anecdotal case reports of using these combinations as a preemptive strategy, and moreover, the higher rates of serious adverse reactions make these combinations unsuitable for preemptive treatment. Other drugs such as SOF and simeprevir (SMV) have not been studied for this purpose. Based on the current evidence, the preemptive therapy using interferon-based regimen is currently not recommended.

4.3 Antiviral Therapy After Histological Recurrence

This approach is currently the most accepted method to treat patients transplanted for hepatitis C. The histological recurrence is established with a combination of invasive and noninvasive factors as discussed in the previous chapter. Most centers would currently recommend therapy only when there is established recurrence of progressive disease, but this strategy may change in the near future with the availability of safer DAA regimens. It is more than likely that most patients with HCV will be treated with these regimens, perhaps after 3–6 months post-LT, with an intention to cure HCV. Although interferon-based regimens are going to become obsolete, it will be discussed for historical perspective on this topic.

4.3.1 Peg IFN/Ribavirin

With combination of Peg IFN and RBV, SVR was achieved in approximately 20–48 % of patients with recurrent HCV as summarized in Table 4.4 [18, 24–29]. Higher viral load and increased prevalence of genotype 1 in the post-transplant setting was associated with a lower response rates when compared to non-LT patients. The major limitations with this regimen were dose reduction (75 %) and discontinuation of treatment (25 %) due to adverse events [30–32].

Table 4.4 Treatment of histological recurrent HCV with interferon-based regimens

First author	Total (*N*), % of genotype 1	Antiviral therapy regimen and duration	Discontinuation (*N*)	ETR	SVR	Adverse events
Gane [24]	30, 47	IFN vs. Ribavirin for 12 weeks	2 in ribavirin group	IFN group: 46 % Rib group: 17; *P* = NS	0	Anemia, leucopenia
Cotler [25]	12, 33	IFN vs. no treatment for 48 weeks	2 in IFN group	IFN group: 4 (50 %) Control group: 0	IFN: 1 (13 %) Control group: 0	Asthenia, depression
Chalasani [18]	67, 77	Peg-IFN vs. no treatment for 48 weeks	10 (30 %) in treated group vs. 6 (19 %) in control group	IFN group: 9 (27 %) Control group: 0	IFN group: 4 (12 %) Control group: 0	Flu like symptoms
Angelico [26]	42, 83	Peg-IFN vs. Peg-IFN + Ribavirin for 48 weeks	Withdrawals: monotherapy: 6/21 combination therapy: 7/21	Monotherapy: 76 combination therapy: 71	Monotherapy: 38 combination therapy: 33	Headache asthenia, thrombocytopenia, hemolytic anemia
Ghalib [27]	10, 80	IFN + Ribavirin for 24 weeks vs. 48 weeks	5	24 weeks group: 3/348 weeks group: 1/2	24 weeks group: 1/348 weeks group: 1/2	Flu like symptoms, mild fatigue
Samuel [28]	52, 83	IFN + Ribavirin vs. no treatment for 48 weeks	12/28 (43 %) in treated group 4 (17 %) in control group	Treated group: 32 % Control group: 0: *P* = 0.02	Treated group: 21 % Control group: 0 *P* = 0.04	Anemia psychiatric disorders 1 chronic rejection
Carrion [29]	81, 90	Peg-IFN + Ribavirin vs. no treatment for 48 weeks	Treatment interruptions 39 %, dose reductions 49/54	n/a	Treated group: 18 (33 %) Control group: 0	Anemia, asthenia, fever

N number of patients, *IFN* interferon, *Peg* pegylated, *Rib* ribavirin, *HCV* hepatitis C virus, *ETR* end of treatment response defined as undetectable HCV RNA at the end of treatment, *SVR* sustained virological response, *NS* not statistically significant, *n/a* not available

4.3.2 *Peg IFN/Ribavirin + First Generation Protease Inhibitors*

TVR and BOC are first generation NS3/4A protease inhibitors with potent activity against HCV replication. There have been few studies with triple therapy (Peg IFN/RBV + TVR or BOC) in post-LT patients with histological HCV recurrence (Table 4.5). The major disadvantage with TVR or BOC was the drug–drug interaction with commonly used immunosuppressive agents. Both TVR and BOC [33–37] are inhibitors of the enzyme cytochrome P450 3A which are also responsible for the metabolism of calcineurin inhibitors such as cyclosporine and tacrolimus, and hence these drugs will increase the blood concentrations of both cyclosporine and tacrolimus significantly. When TVR or BOC is used in transplant recipients, significant dose reductions and frequent drug level monitoring of immunosuppressive agents is required. Despite these limitations, there were many studies that had explored this regimen in liver transplant recipients (Table 4.5).

A US multicenter retrospective cohort study [34] of 81 patients with TVR/BOC-based triple therapy reported undetectable HCV RNA at 12 weeks (SVR12) after treatment completion in 63 % genotype 1 patients. In this study, most patients had advanced fibrosis (stage 3 or 4) and 43 % were prior null responders. The adverse events were significant, particularly anemia requiring blood transfusions in 57 % of patients. Other small series have reported varying response rates, but predominant findings of these studies were the frequent need for either erythropoietin or blood transfusions, and very high drug discontinuation rates because of side effects [35, 36].

Table 4.5 Data on first generation protease inhibitor-based triple therapy for HCV recurrence after liver transplantation

First author (ref)	Coilly [36]	Pungpapong [33]	Werner [35]	Burton [34]
Patients (*n*)	37	60	9	81
Regimen				
Boc/TVR (*n*/*n*)	18/19	25/35	0/9	8/73
SVR 12 (%)	50 (20 % in Tel group vs. 71 % in Boc group)	n/a	n/a	63
Adverse events and management of anemia				
RBV dosage reduction (%)	70	93	56	80
Blood transfusion (%)	35	53	67	57
Infections (%)	27	11.6	NA	27
Death (*n*)	3	2	0	7

SVR 12 sustained virological response 12 defined as undetectable HCV RNA level 12 weeks after treatment discontinuation, *n* number of patients, *Boc* Boceprevir, *TVR* Telaprevir; *RBV* ribavirin, *n/a* not available

Based on the available data, it is fair to conclude that the first generation protease inhibitors, in combination with interferon and RBV, are unlikely to be used in the future because of the high incidence rates of anemia and the serious drug–drug interactions with the commonly used immunosuppressive agents. Moreover, interferon-based treatments, in addition to the hematological toxicity, could be associated with posttreatment immunologic dysfunction (predominantly plasma cell hepatitis) and rarely hepatic decompensation in liver transplant recipients [38]. Interferon-free regimens may not be associated with these completions and are more likely to be better tolerated.

4.3.3 Sofosbuvir + Ribavirin

SOF is a potent HCV NS5B polymerase inhibitor with pan genotypic activity. It also has a high genetic barrier to resistance and has a favorable safety profile. In one study, Charlton et al. [39] evaluated the efficacy and safety of SOF and RBV for 24 weeks in 40 patients with compensated, recurrent HCV and reported 70 % (28/40) SVR rates. No deaths, graft losses, episodes of rejection, or immunological dysfunction were observed with this combination in this setting, and the most common adverse events noted were fatigue, diarrhea, and headache. Since SOF does not use the P450 3A4 metabolic pathway, frequent monitoring of drug level of immunosuppressants is not necessary. Although this was a promising study, a combination of DAA is likely to become the standard of care

4.3.4 Sofosbuvir with Interferon and Ribavirin

There are anecdotal case reports of SOF being used in combination with interferon and RBV with successful outcomes even in the presence of fibrosing cholestatic hepatitis [40]. However, with the availability of more effective interferon-free regimens, it is unlikely that SOF will be used in combination with interferon and RBV in genotype 1 patients.

4.3.5 Sofosbuvir + Daclatasvir

Daclatasvir (DCV) is a potent NS5A replication complex inhibitor with demonstrated antiviral activity in HCV genotype 1 patients when coadministered with Peg IFN and RBV [41, 42]. Pellicelli et al. [43] prospectively evaluated the efficacy and safety of SOF and DCV ± RBV in liver transplant recipients ($N = 12$) with severe recurrent hepatitis C. All patients who completed 24 weeks of therapy had

undetectable viral levels at 24 weeks of treatment (ETR). Posttreatment hepatitis C virus RNA was available for 5 patients (week 8, $n=2$; week 4, $n=3$) and was undetectable in all cases. No immunosuppressive dose changes were required. A case report [44] also reiterated the successful use of SOF and DCV in a severe fibrosing cholestatic HCV patient. In another study, Fontana et al. [45] evaluated the efficacy of interferon-free DCV-containing regimens in 30 liver transplant recipients with severe, life-threatening recurrent HCV. Among the 30 eligible patients, 23 received DCV + SOF while seven received DCV + SMV, both with or without RBV. The SVR12 rate was 75 % among the 12 patients with sufficient follow-up. Although 12 people (40 %) experienced serious adverse events, none were attributed to DCV. There were no cases of acute graft rejection or immunosuppressant-related toxicity due to drug interactions. Most patients experienced stabilization or improvement in their laboratory and clinical status, with significantly improved CPT and MELD scores. These studies supports the utility of DCV-based all-oral antiviral therapy combined with SOF or SMV ± RBV as a potentially safe and effective salvage therapy for patients with severe recurrent HCV infection.

4.3.6 Sofosbuvir + Ledipasvir

Ledipasvir is a HCV NS5A inhibitor (similar to DCV) with potent antiviral activity against HCV genotypes 1a and 1b [46]. In the non-transplant setting, the combination therapy (SOF + ledipasvir ± RBV) has shown higher than 95 % cure rates in a consistent manner in genotype 1, treatment naïve or experienced people with or without cirrhosis [47–51]. A small study has shown that three drug combination of SOF, ledipasvir, and RBV can also cure 77 % of HCV genotype 3 patients with cirrhosis (17 of 22). Two open label studies showed that two-drug regimens with ledipasvir and SOF for 12 weeks is also very effective in HCV genotype 4 (19 of 20, SVR 95 %) and genotype 6 (24 of 25, SVR 96 %) infection [52]. However, the above studies were not done in liver transplant recipients. If these studies are reproduced in transplant recipients, recurrent HCV could be easily cured in almost all genotypes in the near future.

There is a large study (published only as abstract) with SOF/ledipasvir in combination with RBV in liver transplant recipients [53]. In this study, 223 people (of these 112 had developed cirrhosis) with recurrent HCV infection were treated for either 12 or 24 weeks, and most (~90 %) of these people were treatment experienced. The duration of treatment did not make any difference, and 96 % with mild fibrosis (108 of 111) or Child A cirrhosis (49 of 51) was cured. Cure rate was 85 % in Child B cirrhosis (38 of 44), but only 60 % in Child C (5 of 8). Only six patients discontinued treatment because of adverse events and four patients died of complications. The causes of deaths were progressive multifocal leukoencephalitis, thoracic aorta aneurysm dissection, internal bleeding, and complications of cirrhosis. Although this combination has not been approved by FDA for recurrent HCV, it is perhaps the best treatment option that is currently available for genotype 1 (perhaps

for genotype 3–6) infection in liver transplant recipients. This combination regimen does not have an effect on immunosuppressant levels, and therefore, dose modification of immunosuppressants is not necessary. However, anemia could be a problem due to RBV, especially in the presence of renal impairment which is common in many transplant recipients. The only absolute contraindication for this treatment is advanced renal failure.

4.3.7 Sofosbuvir + Simeprevir Regimens

SMV is second generation NS3/4A protease inhibitor that is dosed once daily. In non-transplant patients with genotype 1, it has shown excellent tolerance rates and very good (75–86 %) cure rates in combination with interferon and RBV [54–59]. The discontinuation rates (8–16 %) were lower with SMV than first generation protease inhibitors, but higher than SOF-based regimens. Patients with genotype 1b had higher SVR rates (~90 %) when compared to genotype 1a (71 %), and this difference was principally due to patients with the naturally occurring Q80K polymorphism. Although SMV in combination with SMV has been found to be very effective (93–96 %) in nontransplant genotype 1 patients with Child A cirrhosis [59], the cure rates are lower (~80 %, personal experience) in people with Child B cirrhosis.

4.3.8 Other Studies ("Real-World Experience")

A recent interim report [60] (published only as an abstract) evaluated the real-world experience (HCV-TARGET, a consortium of more than 50 academic and community medical centers in the USA, Canada, and Germany) of 189 hepatitis C patients treated with SOF-containing regimens. The regimens used were: SOF/Peg/RBV ($n=27$), SOF/RBV ($n=50$), SOF/SMV + RBV ($n=27$), and SOF/SMV ($n=85$). In this study, 78 % had HCV genotype 1, 57 % were treatment experienced, and 60 % had progressed to cirrhosis. The SVR4 rate for 68 patients with sufficient follow-up was 90 % (83 % for HCV subtype 1a and 95 % for subtype 1b). SVR rates were similar for previously untreated and treatment-experienced people (89 % vs. 90 %). Non-cirrhotics had a higher response rate than patients with cirrhosis (94 % vs. 86 %). RBV appeared to lower the response rates (82 %), but the number of patients was small to make a firm conclusion on RBV use. Ten of 12 genotype 1 patients (83 %) treated with SOF + Peg IFN/RBV achieved SVR4 (posttreatment week-4). Among those taking SOF + RBV alone, SVR4 rates were 90 % for genotype 2 and 60 % for genotype 3. SOF/SMV combination was generally safe and well tolerated. The most common side effects were fatigue, headache, diarrhea, and nausea. There were only five adverse events leading to treatment discontinuation, but 38 % of patients who received RBV developed anemia.

Another study [61] reported their preliminary experience (published only as an abstract) in 109 liver transplant patients with genotype 1 treated with SOF + SMV, with or without RBV. The majority of these patients were treatment experienced; including 12 % who had previous exposure to first-generation HCV protease inhibitors or SOF, and 29 % had advanced fibrosis or cirrhosis (Metavir stage F3–F4). The overall SVR12 rate was 91 % in an intent-to-treat analysis (88 %—HCV subtype 1a and 96 % for those with 1b). In this study, response rates were a marginally lower for patients who had RBV (SVR 89 %) and those who had previous experience with either protease inhibitors or SOF (SVR 80 %). People with severe fibrosis or cirrhosis did not do as well as those with moderate fibrosis or less (76 % vs. 96 %, respectively). This difference was driven by patients with HCV 1a (64 % vs. 97 %), while those with 1b did well regardless of fibrosis stage (100 % vs. 94 %). The most common side effects were fatigue, elevated bilirubin, nausea, and headache. More than 40 % of those on RBV developed anemia. There were no cases of acute rejection and no immunosuppressant-related adverse events. The results of these real-world experiences are promising, but the availability of cheaper and effective drug combination make it less likely that SMV/SOF would be widely used for recurrent HCV.

The combination of SMV/SOF could be used in liver transplant recipients with impaired renal function as shown by a prospective study [62] of 26 post-transplant patients with impaired kidney function. During treatment, 16 had unchanged renal function, seven showed improvement (one patient was able to stop dialysis), and three showed a decline in renal function. The treatment was generally well tolerated and on treatment virological response was good, but SVR rates were pending at the time of reporting (abstract).

4.3.9 Paritaprevir/Ritonavir, Ombitasvir, and Dasabuvir with or Without Ribavirin

This regimen was developed by Abbvie for genotype 1 infection, and contains a combination of protease inhibitor boosted by ritonavir (paritaprevir/ritonavir), ombitasvir (NS5A inhibitor), and dasabuvir (a non-nucleoside NS5B polymerase inhibitor). This combination therapy with or without RBV (RBV added based on genotype 1 subtypes or presence of cirrhosis) has shown 96–99 % cure rates in non-transplant setting [63–66].

The above regimen with RBV for 24 weeks has been tested in 34 transplant recipients [67] with genotype 1 infection with no fibrosis or mild fibrosis. Both tacrolimus and cyclosporine dose had to be drastically reduced (0.5 mg tacrolimus was given only once a week and cyclosporine dose was reduced to 1/5 of pretreatment dose in the trial) because of drug–drug interactions with paritaprevir/ritonavir, but SVR rates were very high (97 %). The side effect profile was good and only one person discontinued treatment because of side effects. The common adverse events were fatigue, headache, and cough. Despite its efficacy, this combination is less

likely to be used because of drug–drug interactions, and the need for dose adjustment and frequent blood level monitoring of immunosuppressive agents.

4.3.10 Experience with Compassionate Use of DAA Regimens in Severe Recurrent HCV

DAA regimens were recently used in compassionate use programs for patients with severe recurrent hepatitis C after liver transplantation. The French ANRS CO23 CUPILT study [68] evaluated the safety and efficacy of new DAA regimens in 23 patients with post-transplant fibrosing cholestatic HCV. SVR12 was achieved in 88 % of patients on SOF + RBV and 100 % won on SOF + DCV combination. Only one patient with cirrhosis, taking SOF + RBV and coinfected with HIV/HCV, relapsed. Those on SOF and DCV-based regimens had 100 % survival without re-transplantation at week 36, and this regimen had no significant drug interactions with immunosuppressants. Although half of the participants experienced serious adverse events, none were attributed to SOF or DCV.

Another retrospective, compassionate use study [69] evaluated the safety and efficacy of SMV in combination with SOF or DCV for people with severe post-transplant recurrent hepatitis C. This study included a total of 28 liver transplant recipients, 12 patients received SMV + SOF ± RBV while 16 received SMV + DCV ± RBV for up to 24 weeks. Seventeen patients had completed the treatment at the time of reporting, and the end of treatment response was 88 % (15/17) and SVR12 was 70 % (7/10). There were no cases of drug interactions with immunosuppressants, no episodes of graft rejection, and no deaths.

The Italian AISF-SOFOLT compassionate use program [70] reported outcomes using SOF for patients with severe post-transplant HCV recurrence. This analysis included 45 transplant recipients with end-stage liver disease and 24 with fibrosing cholestatic hepatitis. Most were treated with SOF + RBV alone, with smaller numbers receiving SOF + Peg IFN/RBV, SOF + DCV, or SOF + SMV and RBV. SVR 12 was achieved in 100 % treated with SOF + DCV, 89 % of those using SOF + Peg IFN/RBV, and 64 % of those using SOF + RBV alone.

The above preliminary findings show that interferon-free DAA regimens containing varying combinations of SOF, SMV, and DCV are safe and well tolerated and are effective in curing HCV in most liver transplant recipients.

4.4 Treatment Recommendations Based on Current Evidence

Current guidelines have been based on limited data in liver transplant recipients with recurrent HCV, as well as extrapolation of data from patients with chronic HCV infection in non-transplant setting. The field is evolving rapidly, and there is

cumulative data indicating recurrent HCV could be easily managed with the currently available DAA combinations. Based on the current evidence, our recommendations are as follows:

1. Treatment naive
   (a) *Genotype* 1*, compensated cirrhosis*
   - SOF 400 mg daily and ledipasvir 90 mg daily in combination with RBV for 12 or 24 weeks
   - SOF 400 mg daily + DCV 60 mg daily with or without RBV for 24 weeks (Alternate option)
   - SOF 400 mg daily + Simeprevir 150 mg daily with/without RBV × 12–24 weeks (Alternate option)
   - Paritaprevir/ritonavir, ombitasvir, and dasabuvir with RBV for 24 weeks (Alternate option; drug–drug interaction is a major problem requiring dose adjustment and frequent monitoring of drug levels of immunosuppressants)

   (b) *Genotype* 2 *or* 3*, compensated cirrhosis*
   - SOF 400 mg daily + RBV × 24 weeks
   - SOF 400 mg daily with either Ledipasvir 60 mg daily or DCV 60 mg daily in combination with RBV could be an alternative for genotype 3

   (c) *Other genotypes* (4–6)
   - Treat similar to genotype 1 although there are no supporting data

2. Decompensated allograft cirrhosis → treatment is same as that for patients with decompensated cirrhosis in non-transplant setting. Risks and benefits should be carefully considered before treating the patients. Patients should be considered for retransplantation if the treatment is thought to be futile even if patients achieved SVR

4.5 Retransplantation

The outcomes of retransplantation for recurrent hepatitis C have not been as good as for the other indications. There are a number of studies reporting poor overall survival after retransplantation for recurrent HCV [71–76] and these studies were reported before DAA were available to treat recurrent HCV. Because of poor outcomes, many liver transplant centers had reservations about retransplantation for recurrent HCV, but the availability of safer DAA is going to change the outlook of these patients in the near future.

There have been many prognostic models proposed to predict outcomes of retransplantation for recurrent HCV, and these models were designed to select candidates with the best potential outcome. Recently, a score has been proposed based on donor age, serum creatinine, international normalized ratio (INR) and serum

Table 4.6 Survival after retransplantation of the liver

First author	Study period	Number of HCV patients (% of total patients)	Percentage of survival (year's after retransplantation)			
			1 year	2 years	3 years	5 years
Watt [71]	1996–2002 (UNOS)	899 (42.2)	61	50	n/a	45
Rosen [72]	1986–1999 (UNOS and European)	357 (23)	<50	n/a	n/a	<40
Marti [73]	1988–2006 (European single-center study)	8 (20)	70	n/a	n/a	57
Ghabril [74]	1990–2002 (UNOS)	1034 (45.3)	64.5	n/a	55.3	n/a
Organización Nacional de Trasplante (ONT) [75]	1984–2008 (Spain)	273 (22)	63.4	n/a	53	42.4
McCashland [76]	1996–2004 (U.S. multicenter retransplant study)	43 (15.8)	69	n/a	49	n/a

n/a not available

albumin at the time of second transplantation, recipient age at the first transplantation, and the interval between first and second transplantations [77]. Although promising, these models are not applicable in the current era where majority of patients with HCV could be cured with minimal adverse events. Short- and long-term survival outcomes of patients who were retransplanted for recurrent HCV are summarized in Table 4.6 [71–76]. It is more than likely that fewer patients will require retransplantation for recurrent HCV in the near future, and HCV patients could expect similar outcomes as patients transplanted for other reasons.

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Chapter 5
Recurrence of Primary Biliary Cirrhosis Following Liver Transplantation

Russell H. Wiesner

5.1 Primary Biliary Cirrhosis

Primary biliary cirrhosis is a chronic progressive autoimmune cholestatic liver disease which slowly progresses to cirrhosis, portal hypertension, and premature death from liver failure [1]. It is characterized by lymphocytic cholangitis leading to destruction of interlobular and septal bile ducts, and ultimately developing fibrosis and cirrhosis. The only approved drug to treat patients with PBC is ursodeoxycholic acid, a hydrophilic, noncytotoxic bile acid, that has been demonstrated to prolong the course in some patients [2, 3]. However, up to 30 % of ursodeoxycholic acid treated patients have an inadequate response and a recent Cochrane analysis which analyzed 16 randomized clinical trials with 1447 PBC patients concluded that ursodeoxycholic acid did not demonstrate any significant benefit on all-cause mortality, liver transplantation free-survival, pruritus, or fatigue [4]. Ursodeoxycholic acid did have a beneficial effect on liver biochemistry, particularly on serum alkaline phosphatase levels. Finally, a recent study has shown that obeticholic acid when added to ursodeoxycholic acid therapy was associated with a further decrease in alkaline phosphatase levels [5]. However, 10 % of patients had to discontinue the medication because of pruritus, and there was no assessment made with regard to histologic progression or the development of complications of portal hypertension. Thus, further studies of this combination will be needed to determine the overall beneficial effects in PBC.

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5.2 Primary Biliary Cirrhosis and Liver Transplantation

PBC remains one of the top indications for liver transplantation. Up to 2010 over 6000 patients with PBC have been transplanted in Europe and the USA [6]. However, over the past two decades a notable decline in the number of liver transplants for PBC have been observed both in the USA and Europe (Fig. 5.1) [7]. The reason for this decline in the number of transplants for PBC is not clear, but may be related to changing patterns of disease (i.e., earlier diagnosis), improved diagnosis and treatment of varices and spontaneous bacterial peritonitis, and the use of ursodeoxycholic acid which has been shown to prolong the course in some patients [2, 7].

5.3 Survival Following Liver Transplantation for PBC

Patient and graft survival for PBC are excellent compared to other indications. At select centers, 1 and 5 years survival rates may exceed 90 % and 80 %, respectively (Fig. 5.2) [8–11]. In addition, PBC patients who are on the liver wait-list have had excellent survival up until recent times. However, it appears that the recent implementation of the Share 35 UNOS Policy may be a contributing factor to the increasing wait-list mortality recently reported in PBC patients [12].

5.4 Recurrent PBC

Recurrent PBC after liver transplant was first reported in 1982 by Neuberger et al. [13]. Despite initial controversy, the recognition of recurrent PBC is now firmly established in the liver transplant community. Unlike PBC in the native liver,

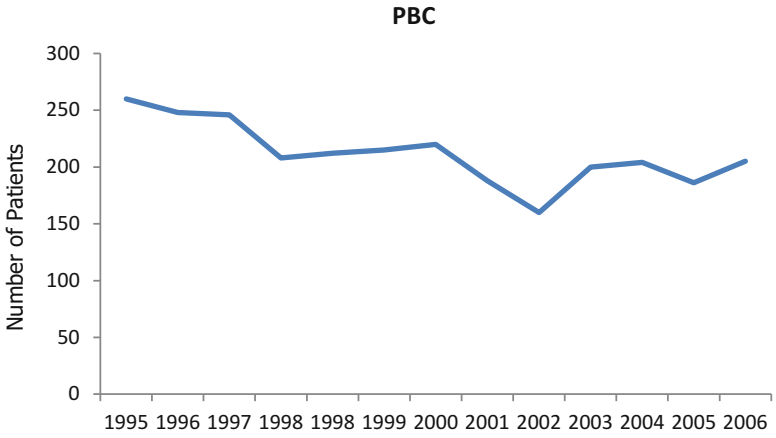

Fig. 5.1 Absolute number of liver transplants for patients with PBC by year [6]

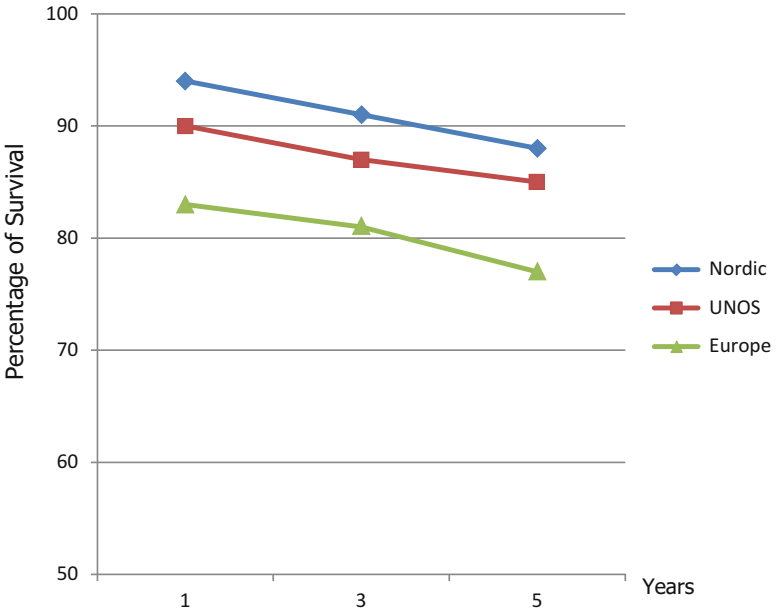

Fig. 5.2 Patient survival for primary biliary cirrhosis following liver transplantation from registry data [8–11]

clinical and biochemical features cannot be used alone for diagnostic purposes [14–17]. The diagnostic hallmark of recurrent PBC is histologic identification of granulomatous cholangitis or the florid duct lesion [18]. While short- and median-term outcomes remain favorable, long-term follow-up is important to identify potential reduced long-term graft survival in patients.

5.5 Diagnosis of Recurrent PBC

Unlike PBC in the native liver, the phenotypic expression of recurrent PBC is limited. Traditionally related symptoms such as pruritus and jaundice are rarely observed particularly in early recurrent disease. Unlike patients with native PBC, the majority of patients with recurrent PBC have normal or clinically insignificant elevations of serum liver biochemistries at the time of diagnosis. The relationship between change in serum alkaline phosphatase and correlation with histologic disease progression over time remains unknown. Multiple reports have described the persistence of serum antimitochondrial antibody following liver transplantation [19]. A common profile includes immediate loss of detectible serum AMA with subsequent identification in serial investigations. There does not appear to be a correlation between the presence or titre of serum AMA and the development of recurrent PBC.

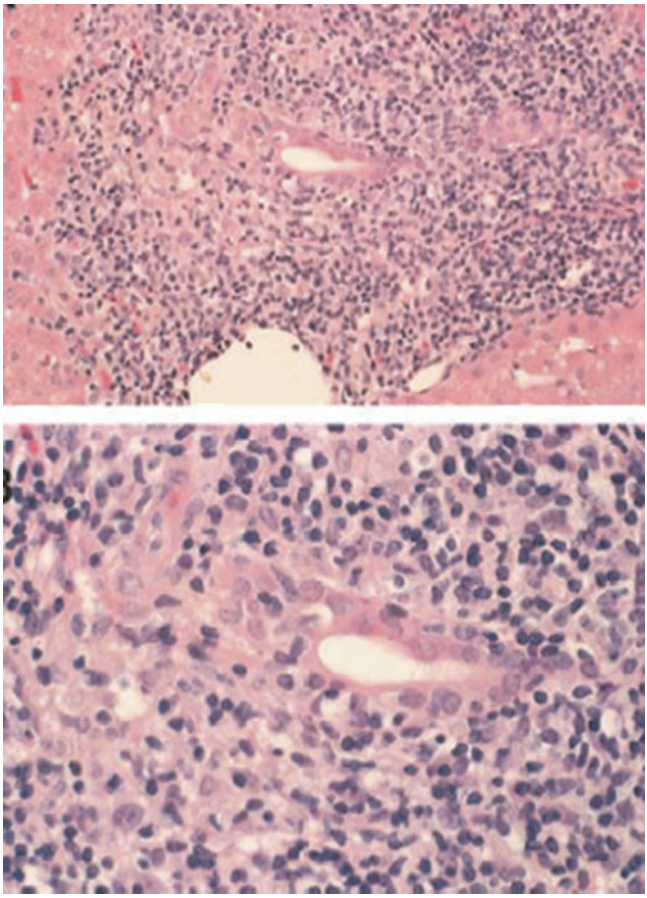

Fig. 5.3 Lymphocytic bile duct destruction (florid duct lesion)

The diagnosis of recurrent PBC after liver transplantation relies heavily on histologic features. The major diagnostic hallmark of recurrent PBC is granulomatous cholangitis or the florid duct lesions which is present in approximately 40–60 % of initial diagnostic liver biopsies (Fig. 5.3) [18, 20].

An important relationship between less specific inflammatory features on liver biopsy in patients transplanted for PBC and the influence on eventual disease recurrence has also been identified. In one study, dense lymphoplasmacytic infiltrates occurring before identification of a florid duct lesion was observed in 40 % of patients [21–23]. The diagnostic criteria for recurrent PBC have been outlined by Neuberger et al. (Table 5.1) [21]. In all cases, alternative etiologies for portal tract injury after liver transplant such as acute or chronic allograft rejection, ischemic cholangitis, and drug-induced hepatotoxicity must be excluded.

Table 5.1 Common criteria used for the diagnosis of recurrent PBC include the following

1. OLT performed for PBC
2. Persistence of AMA or anti-M2 antibody
3. Characteristics portal triad lesions on a liver biopsy
(a) Epithelioid granulomas
(b) Mononuclear inflammatory infiltrate
(c) Formation of lymphoid aggregates
(d) Bile duct damage (3/4 definite; 2/4 probable)
4. Absence of other pathology/disorders, including:
(a) Acute and chronic rejection
(b) Graft vs. host disease
(c) Biliary obstruction
(d) Vascular abnormalities
(e) Cholangitis and other infections
(f) Viral hepatitis
(g) Drug toxicity

5.6 Prevalence of Recurrent PBC

Table 5.2 summarizes the prevalence rate for recurrent PBC reported by individual liver transplant programs which range from 9 up to 42 %. There was no obvious relationship between the frequency of recurrence PBC and overall number of patients undergoing liver transplant for PBC. When examined by year or era of liver transplant, the percentage of patients with recurrent PBC is usually increased in more recent times. A number of center-specific issues affect the detection rate of recurrent PBC. The most important factor relates to the use of timing of liver biopsies and follow-up. The performance of liver biopsy for clinical indications alone will underestimate the true prevalence rate as compared to centers that perform protocol liver biopsies. The inherent sampling error of liver biopsies may also contribute to a false negative diagnosis. Finally, the existence of less restrictive histologic criteria used for the diagnosis of recurrent PBC also influences estimates of disease recurrence.

The average time to recurrence varies between reported studies. In general, more cases have been identified when longer duration of follow-up among eligible patients is possible. This is underscored by examples with serial investigations from the same centers report increasing rates of recurrent disease over time. In all, the cumulative incidence rates vary between 21 and 37 % at 10 years, and may be as high as 43 % with 15 years of follow-up. Figure 5.4 shows the cumulative incidence of recurrent PBC over time at the Mayo Clinic.

Table 5.2 Recurrence rate of primary biliary cirrhosis reported

Center	Time period	LT for PBC	Recurrent %	Mean time to recurrence
Pittsburg	1982–1996	421	11	5.5
Birmingham	1983–2009	248	42	5.1
Baylor	1985–2013	250	19	4.2
Mayo Clinic	1985–2005	154	34	3.5
Royal Free	1988–2008	138	26	3.7
Edmonton	1989–2008	108	26	5.9
Berlin	1989–2003	100	14	5.1
Colorado	1988–2006	70	26	4.8
UCSF	1988–1997	69	14	NA
Washington	1985–1997	56	35	3.3
Kyoto	1994–2004	50	18	1.6
Chicago	1984–2000	46	15	6.5
Lahey Clinic	1983–2001	43	19	3.5
Range			**11–42**	**1.6–6.5**

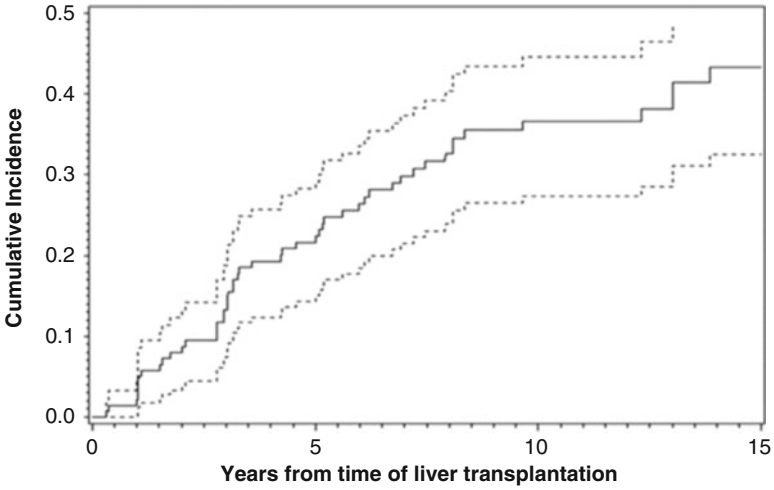

Fig. 5.4 Cumulative incidence of recurrent PBC over time at Mayo Clinic [6]

5.7 Recipient and Donor Risk Factors

Studies attempting to identify risk factors for the development of recurrent primary biliary cirrhosis have yielded conflicting results. Although some studies have identified donor age, recipient age, warm ischemic time, and cold ischemic time as significant risk factors [15, 24–28], others have failed to show significant differences in

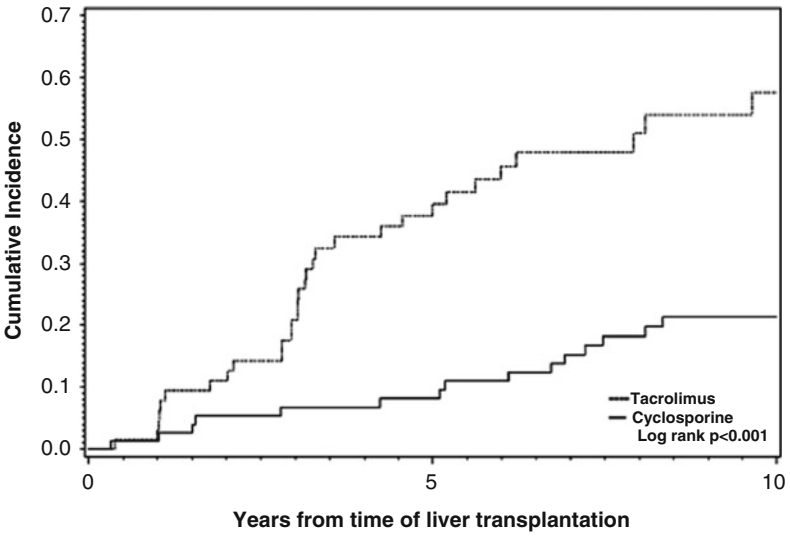

Fig. 5.5 Probability of developing recurrent PBC in patients undergoing LT for PBC according to primary type of calcineurin inhibitors-based immunosuppression [6]

these factors. Thus, the clinical relevance remains unclear. In addition, other factors such as race, ethnicity, gender mismatch, HLA mismatch, serum bilirubin, INR, and creatinine levels were not significantly different in most studies between patients with recurrent PBC and those without recurrent PBC.

Another area of much deliberation is whether specific immunosuppression regimens used to treat PBC posttransplant can be a risk factor for recurrent PBC. Recurrent PBC was initially reported when cyclosporin was the only calcineurin inhibitor that was being utilized. Subsequently, the use of tacrolimus has been associated with recurrent disease in patients undergoing deceased and living donor liver transplant. Compared to cyclosporin-based regimens, tacrolimus has been associated with an increased incidence and a significant reduction in the time to recurrence of PBC (Fig. 5.5) [29–32]. Tacrolimus immunosuppression was found to be an independent predictor of overall risk of recurrent PBC when addressed in the context of recipient age, number of liver biopsies performed after liver transplant, and duration of follow-up. One recent study has shown a relationship between the type of calcineurin inhibitor utilized and the non-HLA locus (rs62276414), which hosts the IL12A gene [33]. Shown in the Kaplan–Meier plot (Fig. 5.6) is the survival curves for different combinations of calcineurin inhibitors at 1 year and the rs62270414 (IL12A) locus genotype AG and GG. However, it remains unclear how IL2 inhibition when interacted with IL2 and IL12 signaling pathways might influence disease recurrence.

On the other hand, there are reports that have not observed the relationship between incidence and time to PBC recurrence based on the type of calcineurin inhibitors used [30–32, 34, 35]. Furthermore, in recent times the steroid-tapering

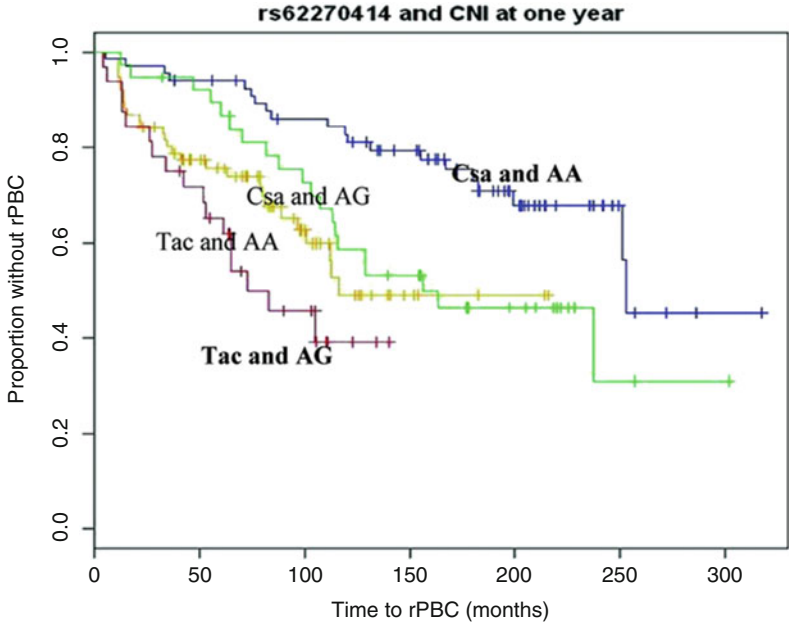

Fig. 5.6 Kaplan–Meier plot showing survival curves for different combinations of calcineurin inhibitors (CNI) at 1 year and genotypes at rs62270414 of IL12A locus [33]

protocols that have been implemented in conjunction with the almost exclusive use of tacrolimus have raised questions regarding the effect of steroids withdrawal on the rapid recurrence of PBC. To date, the timing of corticosteroid tapering immunosuppression, early versus late, with respect to recurrent PBC has not been fully studied, but certainly seems to play a major role on the incidence of recurrent autoimmune hepatitis. Similarly, the comparison between the use of azathioprine and mycophenolic acid on the risk of PBC recurrence has been studied but failed to reveal any real statistical significant difference between PBC patients receiving mycophenolic acid and those receiving azathioprine [16]. At least one report has demonstrated that azathioprine use in patients transplant for PBC may be associated with less disease recurrence and longer time to recurrence [32]. This to date has not been confirmed.

5.8 Natural History of Recurrent PBC

The natural history of recurrent PBC has been reported in a number of studies. However, the development of cirrhosis and the need for retransplantation remains uncommon [24, 36, 37]. In most studies hepatic retransplantation in patients with recurrent PBC is rare. In the largest reported cohort only 3 of 486 patients required a second liver transplant for end stage liver disease related to recurrent PBC [38].

In the Mayo experience, only two individuals have undergone hepatic retransplantation for end stage liver disease from recurrent PBC [14]. Our own experience suggests that short of mid-term survival of patients with recurrent PBC is similar to those patients transplanted for PBC without recurrence. However, long-term follow-up will be needed to truly assess the impact of recurrent PBC on long-term patient survival.

5.9 Treatment of Recurrent PBC

Today, no standard of care exists for the treatment of recurrent primary biliary cirrhosis. Dose modification or reinstitution or clinical steroids, azathioprine, and mycophenolic acid have not been formally reported as an intervening strategy. Given the universal presence of early stage disease at the time of diagnosis, a potential role for ursodeoxycholic acid therapy exists. However, the assessment of drug efficacy is challenging in that many patients have normal or near normal serum liver biochemistries at initial diagnosis and many centers do not do protocol liver biopsies. Among patients with PBC undergoing liver transplant at the Mayo Clinic, 52 % of patients with recurrent PBC were treated with ursodeoxycholic acid and most experienced a normalization of liver enzymes as compared to liver enzyme normalization rate of 22 % among untreated recurrent PBC patients [6]. However, there was no significant difference in histologic progression rate between those patients treated with ursodeoxycholic acid and those untreated patients based on protocol biopsies (Fig. 5.7). Furthermore, the probability of death or the need for

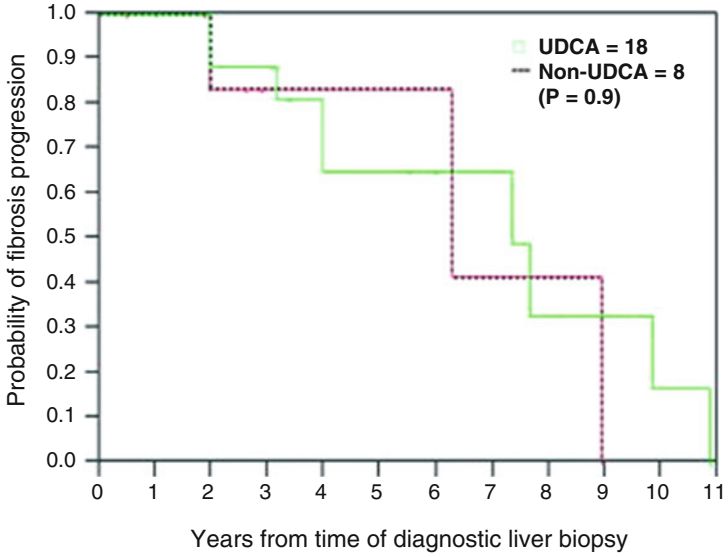

Fig. 5.7 Probability of fibrosis progression of recurrent PBC in patients treated with UDCA (*solid line*) and non-treated patients (*broken line*) [14]

liver retransplantation for patients treated with ursodeoxycholic acid was not significantly different from untreated PBC transplanted patients [14]. These results should be interpreted cautiously due to the small sample size and lack of randomization. To date, there is no evidence to support the use of alteration of steroid taper protocols; however, this remains an area for further investigation. Our own approach at this time is to treat with ursodeoxycholic acid at the time when the diagnosis of recurrent disease is made. Whether prophylactic therapy with ursodeoxycholic acid starting at the time of transplant would prevent recurrent PBC remains unknown and also needs to be further evaluated.

5.10 Summary

It appears that recurrent PBC after liver transplantation for patients transplanted for PBC is common and is often diagnosed on the basis of abnormal histologic findings, particularly the finding of the florid duct lesion. The major risk factor seems to be the immunosuppression regimen used. Cyclosporin-based regimens as compared to tacrolimus-based regimens seem to be associated with reduced incidence, and prolonged time to recurrence. The role of rapid tapering of corticosteroids in the immunosuppressive regimen also remains undefined with regard to recurrent PBC. The effects of ursodeoxycholic acid include the normalization of liver biochemistries (alkaline phosphatase levels), but does not appear to delay histologic progression. Long-term follow-up will be needed to determine whether recurrent PBC impacts long-term patient and graft survival.

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Chapter 6
Recurrence of Autoimmune Hepatitis After Liver Transplantation

James Neuberger

6.1 Introduction

Liver transplantation for AIH is good with a 5-year-patient survival of 80–90 %. Although the quality of life for patients is usually excellent after transplantation only half return to full-time employment.

6.2 Recurrent AIH

Key features for the diagnosis of rAIH include a transplant for autoimmune hepatitis, elevated autoantibodies and immunoglobulins, characteristic histological features and exclusion of other causes of graft inflammation, notably acute rejection (which of course may coexist with rAIH) and HCV infection [1, 2] (Table 6.1).

Since the first report in 1984 [3], recurrent AIH is being increasingly recognised with nearly 20 publications [4–24] reporting recurrence rates of 20–30 % (Table 6.2). The other post-transplant condition resembling autoimmune hepatitis in patients grafted for other indication has been termed de novo AIH (dnAIH) [25]. The median reported time to recurrence varies between 15 and 52 months [11, 14, 16–18, 26]. The length of follow-up also appears to be important in assessing the probability of rAIH. The rate of recurrence has been quoted at 8 % at 1 year and as much as 68 % after 5 years [16]. The median time to reported recurrence varies between series but is around 2–5 years. Studies following patients over a longer period have revealed that the risk of recurrent disease persists even over 10 years post-transplantation with the two patients developing severe recurrence at 10 and 14 years

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Table 6.1 Criteria for the diagnosis of recurrent autoimmune hepatitis

1.	Liver transplant for autoimmune hepatitis
2.	Autoantibodies (anti-nuclear, anti-smooth muscle or anti-liver kidney microsomal) in significant titer (>1:40)
3.	Sustained rise (above twice normal of levels) of serum aminotransferase activity
4.	Elevated serum immunoglobulins (especially IgG)
5.	Chronic inflammatory cell infiltrate of:
	• Plasma cells
	• Interface hepatitis
	• Bridging necrosis and fibrosis
6.	Corticosteroid responsiveness
7.	Exclusion of other causes of graft dysfunction (such as rejection, HCV infection)

HCV hepatitis C virus, *AIH* autoimmune hepatitis

post-transplantation [10]. As protocol biopsies were not performed in all studies, there is the possibility that recurrent AIH is under-reported. This may be related to the tendency to reduce immunosuppression over time. Whether the use of current immunosuppression, particularly tacrolimus has an impact on long-term risk is uncertain, although the evidence so far is that the choice of calcineurin inhibitor (CNI) is not a risk factor for recurrence [23].

Many authors have used the criteria developed by the International Autoimmune Hepatitis Group (IAHG) [27] to define rAIH: this is inappropriate, the IAHG criteria were developed to ensure that there was a consistent approach taken in clinical studies and extrapolation of this definition to the allograft is inappropriate and potentially misleading. The differential diagnosis of the histological findings in the allograft is much wider than in the native liver, and other causes of graft damage must be excluded. In contrast to the patient with a native liver, the liver allograft recipient will be taking immunosuppressive and other drugs, there is usually a different HLA (human leukocyte antigen) and other antigenic environment, rejection itself is associated with the presence of autoantibodies, and there are many other causes of potential graft damage which, of course, may coexist with rAIH.

The role of autoantibodies in the diagnosis: Autoantibodies may be present in low titre post-transplant and do not necessarily correlate with histological features of graft inflammation [28]. Furthermore, histological abnormalities can precede changes in biochemical and immunological tests [10]. Changes in serum aminotransferases do not correlate with chronic hepatitis in children following transplantation [29], and biochemical improvement does not always correlate with histological remission [16]. Assessing response to the treatment of recurrent disease is probably best served by liver biopsy, since liver tests do not correlate with liver histology and significant histological inflammation can be present with normal biochemistry.

The role of protocol liver biopsy is controversial, and the risks of biopsy have to be balanced against the potential benefits associated with earlier and more effective treatment to prevent graft damage. Furthermore, interpretation of graft histology can be challenging and distinction between rAIH and allograft can be difficult, although

Table 6.2 Published series of recurrent autoimmune hepatitis

Study	No. of patients transplanted for AIH	No. with recurrence	Age (OLT)	Autoantibodies				Therapy at recurrence	Outcome
				ANA	ASMA	LKM	IgG		
Wright, 1992 [21]	43	11	–	6	8	–	Elevated	C	
Birnbaum, 1997 [8]	6	5	11	4	4	–	Elevated	C (4), T(4)	Second OLT (2), PTLD (1)
Prados, 1998 [16]	27	9	35	17	11	7	n/a	C (26), T(1)	Resolution
Ratzui, 1999 [17]	15	3	23	15	21	5	2.6	C, + prednisolone/azathioprine	Second OLT (1), cirrhosis and death (1), no change (1)
Narumi, 1999 [15]	40	5	38	–	–	–	n/a	T or C. Prednisolone (1)	No graft loss
Milkiewicz, 1999 [14]	47	13	41	–	–	–	16.5	–	Second OLT (3)
Reich, 2000 [18]	32	6	37	23	24		3	T	Second OLT (3)
Ayata, 2000 [6]	12	5	38	6	6	1	Elevated	T (3), T & C (2), + azathioprine/prednisolone	Cirrhosis (2), chronic rejection (2)
Gonzalez-Koch, 2001 [11]	41	7	38	–	–	–	–	T (4), C (3), + azathioprine/ prednisolone	Lymphoma (2), second OLT (1)
Molmenti, 2002 [5]	55	11	45	–	–	–	–	C (82 %) or T (18 %), + prednisolone	Lymphoma (1), no graft loss
Yusaff, 2002 [22]	12	2		–	–	–	–		
Heffron, 2002 [12]	52	9	32	–	–	–	–	Prednisolone (6), no further data	
Duclos-Vallee, 2003 [10]	17	7	30	9	14	4	23.2	C, Prednisolone, Azathioprine	Second OLT (2)
Vogel, 2004 [20]	28	9	29	24	14	16	6	T	
Renz, 2002 [19]	37	12	39	–	–	–	–	C	Cirrhosis (1)

(continued)

Table 6.2 (continued)

Study	No. of patients transplanted for AIH	No. with recurrence	Age (OLT)	Autoantibodies				Therapy at recurrence	Outcome
				ANA	ASMA	LKM	IgG		
Khalaf, 2007 [13]	16	3	22	–	–	–	–	Steroids	Graft failure (1)
Rowe, 2008 [4]	103	28 %	–	–	–	–	–	Steroids (last 5 years of study)	6.2 % graft loss
Campsen, 2008 [9]	66	23	44	–	–	–	–	C (26 %), T (64 %), prednisolone (50 %), azathioprine/MMF (28 %)	No graft loss
Dbouk, 2013 [24]	63	26	39	52/52					No impact of ANA titer, 4 with recurrence died with liver failure
Sakai, 2014 [58]	9	3							Living donors, review measured use of MLR

T tacrolimus, *C* cyclosporine, *ANA* anti-nuclear antibodies, *ASM* anti-smooth muscle antibody, *LKM* liver kidney microsomal antibody, *IgG* immunoglobulin G, *OLT* orthotopic liver transplant, *PTLD* post-transplant lympho-proliferative disease, *AIH* autoimmune hepatitis, *MLR* mixed lymphocyte reaction

Table 6.3 Histological differences between recurrent AIH and rejection

	Recurrent AIH	Rejection
Portal and periportal changes		
Portal inflammation	Mononuclear cells (plasma cells ++)	Mixed infiltrate (lymphocytes, macrophages, blast cells, neutrophils, eosinophils)
Interface hepatitis	Variable (often prominent)	Mild
Bile duct inflammation	Mild (lymphocytes)	Prominent (mixed infiltrate)
Bile duct loss	Minimal/none	Variable (may progress to chronic rejection)
Venous endothelial inflammation	None/mild	Yes
Fibrosis	Yes	No
Parenchymal changes		
Parenchymal inflammation	Variable	Generally mild
Composition	Mononuclear (mainly plasma cells)	Mixed (mainly lymphocytes)
Pattern	Spotty or confluent	Confluent
Distribution	Random or zonal	Zonal (acinar zone 3)
Associated features	Lobular disarray	Hepatic vein endothelial inflammation
Cholestasis	Rare	Common

there are some typical features in both as detailed in Table 6.3 [28]. One of the earliest findings is that of lobular lymphoplasmacytic hepatitis with acidophil bodies [6].

Rigamonti [30] suggested that transient elastography (TEG) may be helpful in diagnosing recurrent disease but the numbers in their series were very small, and there was no comparison with other causes of allograft damage. However, routine use of TEG may help guide the need for liver biopsy.

6.2.1 Factors Contributing to Recurrence

Published series have reached conflicting conclusions for the risk factors for rAIH: this is due, in part at least, to the variable diagnostic criteria for rAIH, the different factors analysed and whether protocol biopsies were taken. Those factors associated with recurrence include the type of immunosuppression, HLA status of donor and/or recipient, severity and type of AIH in the recipient, and the length of follow-up. Levels of autoantibodies (anti-nuclear and anti-smooth muscle) do not seem to be associated with recurrence [24].

Early weaning off corticosteroids may increase the risk of rAIH. In patients transplanted for AIH most units now continue steroids at a low dose (such as prednisolone 5–7.5 mg/day), although attempts at steroid withdrawal have led to

mixed outcomes. One recent study reported that attempts at complete steroid withdrawal 1 year following live donor liver transplantation were unsuccessful [13]. Others have attempted alternative immunosuppression [31]. In a small randomised controlled trial, tacrolimus and prednisolone was compared with mycophenolate mofetil and tacrolimus with steroid withdrawal at 3 months. There was no difference in graft and patient survival, and a better glycemic profile in the steroid-free arm. However, follow-up was short (2 years) and histological findings were not reported. Of those who had recurrence of AIH (17 %) the majority were treated with steroids, with no correlation between steroid weaning and recurrence [12]. A larger study with longer follow-up demonstrated encouraging data on steroid withdrawal, although the recurrence rate at 35 % was high [9]. Protocol biopsies were not performed.

Several studies have quoted high rates of rejection at up to 83 % [15], and a 1.76 times increase risk of recurrence if there was a previous episode of rejection [12]. This observation has not been confirmed in other case control studies, where rejection was not any higher than patients who did not have AIH recurrence (5.11). Therefore, there is no universal acceptance at present that graft rejection has any effect on the risk of recurrence, although some studies suggest that early cellular rejection, unlike late cellular rejection, does not affect long-term outcomes [32].

Greater disease severity (as shown by more necro-inflammatory activity) in the recipient liver prior to transplant has been reported as a risk factor for rAIH [6] and the authors concluded that explant histology could help to guide post-transplant immunosuppression. Patients grafted for AIH may also be less responsive to immunosuppression post-transplantation.

There is conflicting evidence on the role of HLA phenotype on the risk of recurrence. Some studies have noted an association between HLA-DR3 positive recipient/HLA-DR3 negative graft and recurrent disease [15, 33]. Others have demonstrated a link between recipient HLA-DR3 positivity and recurrent disease, although HLA phenotype mismatch between donor and recipient was not confirmed [11]. There are other studies which have failed to demonstrate a link with the HLA-DR3 phenotype [5, 34]. Dbouk and Parekh suggested that Afro-American race was a risk factor for recurrence or death [24].

6.2.2 Management of Recurrent Disease and Outcome

In the majority of cases increased immunosuppression is successful, in contrast to early reports where over 50 % of patients failed to respond [16]. Treatment usually involved increased doses of steroids and maintaining patients on steroids [4, 6, 10, 11, 13, 18, 19], although in some cases azathioprine was introduced [5, 16] and patients were switched from cyclosporine to tacrolimus [35]. Tacrolimus has been used successfully as a salvage therapy for lack of response to steroids, azathioprine and cyclosporine [35]. The effect was dramatic and occurred within days. Others have used other agents such as cyclosphosphamide [6, 15]. The consequences of

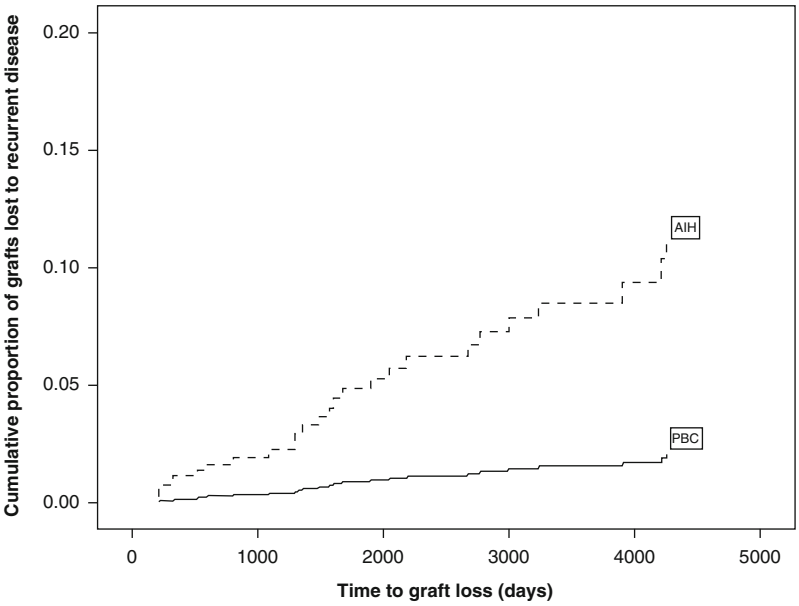

Fig. 6.1 Proportion of patients transplanted for AIH and PBC in Birmingham UK who develop recurrent disease in the graft after OLT (Rowe et al. [13])

additional immunosuppression have to be balanced against the risk of side-effects such as the increased risk of some cancers and infections, renal impairment, diabetes and osteopenia. Three deaths have been reported from post-transplant lymphoproliferative disorder [5, 11]. All these patients were aggressively immunosuppressed with cyclophosphamide. As mentioned earlier, MMF has also been used with success as part of a steroid withdrawal regimen [31]. In a paediatric population, sirolimus was used in recurrent disease not responding to azathioprine or mycophenolate, steroids and tacrolimus [36] and was successful in achieving a response in 3 out of 4 non-responders. One patient did not tolerate sirolimus because of infective complications, and colitis and possible post-transplant lymphoproliferative disease. Sirolimus may therefore have a role as salvage therapy.

The outcome in patients with recurrent disease in terms of graft and patient survival does not appear to be significantly worse than patients without disease recurrence, with 5-year survival quoted at over 78 % [5, 12, 18, 20]. A large study compared outcomes of recurrent disease following transplantation for AIH, primary sclerosing cholangitis, alcoholic liver disease, hepatitis C, cryptogenic cirrhosis/non-alcoholic liver disease and fulminant liver failure from acetaminophen and non-acetaminophen causes [4]. When compared with recurrent primary biliary cirrhosis, there was a 4.1 times increased risk of graft loss (>90 days post-transplantation) in patients with recurrent AIH (Fig. 6.1). The greatest risk of graft loss was for recurrent hepatitis C with a hazard ratio of 11.6. Graft loss occurred in the shortest time post-transplantation in the recurrent AIH group at 525 days.

There was also a trend towards reduced graft loss since the introduction of maintenance steroids.

Recurrent disease can have an aggressive course unresponsive to immunosuppression, resulting in the need for re-grafting or death [8]. Others have suggested that patients who develop significant fibrosis may deteriorate despite immunosuppression [19]. This highlights the need for early detection and treatment of these patients, and perhaps supports the argument for protocol biopsies.

The optimal regimen for immunosuppression for patients transplanted for AIH is not clearly established. The choice of agents used for allograft recipients will depend on many factors, including the indication and risk of recurrence but also social factors (such as the need to avoid mycophenolate in those who wish to become pregnant and the need to simplify regimens in those who may be less compliant) as well as comorbid conditions (such as avoiding or minimising CNIs in those with renal disease or corticosteroids in those with osteopenia or unstable diabetes mellitus).

The patient grafted for AIH is at greater risk of developing acute cellular and possibly ductopenic rejection than those grafted for other indications. In our series in Birmingham for example, severe acute rejection was diagnosed in 61 % of those grafted for AIH compared with 42 % for those grafted for alcohol-related liver disease [37]. Reasons for this increased susceptibility to rejection is not clear although those grafted for other indications with a presumed autoimmune aetiology (such as primary biliary cirrhosis and primary sclerosing cholangitis) have acute rejection rates similar to those seen in AIH. It is also our experience that early acute cellular, if adequately and promptly treated, and in contrast to late acute rejection, is not associated with an inferior graft survival.

Most regimens for immunosuppression include a CNI (usually tacrolimus), either alone or with an anti-metabolite (usually mycophenolate or azathioprine). The use of corticosteroids with other agents remains controversial. Our own practice is to wean steroids in 3 months for most recipients within 3 months with the exception of those grafted for AIH where low-dose steroids (together with bone protection therapy) are maintained long-term. Whether this regimen is associated with an improved graft survival is not established although preliminary analysis of our own data suggests that this is indeed the case (T Krishnamoorthy, Y Oo, personal communication).

One small study [38] suggested that splenectomy before or during transplantation may reduce the risk of recurrence but this needs confirming in larger series before its use can be recommended, even in high risk patients.

6.3 De Novo AIH

The development of the clinical, serological and histological features of autoimmune hepatitis in patients transplanted for other aetiologies was initially described in children [25]. Subsequent studies (see below) have suggested that there may be other pathophysiological mechanisms and so this syndrome has also been labelled

plasma cell hepatitis, as a category of allograft dysfunction strongly resembling autoimmune hepatitis [39].

There have been numerous reports since then with a predominance of pediatric patients, although adult patients also appear to be at risk [40–42]. The condition usually presents 2–10 years after transplant. The typical clinical, serological and histological features of AIH are seen with elevated immunoglobulins, autoantibodies and histological features of portal inflammation and interface hepatitis. Some have reported cases presenting predominantly with central peri-venulitis prior to the development of typical portal inflammation [43, 44]. However, comparing the histological features of rAIH with AIH, Castilo-Rama [39] noted a higher frequency of HLA DR15, fewer females and a higher proportion with IgG4-positive cells. Hadzic [45], in a study on paraffin-embedded sections that those with dnAIH, reported a trend towards a Th1 polarisation of the necro-inflammatory infiltrate.

These differences suggest that rAIH and ADIH have a different pathophysiology with differences between allo- and auto-immunity. Montano-Loza [26] found that risk factors for developing dAIH included donors who were female, over 40 years and were treated with tacrolimus and with mycophenolate; those treated with cyclosporine had a lower risk. These findings need confirmation.

The exact pathogenesis is not clear. Both dnAIH and rAIH may develop after interferon therapy (IFN) for HCV infection [46]; there may be a significant interval between the use of IFN and the diagnosis so causation is unclear. It has been suggested that CNIs may interfere with the maturation of T-cells and the function of regulatory T-cells as has been demonstrated in animal studies. The predominance of dnAIH in children may be due to CNIs causing thymic dysfunction [47]. Molecular mimicry may play a role, due to the release of cross-reactive antibodies produced by the immune response to infection by cytomegalovirus, Epstein–Barr virus and parvovirus [43, 48]. This observation has not been supported by others [49].

Some support for this theory comes from studies where an association between dnAIH and previous episodes of acute cellular rejection was noted [49–51]. Further evidence comes from studies where patients negative for Glutathione-*S*-Transferase T1 (GSST1) antibodies were transplanted grafts positive for GSST1 subsequently developed antibodies to GSST1 [40, 52]. These observations require further validation.

dnAIH generally responds to modification of immunosuppression, although there are studies reporting poor outcome in certain groups of patients. Gupta and colleagues described a series with an atypical histological feature of ductal proliferation [53]. Most of the patients developed progressive fibrosis. Others have noted in cirrhosis in half the cases with remission of interface hepatitis in one patient only [51]. Azathioprine was not used. The combination of azathioprine and steroids appears to be the key to successful therapy. Azathioprine has also successfully treated patients who did not respond to high-dose steroids or changes in calcineurin therapy [54]. Similar findings were noted by Andries [55] in whose series, one patient responded to treatment with mycophenolate therapy after relapse following withdrawal of azathioprine. The lack of effect of CNIs was also demonstrated in one study where cyclosporine was withdrawn, and patients subsequently responded to

azathioprine and steroid therapy [56]. Others have suggested that a combination of cyclosporin and everolimus may be effective [57]. The importance of maintenance therapy with steroid therapy was shown in a study comparing treatment with and without steroids [43]. Patients on steroids did well, and all patients treated only with cyclosporine and azathioprine developed cirrhosis of the graft. Steroids were also effective in treating patients who relapsed.

6.4 Conclusions

Recurrent autoimmune hepatitis after liver transplant (rAIH) is defined on the basis of the original indication, autoantibodies and histology. rAIH occurs in about 30–40 % cases but data are difficult to define because of the variation in definitions and in clinical practice to look for recurrent disease. There needs to be a consistent approach to both the diagnosis and detection of disease. This will enable risk factors and therapeutic interventions to be better defined. While most cases respond to increased immunosuppression and increase/introduction of corticosteroids, some progress to graft cirrhosis and failure. Long-term use of steroids may reduce the risk of rAIH.

A syndrome resembling AIH in the graft of patients transplanted for other indications has been determined dnAIH; this is characterised by a plasma cell hepatitis and may represent a form of allograft rejection. Treatment is with increased immunosuppression. As with rAIH, a consistent approach to diagnosis is needed to define more accurately the etiopathogenesis and treatment.

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Chapter 7
Alcoholic Cirrhosis, Transplantation, and Recurrence of Disease

Eric Siskind and Rolf N. Barth

7.1 Introduction

Transplantation for alcoholic liver disease represents the second largest indication for liver transplantation in North America and Europe. Initial concern regarding this indication was that liver transplantation in this patient population would misuse a limited resource of donor organs. Beliefs that post-transplant recidivism would result in poor outcomes were contradicted by early experiences. Widespread adoption of a policy of 6 months of pretransplant sobriety ("6-month rule") as a requirement for liver transplantation has been the predominant approach in the field. More recently, some centers have generated data supporting expanding consideration of liver transplantation for acute alcoholic hepatitis. Rates of recidivism have been stable throughout most reported studies of approximately 30 %. These rates are not substantially influenced by various approaches that complement the 6-month rule. Nonetheless, graft outcomes remain either comparable or improved compared to transplantation for other indications. Liver transplant patients with heavy post-transplant alcohol use have poor outcomes, while less significant use has not been linked to poor outcomes. These patients, however, have long-term outcomes that are compromised by development of malignancy and cardiovascular disease that can be associated with the long-standing alcohol use (and tobacco) that precede liver transplantation.

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7.2 Biology of Alcoholic Liver Disease

The hepatotoxic effects of excessive alcohol ingestion induce both acute and chronic liver disease that can result in end-stage organ disease. Acute effects of heavy alcohol use include fat deposition within hepatocytes and subsequent inflammation and increase in liver enzymes. The histologic findings of acute alcoholic hepatitis include micro- and macrosteatosis, hepatocyte ballooning, neutrophilic infiltrate, and Mallory-Denk bodies [1]. Early histologic changes are first observed in the perivenular region and extend to the portal regions as disease severity increases. Acute alcoholic hepatitis may result in progressive inflammation and necrosis, and often in conjunction with jaundice, ascites, coagulopathy, encephalopathy, and renal dysfunction, and more than 50 % of patients who present with symptomatic alcoholic hepatitis may have preexisting cirrhosis. The greater burden of alcoholic liver disease is recognized in chronic exposure of alcohol consumption that results in subclinical inflammatory changes over years to decades which results in progressive fibrosis and eventually cirrhosis. Patients with both alcoholic cirrhosis and alcoholic hepatitis have worse clinical outcomes when compared to those with alcoholic cirrhosis only [2]. The prevalence of alcoholic cirrhosis is significant worldwide and accounts for the second leading indication for liver transplantation.

7.3 Medical Therapies

There are few effective medical therapies for alcoholic liver disease. In the acute phase of alcoholic hepatitis, pharmacologic therapy may include consideration of steroids or *N*-acetyl cysteine (NAC). Recent data show that pentoxifylline is ineffective when used alone or in combination with prednisolone. Calculation of Maddrey discriminant function scores determined by serum bilirubin and prothrombin times identifies patients whom have higher mortalities and may benefit from steroid therapy [3]. Therapies are generally administered as a 4-week course of prednisolone at 40 mg daily then tapered over an additional 2–4 weeks [4]. About 40 % of patients do not respond to prednisolone, and in those people 6-month mortality is about 70 %. In cases of acute and subacute liver failure, few options exist when the damage is refractory to medical therapy. Supportive measures, including renal replacement therapy, may be administered in combination with these therapies, but consideration of liver transplantation may be the only option for cure when optimal medical therapies fail. Similarly, alcohol-induced cirrhosis has no curative therapy, and management is directed towards the symptoms of decompensation consistent with cirrhosis from other causes. Complete alcohol abstinence is the central component in the treatment of any alcoholic liver disease. In acute settings, this may be accompanied by recovery

of more normalized liver function and significant improvement of symptoms. In chronic settings, alcohol avoidance is necessary to prevent further progressive damage.

7.4 History of Transplant for Alcoholic Liver Disease

The first liver transplants were performed for children with biliary atresia. There was little public objection to this surgical innovation for a pediatric patient population with no other hope of survival. When the application of liver transplantation was broadened as a cure for all patients with end-stage liver disease, transplantation for alcoholic cirrhosis was a subject of considerable controversy. Alcoholism was felt to be self-induced through poor lifestyle choices and carries with it the stigma of association with domestic violence and vehicular manslaughter. Alcoholism was often seen not a disease but a fault. This opinion still prevails among many medical professionals as well [5]. For this reason, liver transplantation for alcoholic cirrhosis was only offered to patients who have demonstrated sobriety.

Studies from patients transplanted in the 1980s supported that outcomes of liver transplantation for alcoholic liver disease were associated with good clinical and social outcomes comparable to other etiologies [6]. While recidivism was observed in 31 % of patient with a median follow-up of 33 months, patients had good overall outcomes. Refusing liver transplantation based on expectations of 100 % abstinence post-transplant was not consistent with evolving outcomes data.

7.5 Listing Criteria and Alcohol Use

Most transplant centers use the "6-month rule," where patients must stay sober for 6 months prior to being listed for transplantation. Since it was introduced in 1990 [7], the 6-month rule has been the most widely used criterion to evaluate patients with alcoholic cirrhosis eligibility for transplantation. This criterion has recently come into question for multiple reasons reflecting the changing landscape of end-stage liver disease and liver transplantation. Since the establishment of the model for end-stage liver disease (MELD) system, livers are preferentially allocated to the patients with highest scores reflecting the greatest medical need. Ideally, lower MELD score patients with alcoholic cirrhosis could demonstrate long periods of sobriety and medical monitoring during pretransplant evaluation. However, it is also possible for patients to first come to medical attention with MELD approaching 40. Some of these patients can be unaware

of the development of advanced liver disease or even cirrhosis, and do not completely understand the general health and hepatotoxic consequences of their alcohol consumption. These patients often cannot demonstrate 6 months of sobriety either because they are too sick to leave the hospital or because their life expectancy is less than 6 months. Even if a patient may survive 6 months, the purported advantage gained by demonstrating sobriety may be offset by transplantation at a later date with a higher MELD and higher risk of postoperative morbidity and mortality. In these cases, a decision must be made whether an individual patient is a viable candidate for transplantation without demonstration of sobriety. The calculus of this determination has heightened gravity as the patient who is not listed for transplantation will likely die. The same can be said for a patient with acute fulminant alcoholic hepatitis that is not responsive to best medical therapy. When a patient's condition does not allow for longer periods of evaluation, multidisciplinary assessment of other factors must be considered to predict the risk of recidivism and successful clinical course post-transplant. Even though it is widely used as a listing criterion, 6 months of pretransplant alcohol abstinence has not consistently predicted recidivism rates post-transplant [8]. It has been shown that incremental periods of sobriety pretransplant decreases post-transplant recidivism; however, no specific length of time of abstinence can be determined to assure post-transplant sobriety [9]. Some reports suggest that length of pretransplant sobriety is only a significant predictor when it is greater than 5 years [10]. The ideal predictive model for liver transplant patient selection in alcoholic cirrhosis has not been clearly defined.

The "6-month rule" is based on the presumption that during this time the patient will participate in the treatment of alcoholism. In cases where there is no time to treat alcoholism pretransplant, the likelihood of success of disease treatment post-transplant should be determined. Like other diseases, severity can be ascertained by analyzing other comorbid conditions. Patients with preexisting psychiatric disease or polysubstance abuse are at risk for recurrence. Similarly, patients who have strong family history of alcoholism, specifically a first degree relative with alcoholism have higher rates of disease recurrence [11]. There are also higher rates of disease recurrence for patients who are not married, live alone, and have poor social support from other means [12]. Smoking has also been identified as a risk factor for recurrence of disease, and patients should be counseled on tobacco cessation [13].

The 6-month rule has been adopted by most transplant programs as an effort by the majority of liver transplant programs to select patients with alcoholic cirrhosis that are deemed eligible for transplantation [14]. The 6-month rule has also been acknowledged by the United Network for Organ Sharing as criteria for listing patients for liver transplantation [15]. Nonetheless, bioethicists have provided contradictory guidance to strict adherence to application of a 6-month rule in consideration for liver transplantation [16]. While consideration of patients with acute alcoholic hepatitis may occur in the current era, these cases are approached on a case-by-case basis, and many centers com-

Table 7.1 Factors in consideration when listing patients for liver transplant for acute alcoholic liver disease

Medical factors
Failure of medical therapy
Probability of survival without transplant
MELD score
Pulmonary status
Renal failure
Infection
Surgical factors
Probability of survival with transplant
Age
BMI
Technical complexity (anatomic considerations, prior operations)
Social factors
Family support
Employment
Legal history related to alcohol
Polysubstance use
Insurance status (approval requirements by medical directors)
Contract for rehabilitation

The combination of clinical factors predicting extremely poor outcomes without transplant (medical), and good outcomes after liver transplant (medical and surgical) are weighed with overall context of the social factors that may predict the ability to lead productive life and care for liver allograft post-transplant

pletely defer. Relevant factors for consideration by the listing committee include the current medical condition and potential for survival without transplant (Table 7.1). The social factors that are predictive for the patient to lead productive life and care for liver allograft post-transplant are balanced with the medical considerations.

Another consideration of patients who present with decompensated alcoholic cirrhosis and high MELD score is that their disease may not be entirely due to cirrhosis. For patients with alcoholism and obesity, alcoholic cirrhosis can coexist with nonalcoholic steatohepatitis, and leads to a more precipitous clinical deterioration [17]. A patient may have a long-standing history of NASH that has been undiagnosed and can be pushed to fulminant hepatic failure or decompensated cirrhosis by acute drinking episodes. In these cases, a 6-month waiting period may not be warranted if the patient's decompensation is due to NASH rather than alcoholism.

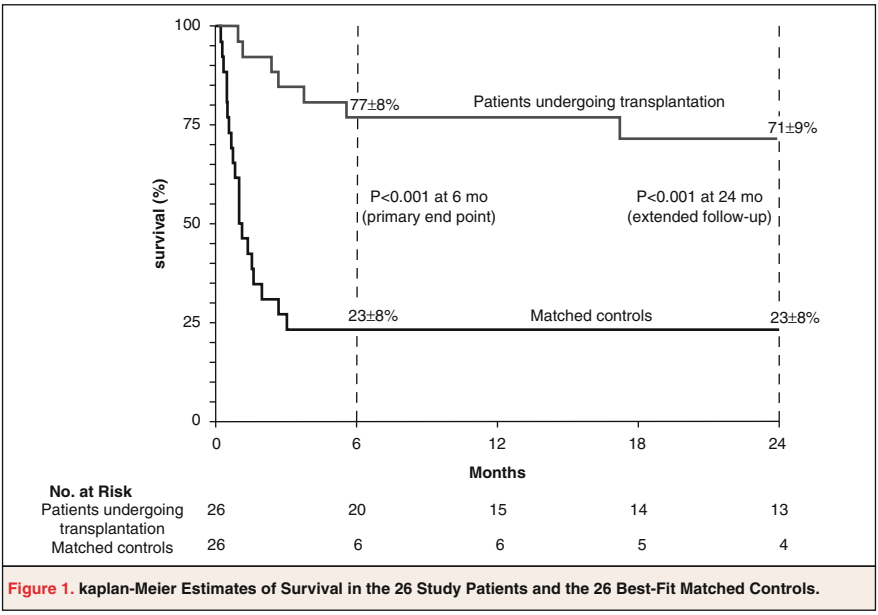


Fig. 7.1 Kaplan–Meier survival of liver transplant versus medical therapy for alcoholic hepatitis. Significant early and durable survival benefit is offered by liver transplantation to patients who do not respond to medical therapy for alcoholic hepatitis. NEJM 2011, 365: 1790–1800

7.6 Acute Alcoholic Hepatitis

The recent publication of clinical outcomes of liver transplantation for alcoholic hepatitis, who failed medical therapy, has validated the durable survival benefit of transplant compared to medical therapy [18]. This study selected 26 patients (failed prednisolone therapy, and had Lille score >0.80) that were highly selected based on medical and social evaluations and represented less than 2 % of patients evaluated with alcoholic hepatitis. The impressive survival benefit at 6 months for liver transplant (77 %) versus matched controls on continued supportive therapy (23 %, $p < 0.001$) confirmed the clinical knowledge of the excellent outcomes of transplantation for this disease (Fig. 7.1). The authors reported that with 2 years of follow-up, only 3 of the 26 had recidivism. One stopped with intervention and none had detectable graft dysfunction.

In the most severe cases of alcoholic hepatitis that result in renal failure requiring renal replacement therapy, the results of medical therapy almost universally fail. The near 100 % mortality of these patients further enhances the survival benefit of liver transplantation [19]. In these patients, the theoretical ability to demonstrate a period of sobriety that would reduce recidivism post-transplant is not only unlikely, but would necessitate the additional requirement for combined liver and kidney transplantation. The use of two organs in these patients to achieve

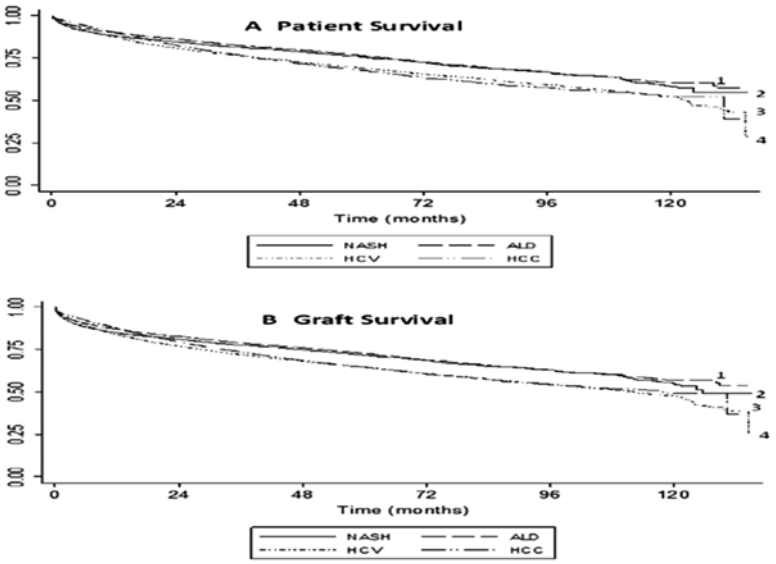


Fig. 7.2 Liver allograft and patient survival post-transplant by disease etiology. Liver transplantation for alcoholic liver disease (ALD) and non-alcoholic steatohepatitis (NASH) demonstrate superior graft (**a**) and patient survival (**b**) as compared to etiologies of hepatitis C (HCV) and hepatocellular carcinoma (HCC). From Wong RJ *et al*. Clin Transplant. 2014 Jun;28(6):713–21

limited sobriety pretransplant is challenged by the high probability of renal recovery with early isolated liver transplantation. Taking these organs away from the long list of nearly 100,000 patients awaiting renal transplantation is further challenge to approaches to alcoholic liver disease that come at the cost of concomitant renal failure.

7.7 Clinical Outcomes

The discussion of liver transplantation for alcoholic cirrhosis must be placed in the context for liver transplantation for other diseases. According to the most recent UNOS data, 5-year patient survival and graft survival was 76.5 and 72.8 % for patients transplanted for alcoholic cirrhosis. These outcomes were better than those for hepatitis C, hepatocellular carcinoma, and nonalcoholic steatohepatitis [20]. The improved outcomes have been most consistently demonstrated within the first 5 years after transplant (Fig. 7.2).

Some recent data suggest a poorer outcome beyond 5 years for patients transplanted for alcoholic liver disease [21]. Although these patients had similar rates of graft failures before and after 5-year time periods, the overall long-term survival was worse, but it was not related to recidivism or graft-related issues. The

poor long-term survival is likely associated with the medical conditions that may accompany alcohol-induced cirrhosis that require unique attention compared to etiologies for other liver disease. These patients are at increased risks for head and neck, esophageal, and lung malignancies, and require lifelong monitoring because of this overall risk [12]. Reports support that up to 40 % of patients transplanted for alcoholic liver disease will also resume smoking tobacco post-transplant [22]. These patients often resume smoking early post-transplant, and thus increase their risk of cardiovascular and malignant disease. Thus, monitoring and treatment for tobacco dependency is highly relevant in this patient population. Head and neck squamous cell cancers are specifically increased in patients transplanted for alcoholic liver disease and occur in up to 5 % of patients with overall survivals at 1, 3, and 5 years of 74, 47, and 34 % [23]. The risk of head and neck cancer increases incrementally with the addition of tobacco use. Alcoholism treatment both pre- and post-transplant has been centered on psychological and social surveillance and counseling. Efforts should be expanded to encourage tobacco cessation in this susceptible population.

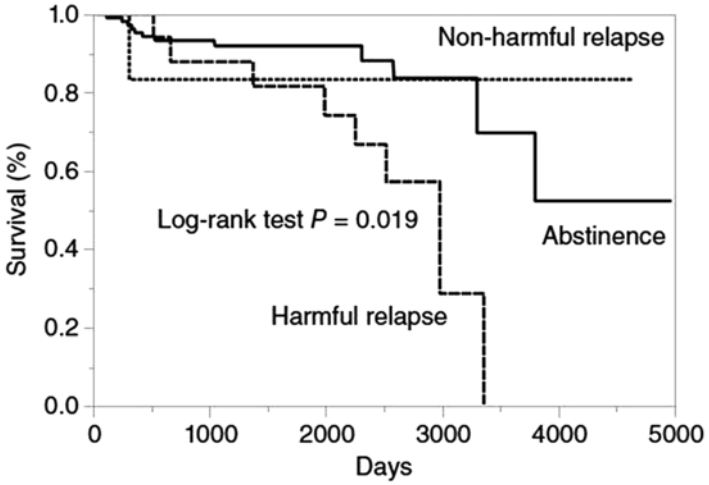
7.8 Recidivism

Liver transplantation in the context of the 6-month rule still is associated with 20–30 % patients returning to significant alcohol consumption [24]. More specific investigations of patterns alcohol use provide greater insight into overall burden and subsequent problem of alcohol consumption post-transplant. Self-reporting surveys of liver transplant patients from Finland demonstrated that overall 43 % of liver transplant recipients transplanted for any cause used alcohol post-transplant and 28 % had consumed within the last month [25]. These rates were similar to liver transplant recipients transplanted for alcoholic liver disease who reported rates of 39 % for any alcohol use and 34 % within the last month. These rates of alcohol use were similar to societal patterns within Finland. Another study from Sweden reported a 33 % rate of recidivism. Recidivism rates were equivalent whether or not the transplant recipient had a 6-month period of sobriety preoperatively. Interestingly, resumption of drinking was not associated with increased mortality or graft loss. Repeat biopsies revealed mild steatosis without recurrence of cirrhosis. Morbidity and mortality was more commonly associated with the development of aerodigestive malignancy [26]. In another study, approximately 25 % of deceased donor transplant recipients acknowledged alcohol relapse with associated laboratory abnormalities, but the laboratory values normalized to pre-relapse values after ceasing alcohol intake [27]. Only one of 16 of these patients demonstrated histologic evidence of toxic liver damage related to alcohol.

Living donor liver transplant recipients demonstrate similar patterns of recidivism. A study of living donor liver transplant recipients from Japan demonstrated an

Table 7.2 Quoted rates of recidivism post-transplant

Endnote number	Study	Study population	Rate of recidivism post-transplant (%)
6	Berlakovitch	*N* = 58, Austria	31
9	Dimartini	*N* = 167, USA	42
25	Lim	Meta-analysis	20–30
26	Koljonen	*N* = 207, Finland	39
27	Björnsson	*N* = 103, Sweden	33
29	Egawa	*N* = 195: 187 living donor, 5 deceased donor, 3 domino. Japan	23
32	Hilke	*N* = 31, Germany	32



Number at risk	0 y	3 y	5 y	7 y	10 y
Abstinence	108	65	39	22	4
Non-harmful relapse	6	4	2	1	1
Harmful relapse	18	14	11	5	1

Fig. 7.3 Kaplan–Meier survival after living donor liver transplantation as influenced by alcohol relapse. Post-liver transplant patient survival was significantly worsened in patients with harmful relapse compared to either abstinent or non-harmful relapsing patients. From Egawa H *et al.* Hepatol Res. 2014 Dec;44(14):E428–36

overall relapse rate of 23 % defined by self and physician reporting (see Table 7.2 for summary of recidivism rates). Harmful alcohol use defined as histologic damage, biochemical abnormalities, or mental health consequences was associated with significantly worse outcomes (Fig. 7.3) [28]. Interestingly, non-harmful relapse was not associated with poor outcomes in this study.

Table 7.3 Multivariate logistic regression model for prediction of relapse to any alcohol use after liver transplant

Predictor variable	Regression coefficient	Odds ratio (95 % CI)	*P*
Presence of hepatocellular carcinoma	−1.89	0.15 (0.06, 0.40)	<0.001
Tobacco dependence	2.24	2.46 (1.18, 10.65)	0.01
Continued alcohol use after liver disease diagnosis	1.80	1.79 (1.13, 3.27)	<0.001
Low motivation for relapse prevention treatment	1.62	1.59 (1.06, 2.41)	0.02
Poor stress management skills	1.31	3.61 (1.09, 14.12)	0.049
Lack of a rehabilitation relationship	1.67	2.09 (1.13, 4.65)	0.04
Limited social supports	1.59	3.02 (1.72, 10.19)	0.03
Lacks nonmedical behavioral consequences	1.89	6.15 (1.23, 18.42)	0.01
Continued engagement in social activities with alcohol present	2.31	8.77 (2.01, 42.17)	0.004

From Rodrigue JR et al. Prog Transplant. 2013 Dec;23(4):310–8
Significant factors that have been associated with alcohol use and odds ratio of increased risk

Monitoring for recidivism can be challenging for the transplant team. Traditional assessments of patient interview and urine or blood screening are most commonly utilized. Risk stratification scoring systems, such as the Alcohol Relapse Risk Assessment have been used as valid predictive tools to identify patients at risk for alcoholism recurrence post-transplantation (Table 7.3) [29]. Nine independent variables are identified to predict post-transplant relapse, with higher scores associated with greater recurrence frequency and intensity. Another scoring system is the High Risk Alcoholism Relapse Scale, which assesses drinking severity pretransplant to determine the risk of relapse post-transplant. Higher scores were associated with greater rates of recidivism (Table 7.4) [30]. Recidivism rates often decrease with time since transplant (see Figs. 7.4, 7.5, and 7.6).

Measurements of hair samples for ethyl glucuronide (hEtG), a metabolite of ethanol, provide a highly accurate way to detect alcohol consumption and quantitative data regarding the amount of alcohol consumed [31]. Studies with this technique detected that 32 % of patients transplanted for alcoholic liver disease, and 8 % of nonalcoholic liver disease patients consumed alcohol post-transplant. This highly accurate technique is rarely employed, but nonetheless contrasted highly unreliable methods of patient self-reporting (27 % sensitivity), and physician assessments (64 % sensitivity).

Alcohol consumption is indeed self-induced; however, alcoholism is not. Extensive research and experience in the field of addiction psychiatry has properly defined alcoholism as a disease. A patient who continues to drink alcohol post-transplant may be better characterized as having recurrence of disease rather than recidivism. Even after an alcoholic stops drinking, their disease may require continued treatment. The best treatment for alcoholism includes a multidisciplinary

Table 7.4 High-risk alcoholism relapse score

Item	Score
Duration of heavy drinking, *y*	
≤11	0
11–25	1
≥25	2
Daily drinks, no.[a]	
≤9	0
9–17	1
≥17	2
Prior alcoholism inpatient treatments, no.	
0	0
1	1
≥	2

De Gottardi A et al. Arch Intern Med. 2007 Jun 11;167(11):1183–8
Pretransplant alcohol abuse patterns are identified and scored to give cumulative scores that are associated with higher risk of recidivism as the scores increase

[a]One drink = 12 g of ethanol

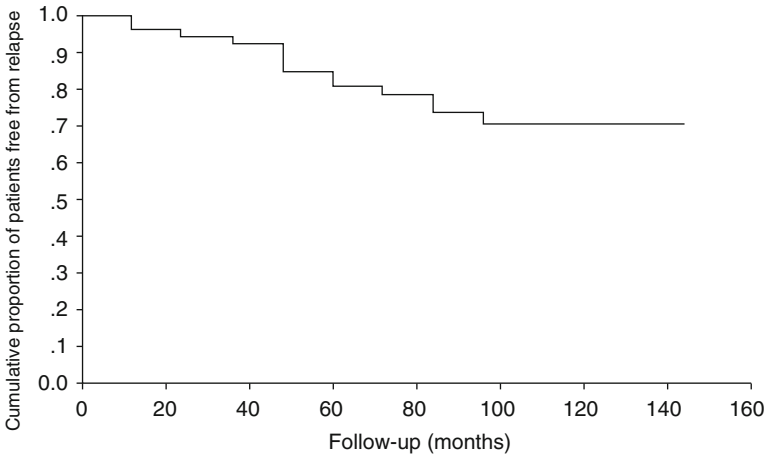


Fig. 7.4 Cumulative proportion curve for the risk of alcohol relapse during follow-up. Cuadrado A, Fábrega E, Casafont F, Pons-Romero F. Alcohol recidivism impairs long-term patient survival after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl. 2005 Apr;11(4):420–6

approach where the entire transplant team is engaged. Surgeons, hepatologists, psychiatrists, social workers, and nursing staff can all provide guidance and support. A psychiatrist with experience in treating addiction can be most helpful in assessing what programs and interventions would be most helpful for each individual patient [32]. Programs such as Alcoholics Anonymous have also shown to be effective.

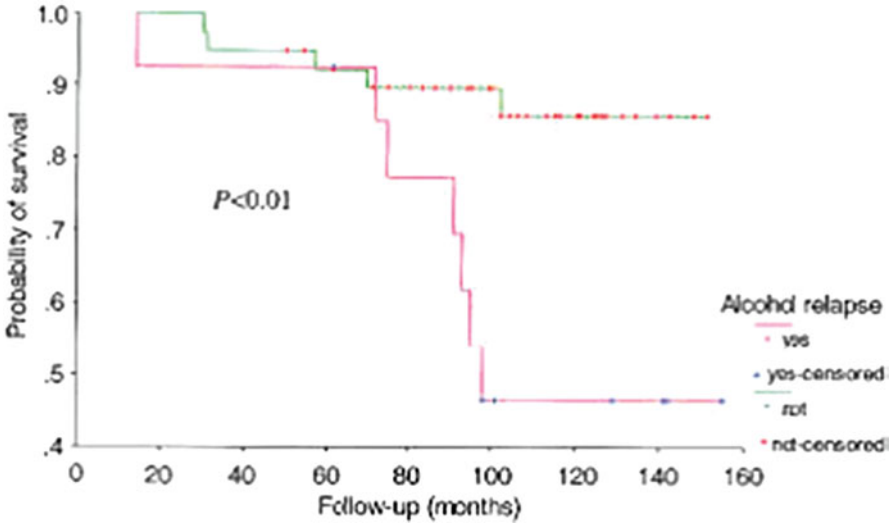


Fig. 7.5 Kaplan–Meier survival curves for patients with alcoholic liver disease, with or without alcohol recidivism [40]

7.9 Recurrence of Liver Disease Associated with Recidivism

Alcohol consumption is associated with abnormal biochemical testing among liver transplant recipients [25, 26]. Studies of patients who resume significant alcohol use post-transplant confirm accelerated and recurrent liver disease [33]. However, available data supports an important distinction between excessive drinking and any amount of drinking. While all transplant physicians would recommend complete abstinence from alcohol after liver transplantation, it has not been established that casual or sporadic alcohol consumption increases the risk of graft loss. Continuous heavy drinking at the level of abuse consistent with pretransplant patterns has clearly been associated with graft loss (hazard ratio of 2.4) and decreased survival (see Fig. 7.7). Common definitions of abusive drinking are alcohol consumption greater than 60 g per day (approximately 4–5 drinks) consumption leading to mental decompensation, or histological damage [30]. Graft loss was related to medication noncompliance due to intoxication, leading to greater episodes of rejection. Comparisons of alcoholic liver disease patients to non-hepatitis C liver transplant recipients demonstrated highly significant associations of alcohol relapse with histological evidence of steatosis (odds ratio 3.5), steatohepatitis (odds ratio 6.2), and advanced fibrosis of stage 3 or greater (odds ratio 23.2).

The return to heavy-drinking post-transplant is linked to very poor outcomes. One study that evaluated 68 patients transplanted for alcoholic liver disease, revealed that 8 % (6 patients) returned to heavy drinking post-transplant, and that 3 of these patients died within 4 years with evidence of alcoholic hepatitis and bridging fibrosis or cirrhosis [34]. The presence of steatosis or Mallory bodies in the explanted native liver at the time of transplant was demonstrated to be predictive of a return to

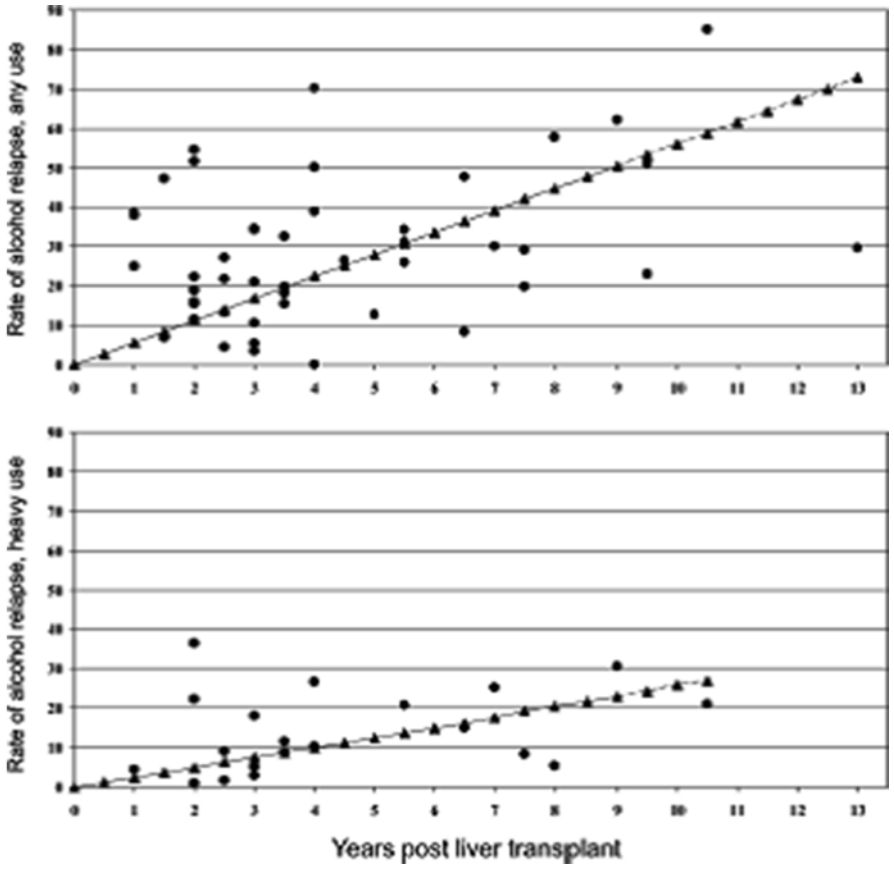


Fig. 7.6 Rate of alcohol relapse as a function of time since transplant [41]

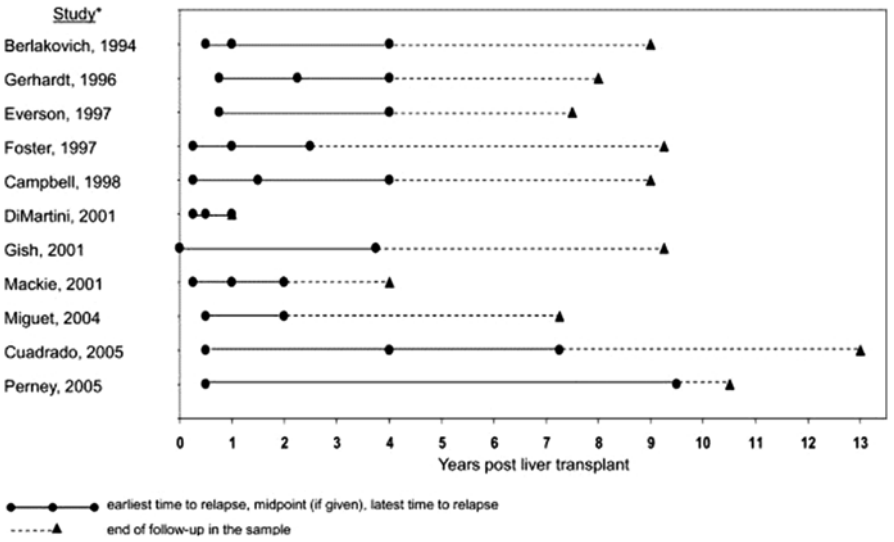


Fig. 7.7 Time to alcohol relapse after liver transplant based on meta-analysis data [41]

heavy drinking. Estimates of drinking postoperatively are approximately 30 %, with the harmful alcohol use in the range of 16–19 % [35].

Alcohol is also a primary cause of hepatocellular carcinoma in European and North American studies. Studies have estimated that 32–45 % of hepatocellular cancers are related to alcohol as a causative agent [36]. While the genotoxic and cirrhosis-related risks from alcohol may be eliminated after transplantation, standard recommendations regarding follow-up of patients with tumors apply. Risks of tumor recurrence exist consistent with other etiologies and dependent on certain pathologic features of explanted tumors.

Transplant centers may attempt numerous methods to try and reduce recidivism. Nonetheless, attempts to mitigate recidivism by contracting with the patient written agreements regarding post-transplant sobriety have demonstrated little or no effect on post-transplant alcohol consumption [37]. More aggressive pharmacologic approaches have been attempted in non-transplant patients including implantable naltrexone in problematic alcohol use resulting in hospital admission [38]. The use of implantable naltrexone was associated with decreasing the costs of readmissions by over 50 %, and a significant reduction in emergency room costs over 6 months of use.

Preventing the damage of excessive alcohol exposure or reversal of the hepatotoxic effects has made few significant breakthroughs. Recent data generated in a rodent model demonstrated that zeaxanthin (an antioxidant that naturally can occur in vegetables) was effective in reducing the accumulation of fat, oxidative stress, inflammation, and apoptosis [39]. This model utilized oral treatment with zeaxanthin dipalmitate after 5 weeks of heavy alcohol ingestion. Clinical trials have not been conducted.

7.10 Conclusions

Alcoholic liver disease is a leading indication for liver transplantation. Clinical indications are evolving beyond strict adherence to a rule of 6 months of sobriety. Rates of recidivism are relatively fixed at approximately 30 % and recurrent disease in the liver is limited to the minority who resume significant and abusive patterns of alcohol consumption. Longer term outcomes are challenged by increased risks of cardiovascular and aerodigestive malignant disease associated with alcohol and tobacco. Psychological and social surveillance and counseling should focus on both alcohol and tobacco use in this susceptible population.

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Chapter 8
Recurrence of Primary Sclerosing Cholangitis After Liver Transplantation

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Abbreviations

ACR	Acute cellular rejection
CMV	Cytomegalovirus
GWAS	Genome-wide association study
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
OKT3	Orthoclone
PBC	Primary biliary cirrhosis
PSC	Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease characterized by diffuse inflammation and fibrosis that can involve the entire biliary tree. Population-based studies observed annual incidence rates ranging from 0.9 to 1.3 per 100,000 population [1–3]. The pathogenesis of PSC remains unknown, but it is established as being immune mediated, occurring in genetically predisposed individuals and strongly associated with inflammatory bowel disease (IBD), which often runs an independent course from the liver disease [4]. The clinical presentation of PSC is variable. Patients frequently present without symptoms, but many develop progressive biliary strictures, leading to recurrent cholangitis and

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ultimately end-stage liver disease. To date, no medical therapy has yet been proven to prolong survival or improve outcome of PSC [5]. Liver transplantation remains the only effective therapeutic option for patients with advanced liver disease from PSC. It is estimated that PSC accounts for approximately 4–5 % of adult liver transplantations performed each year in Europe and the United States [6, 7]. As the long-term outcome of PSC patients following liver transplantation continues to improve, reaching over 80 % at 5 years [7], there appears to be an increase in the number of patients developing recurrent PSC, which has emerged as clinically and academically important. In this chapter, the authors review diagnostic criteria, epidemiology, risk factors, graft and patient survival, and treatment of recurrent PSC after liver transplantation.

8.1 Diagnostic Criteria and Epidemiology of Recurrent PSC

Recurrent PSC usually manifests more than 1 year after liver transplantation as elevation of alkaline phosphatase and gamma glutamyl transpeptidase. The diagnosis of recurrent PSC can be challenging, as biliary strictures in the allograft suggesting recurrent disease are nonspecific and a variety of potential insults to the hepatic graft may result in biliary injury and stricturing. In particular, nonanastomotic biliary strictures in the liver allograft can occur because of the use of an ABO-incompatible allograft, chronic rejection, biliary tract infection, hepatic artery thrombosis, preservation injury, and prolonged cold ischemic time [8, 9]. Nonanastomotic intrahepatic strictures developing before 90 days after transplantation are usually not attributable to recurrent disease. The diagnosis of recurrent PSC can be difficult to establish with certainty and is therefore dependent on extensive histological and radiographic evaluation. Previously, a set of criteria has been proposed by a group of investigators from the Mayo Clinic [10] to serve as a uniform clinicopathologic standard for the diagnosis of recurrent PSC as shown in Table 8.1. The diagnostic criteria consist of a confirmed diagnosis of PSC before liver transplantation; cholangiogram showing nonanastomotic biliary strictures occurring 90 days after liver transplantation; exclusion of other conditions associated with biliary strictures; and/or liver biopsy showing fibrous cholangitis and/or fibro-obliterative lesions. Thereafter, these diagnostic criteria have been increasingly used as the standard tool for diagnosis of recurrent PSC.

A diagnosis of recurrent PSC can be made by means of cholangiography revealing nonanastomotic biliary strictures of the intrahepatic and/or extrahepatic biliary tree with beading and irregularity, occurring more than 90 days post-transplantation. However, assessing the bile ducts via the endoscopic route after liver transplantation for PSC is usually not feasible because most recipients have a Roux-en-Y loop rather than a duct-to-duct anastomosis. Given recent and considerable improvement of magnetic resonance imaging technique with its noninvasive nature, magnetic resonance cholangiography (MRC) has become the first choice to evaluate abnormalities of the biliary tract following liver transplantation, instead of percutaneous

Table 8.1 Diagnostic criterion for recurrent primary sclerosing cholangitis after liver transplantation

Inclusion criteria	Exclusion criteria
Confirmed diagnosis of primary sclerosing cholangitis before liver transplantation	Hepatic artery thrombosis or stenosis
And	Chronic ductopenic rejection
Cholangiographic evidence of intrahepatic and/or extrahepatic biliary stricturing, beading, and irregularities more than 90 days after liver transplantation	Anastomotic strictures
Or	Nonanastomotic strictures less than 90 days after liver transplantation
Histological evidence of fibrous cholangitis and/or fibro-obliterative lesions with or without ductopenia, biliary fibrosis, or biliary cirrhosis	ABO incompatibility between donor and recipient

Note: This table has been adapted from Graziadei et al. Recurrence of primary sclerosing cholangitis following liver transplantation. *Hepatology*. 1999; 29: 1050–1056

transhepatic cholangiography. MRC has been validated as an imaging modality to accurately assess the degree of biliary strictures with identification of mural irregularities and diverticulum-like outpouchings specific of PSC [11]. However, in the transplant setting, emphasis must be put on exclusion of other etiologies that can cause similar cholangiographic change. In a published series by Brandsaeter et al., a thorough examination with magnetic resonance angiography revealed a high rate of hepatic artery thrombosis and hepatic artery stenosis that explain some of the biliary stricture after liver transplantation in the non-PSC cohort [12]. Thus, apart from its assistance in diagnosing recurrent PSC, magnetic resonance imaging is of value for identifying a differential diagnosis of vascular complications.

Histopathological findings suggestive of PSC recurrence are identical to those described in the native liver with PSC. The early features in recurrent PSC are characterized by mild nonspecific cholangitis; acute and chronic "pericholangitis" often accompanied by a mild type 1 ductular reaction involving a variable percentage of portal tracts. As the disease progresses, increased ductal proliferation and neutrophilic and eosinophilic inflammation in the portal tract and periportal edema become apparent [13]. Other chronic cholangiopathic features including intralobular foam cell clusters and marked deposits of copper with Mallory's hyaline in periportal hepatocytes may be visualized [13]. In the late stage, the typical features of fibro-obliterative lesions may be observed with focal loss of medium and small bile ducts. However, similar changes can be seen with other causes of bile duct injuries in the allograft. Such an overlap particularly with chronic rejection questions the validity of liver histopathology as a sole definition of PSC recurrence. Histologically, the diagnostic criteria for chronic rejection are as follows: (1) senescent changes (including cytoplasmic eosinophilia, cell enlargement and multinucleation, uneven nuclear spacing, loss of polarity), affecting a majority of the bile ducts with or without bile duct loss; (2) convincing foam cell obliterative arteriopathy; or (3) bile duct

loss affecting greater than 50 % of the portal tracts [14]. In a transplant study by Jeyarajah et al., histopathologic analysis suggests that chronic rejection and recurrent PSC represent a spectrum of indistinguishable disease [15]. However, the distinct difference in clinical outcome, as evidenced by an increased repeat transplantation rate and lower graft and patient survival in PSC recipients with chronic rejection, clearly suggests that they are two distinct entities that require very different treatment strategies [15]. A history of suboptimal immunosuppression and severe or unresolved acute rejection constitute strong arguments in favor of diagnosing chronic rejection. Therefore, a definitive diagnosis of recurrent PSC mandates documentation of the characteristic cholangiographic findings combined with compatible histological features after exclusion of the other possible causes of biliary strictures.

Recurrence of PSC in the hepatic graft was first reported by Lerut et al., in 1988 [16]. Despite controversy that followed shortly after this concept was introduced; the recognition of recurrent PSC is now firmly established in the liver transplant community. The reported cumulative incidence of recurrent PSC has ranged from 10 to 55 % of the transplanted grafts with a median time to recurrence ranging from 8 to 68 months as shown in Table 8.2 [10, 12, 15, 17–25]. The variation is related in part to differences in diagnostic criteria and duration of follow-up. The use and timing of the protocol applied to detect biliary strictures and/or liver histology appears to be the most important factor for the disparity in the reported cumulative incidence of recurrent PSC. Considering that cholangiographic and histologic features of recurrent PSC are not correlated with biochemical indices, protocol liver biopsies, and cholangiography with a magnetic resonance technique may allow systemic and noninvasive evaluation of recipients with possibly full documentation of disease recurrence.

8.2 Risk Factors Related to Pathogenesis for Recurrent PSC

Reappearance of PSC in the liver allograft suggests that the mechanisms that lead to the initial development of the disease persist after liver transplantation. This would provide a wonderful opportunity to learn about the pathogenesis of the disease. However, factors determining disease development in the post-transplantation situation have been studied only to a limited extent. Several transplant groups have attempted to identify peritransplantation variables that may predict patients who will develop recurrent PSC. The results in general have been heterogeneous. Potential risk factors associated with disease recurrence included recipient age [15], male gender [26], donor-recipient gender mismatch [17], human leukocyte antigen (HLA)-DR1*08 [21], coexistent IBD [20], intact colon before transplantation [22, 26], episodes of acute cellular rejection (ACR) [21, 24], steroid-resistant ACR [12], orthoclone (OKT3) therapy for steroid-resistant ACR [18], maintenance steroid therapy for greater than 3 months post-transplantation [20], the presence of cholangiocarcinoma before transplantation [19], and concurrent cytomegalovirus (CMV)

Table 8.2 Cumulative incidence, risk factors, and outcomes of recurrent primary sclerosing cholangitis after liver transplantation

Authors, year	Cohort size	Follow-up period	Cumulative incidence	Risk factors for recurrence	Outcomes of PSC recurrence		
					5-year patient survival (PSC recurrence vs. non-recurrence)	5-year graft survival (PSC recurrence vs. non-recurrence)	Re-OLT
Jeyarajah et al. (1998) [15]	100	21 months (mean)	18 (18 %)	ACR	76 % vs. 89 %	65 % vs. 76 %	5/18
Graziadei et al. (1999) [10]	120	55 months (mean)	24 (20 %)	NA	Unchanged (86 % vs. 91 %)	Unchanged (79 % vs. 82 %)	2/24
Khettry et al. (2003) [17]	42	24–168 months (range)	6 (14.3 %)	Recipient-donor mismatch	NA	NA	None
Kugelmas et al. (2003) [18]	71	14–91 months (range)	15 (21.1 %)	OKT3 use	Unchanged (92 % vs. 86 %)	NA	NA
Brandsaeter et al. (2005) [12]	49	77 months (median)	9 (18 %)	Steroid-resistant ACR	NA	NA	NA
Campsen et al. (2008) [19]	130	66 months (median)	22 (16.9 %)	Cholangiocarcinoma before OLT	45 % without re-OLT	NA	7/22
Cholangitas et al. (2008) [20]	53	11 months (median)	7 (13.2 %)	Steroid use for ulcerative colitis >3 months post-OLT	Unchanged (85 % vs. 76 %)	NA	3/7
Alexander et al. (2008) [21]	69	50 months (median)	7 (10 %)	ACR, steroid-resistant ACR, HLA-DRB1*08	NA	NA	NA
Alabraba et al. (2009) [22]	230	82.5 months (median)	54 (23.5 %)	Intact colon at the time of OLT	Decreased in PSC recurrence	NA	11/54

(continued)

Table 8.2 (continued)

Authors, year	Cohort size	Follow-up period	Cumulative incidence	Risk factors for recurrence	Outcomes of PSC recurrence		
					5-year patient survival (PSC recurrence vs. non-recurrence)	5-year graft survival (PSC recurrence vs. non-recurrence)	Re-OLT
Egawa et al. (2009) [23]	20	63 months (median)	11 (55 %)	CMV injection within 3 months	NA	NA	6/20
Moncrief et al. (2010) [24]	59	68 months (median)	15 (25 %)	ACR, CMV mismatch	Unchanged	Unchanged	4/15
Egawa et al. (2011) [25]	114	42 months (median)	26 (27 %)	High MELD score, first-degree-relative donors, CMV infection, early biliary anastomosis complication	NA	39 % vs. 74 %	11/26

PSC primary sclerosing cholangitis, *ACR* acute cellular rejection, *NA* not assessed, *OKT3* orthoclone, *HLA* human leukocyte antigen, *CMV* cytomegalovirus, *MELD* model for end-stage liver disease

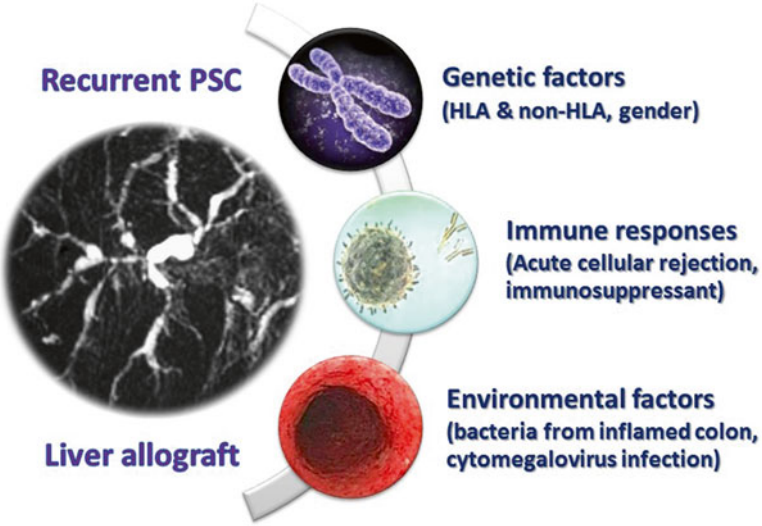

Fig. 8.1 Risk factors related to pathogenesis of recurrent primary sclerosing cholangitis

infection in the recipient [24]. The reasons for these discrepant findings among these studies may be due to the small number of patients with recurrent disease as well as the differences in the study design, the diagnostic criteria, and the interesting and confounding variables considered in the regression model.

Although the pathogenesis of PSC remains unclear, epidemiological and laboratory studies consistently indicate that PSC is a complex autoimmune disorder resulting from the interaction between genetic and environmental factors [27] as proposed in Fig. 8.1. In the last decade, there have been major efforts to delineate the genetic architecture of this condition. Recently, genome-wide association studies (GWAS) and immunochip-based studies identified numerous risk loci for PSC that host genes involved in innate or acquired immune responses [28–34], consistent with an autoimmune component to pathogenesis. Also, GWAS have clearly demonstrated that the major component of the genetic architecture of PSC is within the HLA region. To some extent, the genetic findings from non-transplant setting may guide the discovery of interacting and coexisting environmental susceptibility in PSC patients who developed recurrent disease after liver transplantation. The prognostic relevance of the particular HLA genes that confer recurrent PSC after liver transplantation was investigated by many investigators [15, 21]. In a report from the University of Washington transplant group, the overall frequency of the HLA-DRB1*03, DQB1*02 haplotypes among their PSC recipients was higher than that among donor populations, and this confirms that this genotype is more commonly expressed in patients who have PSC [21]. However, there was no difference in the frequency of this HLA haplotype between patients with recurrent PSC and those not having recurrence, and this suggests that the recipient HLA-specific haplotype represents a genetic predisposing factor rather than an antigen for immune

recognition in disease development. Interestingly, there was a higher incidence of HLA-DRB1*08, particularly in the absence of HLA-DQB1*04, in their recipients that eventually developed recurrent disease than in those that did not [21]. However, more work is required to confirm candidate genes, to evaluate the functional consequences of risk variants, and to understand how functional changes contribute to disease-specific pathologies. If the association between HLA haplotypes and risk of disease recurrence is validated in further studies, HLA typing would be useful in donor selection as well as to provide valuable prognostic information at the time of transplantation.

Of great interest is the reported higher rate of disease recurrence in 114 Japanese recipients of grafts from living-related donors, with recurrent PSC occurring in 32 % at 5 years and 52 % at 10 years after transplantation [25]. A potential explanation may be the first-degree-relatives and sibling have a prevalence of PSC about 100-fold that of nonrelatives [35]. Another possible mechanism contributing to the effect of first-degree-related donors might be linked to the effect of a shared genetic disposition in blood-related recipient and donor pairs including the HLA system. However, the incidence of recurrent PSC in recipients with grafts from related donors other than parents as well as nonrelated donors was similar to those reported for deceased donor liver transplantation [10, 12, 17–22, 26].

The pathogenesis of recurrent PSC could hypothetically be linked to autoimmunity, cross-sensitization between biliary and colonic antigens due to common epithelial epitopes, or leak of bacterial toxins from the inflamed colon with genetic predisposition [36]. The leaky theory is supported by observation of the absence of inflammation in the colon, either due to the absence of concurrent IBD or colectomy before or at the time of liver transplantation has a protective effect against disease recurrence [20, 22, 26]. This was first reported in a study by Vera et al., which demonstrated a dramatic reduction in the risk of PSC recurrence if the colon was removed before or during transplantation [26]. This finding was considerably strengthened in a study by Cholangitas et al., in which no PSC patients without ulcerative colitis or those undergoing pretransplant colectomy developed recurrent PSC [20]. The protective effect of colectomy before or during liver transplantation on the risk of developing recurrent PSC was confirmed in the largest prognostic study of recurrent PSC involved 230 consecutive adult patients who underwent liver transplantation for PSC [22]. Taken together, these findings are consistent with the hypothesis of aberrant homing of mucosal lymphocytes to the liver in the development of PSC [36] that may also be relevant in recurrent PSC. Importantly, these data should not be interpreted as an advocation for pretransplant colectomy but rather as input to understanding the mechanism of developing recurrent PSC.

The susceptibility of the transplanted liver to recurrent PSC may be influenced by the use of immunosuppression. A previous study by Kugelmas et al. [18] of immunosuppression after liver transplantation showed that disease recurrence was often seen in recipients who received maintenance corticosteroids, but the time to recurrence was not associated with length of corticosteroid administration. This was emphasized by published observation from the Royal Free Hospital transplant group showing that maintenance corticosteroids after liver transplantation were

associated with an increased risk of recurrent PSC [20]. The reason for this correlation remains unclear, whether it is greater immunosuppression, associated with graft rejection, or opportunistic (yet undefined) biliary infections, which may be from a leaky mucosa in IBD that leads to recurrence. On the basis of a higher likelihood of recurrent PSC and adverse metabolic consequences in patients exposed to corticosteroids chronically, early corticosteroid withdrawal should be recommended in the management of these recipients. This, however, must be weighed against the need for corticosteroids for control of graft rejection or colitis in patients with coexistent IBD. Furthermore, differences in the type of immunosuppression used after transplantation have been hypothesized to be related to the risk of recurrent PSC; however, no such effect has been observed [20, 22]. Also, no beneficial effect has been found according to post-transplant use of ursodeoxycholic acid (UDCA) [22].

The association between ACR and recurrent PSC has arisen because ACR may increase autoimmune epitopes that can lead to ductal damage. In a reported transplant series by Jeyarajah et al., they found a significantly higher incidence of ACR in recipients that later developed recurrent PSC [15]. Also, the University of Washington transplant group found ACR, particularly steroid-resistant ACR, as an increased risk for recurrent PSC [21]. However, it is unclear whether recurrent PSC results from a response to an immunogenically damaged biliary system due to ACR, or the existence of a common factor predisposing to both ACR and recurrent disease. Furthermore, OKT3 monoclonal antibody therapy for refractory ACR has been noted to be associated with a greater incidence of recurrent PSC [15]. This observation, rather than indicating an adverse effect of OKT3, is more likely to represent an increased risk of recurrent PSC as a by-product of ACR.

CMV infection has been reported as a risk factor for recurrent PSC, although the mechanism has not yet been clarified [37–39]. In the experimental studies, there is increasing evidence that CMV could provoke inflammation leading to biliary damage through ischemic insults or immune reaction activation [40–42]. Thus, CMV prophylaxis might be important to reduce the recurrence of PSC after liver transplantation. Valganciclovir, an oral pro-drug of ganciclovir, is an attractive agent for both antiviral prophylaxis and the preemptive treatment of CMV viremia [43].

8.3 Impact of Recurrent PSC on Graft and Patient Survival

Based on the analysis of the United Network for Organ Sharing (UNOS) database of 3309 PSC patients compared to 3254 patients with primary biliary cirrhosis (PBC) who had liver transplantation during 1987–2001, retransplantation rate was significantly higher in PSC (12.4 % vs. 8.5 %) than in PBC, and PSC was an independent predictor for retransplantation [44]. PSC patients had significantly lower graft and patient survival during the 10-year period of follow-up compared to PBC patients after adjusting for age, serum creatinine, UNOS status, ABO compatibility, and donor age. Importantly, the reduced survival in PSC did not become evident until 7 year after the primary transplantation [44]. The reasons for higher

retransplantation rate in PSC patients could not be determined from the database due to insufficient information. However, based on previous publications, it was probably due to a number of reasons including a higher rate of biliary complications, disease recurrence, and chronic rejection.

Earlier studies reported that recurrent PSC had no impact on graft and patient survival in the intermediate term of follow-up [10, 45]. However, there is increasing evidence that disease recurrence might lead to graft dysfunction and need for retransplantation related to recurrent PSC as longer follow-up became available [23, 46]. Campsen et al. reported that once a patient was diagnosed with recurrent disease, the median survival time without receiving a second transplant was 39.1 months [19]. Though most published studies failed to demonstrate a significant decrease in patient survival of recurrent PSC as shown in Table 8.2 [10, 15, 18, 20, 24], in the largest series of 230 patients transplanted for PSC, there was a trend toward reduced patient survival in patients with disease recurrence compared with those did not [22]. However, after exclusion of all patients who died before 6 months post-liver transplant, restriction to single-transplant patients and adjustment for age, patient survival was significantly better in patients without recurrent PSC [22]. This is not surprising, considering that retransplantation usually is a much more complicated procedure than the primary operation. The risk of perioperative death increases significantly from less than 5 % in the primary procedure to almost 20 % in retransplantation [47, 48].

8.4 Treatment for Recurrent PSC

As for PSC in the native liver, there is no established treatment for recurrent PSC. Several trials have been performed in PSC patients before transplantation to evaluate whether immunosuppressive or immunomodulating drugs could halt the progressive course of PSC and prolong transplant-free survival [4, 5, 7]. So far the trials have not shown conclusive results. One of the proposed theories for the lack of effect has been that the therapy is initiated too late. When the PSC diagnosis has been established and immunosuppressive drugs administered, the disease process is already advanced. Hence, if immunosuppressive treatment could be started earlier, the patients would possibly have a better chance of responding to such therapy. In PSC patients undergoing transplantation, immunosuppressive therapy was started during transplant surgery and all receive lifelong immunosuppression. Still, a group of patients developed recurrent PSC in presumably healthy liver graft. Furthermore, UDCA has been advocated in the majority of transplant centers for PSC recipients; however, there is no supporting evidence that the use of UDCA is beneficial in preventing or treating recurrent PSC [49]. UDCA may be of benefit in those with coexisting ulcerative colitis, as some suggest it reduces the risk of colon cancer [50]. Patients with end-stage liver disease from recurrent PSC should be considered for retransplantation.

Interventional cholangiographic treatment of biliary strictures should be considered when dominant strictures or their complications, such as cholangitis or choledocholithiasis are present. However, such approaches are rarely feasible since most strictures are multiple and most recipients have a Roux loop. Some centers have addressed this challenge using single or double balloon enteroscopy to perform endoscopic retrograde cholangiography in patients with complex postsurgical gastrointestinal anatomy [51, 52]. These experienced groups illustrated the usefulness and feasibility of an endoscopic approach using an enteroscope for diagnosis and treatment of biliary strictures in liver transplant patients with biliary-enteric anastomosis. However, development of a therapeutic channel of enteroscope for delivery of larger-diameter stents as well as longer-length accessories is needed. In the native liver, three retrospective studies evaluating the beneficial effect of endoscopic treatment of dominant strictures in PSC patients have suggested the improvement of 3- and 5-year patient survival rates [53–55]. Whether endoscopic treatment influences the progression of recurrent PSC is currently unknown. Therefore, further studies of endoscopic treatment modalities in patients with recurrent PSC should be encouraged.

8.5 Conclusion

Recurrent PSC is now established as an important clinical outcome after liver transplantation. Over time, this problem is likely to increase and exert more impact on patients and graft survival. Several transplant groups have tried to identify risk factors for recurrent disease; however, reported predictors in general have not been confirmed across different studies. Current available data lend support to an association of the inflamed colon with recurrence of PSC in susceptible patients. Treatment of this condition relies mainly on relief of symptomatic biliary strictures, but no evidence of medical or endoscopic therapy has been able to alter the disease course. Although the rarity of the disease has made observational and treatment studies difficult to perform, the future looks bright with the ongoing international collaborations and strong support from patients for research efforts.

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Chapter 9
Recurrence of Metabolic Disorders After Liver Transplantation

Bijan Eghtesad and Charles Miller

9.1 Introduction

The liver is often either affected by metabolic disorders or is the cause of certain metabolic diseases. Liver transplantation has proven to be effective in correction of these disorders. Most, if not all these diseases are cured with LT when medical and supportive measures fail to correct the problem or abnormalities as the result of these disorders. However, depending the timing of LT, certain consequences of these problems may persist in the long round. These disorders could be as a result of inherited disorders of copper and iron metabolism (Wilson's Disease and hemochromatosis), storage of abnormal production of certain proteins (amyloidosis), abnormalities in metabolic pathways of production or elimination of certain proteins (hepatic porphyria, primary hyperoxaluria), or other inherited genetic disorders (familial hypercholesterolemia).

In this chapter, we will briefly discuss about these disorders and outcomes of LT and will focus on possible recurrence of these diseases and effects of LT on the disease process.

9.2 Familial Amyloidosis

Transthyretin (TTR) is a soluble transport protein for thyroxin and vitamin A. The protein is mainly synthesized by the liver. Amyloid fibril formation and deposition is the product of mutation in only one allele. TTR amyloidosis is a hereditary

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autosomal dominant disease and more than 100 mutations associated with the disease have been described [1, 2]. Familial amyloid polyneuropathy (FAP) manifests itself in adult life and usually after the fourth decade of life [1], with variable disease pattern based on the TTR mutation. The neuropathy caused by the disease is induced by deposits of fibril protein alongside the nerves leading to loss of pain and temperature sensation in the feet with long-term impairment of walking, and autonomic dysfunction leading to cardiac conduction defects, and gastrointestinal and bladder motility disorders, leading to death in 10–15 years [2]. The clinical manifestations of the disease vary according the type of mutation. The most common mutation worldwide is TTR V30M, which is mostly seen in Portugal, Sweden, and Japan. The abnormal protein is made in the liver, and this is the basis for LT in this disease to stop the formation of the abnormal protein. Because of the short half-life of TTR in the blood, the concentration of abnormal protein should decrease to undetectable levels in few days.

The first LT for TTR amyloidosis was done in 1990 [3]. In 1993 with more encouraging outcomes, LT became acceptable treatment for FAP [4]. According to the Familial Amyloidotic Polyneuropathy World Transplant Registry, over 2060 patients with TTR amyloidosis have been transplanted [5]. The estimated 10-year survival probability of LT for common variant amyloid is about 100 % compared to 56 % for non-transplant patients [6]. Result of 5-year survival for LT in non-V30M patients is far inferior (59 %) [7].

Effect of LT on improvement of pre-transplant neurological manifestation is guarded. Despite disappearance of abnormal protein from circulation, the old deposits are there to stay with less chance of recovery. Regression of amyloid deposits in the peripheral nerves is uncertain [8]. There is contradictory histological evidence in favor of persistence of autonomic neuropathy after LT [9]. There are several reports of progression of cardiomyopathy after LT for FAP, predominantly for non-V30M patient [10], with more progression in older age group [11].

There are several factors to consider for more successful liver transplantation: (1) Age less than 50; (2) Duration of symptoms less than 7 years; (3) Low level of polyneuropathy; (4) Low BMI; (5) No severe autonomic dysfunction; (6) Absence of amyloid cardiomyopathy; (7) No significant renal dysfunction [12, 13].

Multiple organ transplantation is common in patients with severe amyloid cardiomyopathy (liver–heart) and renal insufficiency (liver–kidney). According to the report from FAPWTR, there have been 46 combined heart–liver transplants and 47 combined kidney–liver transplants in FAP patients [5]. Most of the combined heart–liver transplants were performed in non-V30M cases. This is indicative of higher and earlier predisposition of cardiomyopathy in these patients [14, 15].

Liver transplantation is a curative procedure to stop formation of abnormal protein in TTR-FAP; however, the preexisting problems and symptoms may remain unchanged or even continue to progress. The patient selection for LT in FAP is extremely important to have good outcomes. The potential risk factors for poor outcome should be considered when evaluating a patient to be placed on the waiting list for LT. With novel medical therapies directed at prevention of protein deposits or mobilization of the already-deposited fibrils, there is a hope to have better results

in prevention of progression of the disease early on after diagnosis, or prevention of deterioration of neurological manifestation when combined with LT in these patients.

9.3 Hemochromatosis

Hemochromatosis is a state of pathological iron overload which is due to a genetic disorder that results in excessive intestinal iron absorption. The nature of symptoms is nonspecific making it difficult to diagnose the disease. It was not until 1996 where the discovery of the hemochromatosis gene (HFE) brought new insights about the disease and learning of its natural history and making strategies to diagnose the disease [16, 17]. The most common form of hereditary hemochromatosis is due to mutation C282Y and its homozygosity [18]. The discovery of hepcidin and ferroprotein and their regulatory function in release of iron from enterocytes and monocytes to plasma were the essential steps in learning about the disease process and role of the liver transplantation in the treatment of the disease. The liver is the major site of hepcidin synthesis and at the same time site of excess iron storage. This makes the organ essential in maintaining normal systemic iron homeostasis. In patients with HFE-hemochromatosis, production of hepcidin is down regulated and as a result iron homeostasis is disturbed leading to increased absorption of iron from the intestine and accumulation of it in the hepatocytes leading to the development of hepatocyte damage and eventually to end-stage liver disease. Liver transplantation has shown to lead in normal hepcidin production and its plasma levels and this leads to iron homeostasis and prevention of excess accumulation of iron in the transplanted liver [17].

The initial report on LT for hemochromatosis was from Pittsburgh on six patients. Based on this report, all the patients were alive 6 months after transplantation [19]. Following this report, several uncontrolled studies suggested that patients with iron overload have poor outcome after LT and mostly die of infection and cardiac issues [20–22]. This was further proven in the first multicenter study based on the report from national hemochromatosis transplant registry [21]. However, another study based on information from United Network for Organ Sharing from 1990 to 2006, Yu and Ioannou looked at two periods of transplantation between 1990–1996 (177 patients) and 1997–2006 (217 patients). One-, 3-, and 5-year survival in the first period was 79.1 %, 71.8 %, and 64.6 %, respectively, compared to national average post-LT recipient survival of 86.4, 79.5, and 73.8 % with hazard ratio of 1.38 for those who were transplanted for hemochromatosis. In contrast, in the second period patients with hemochromatosis had excellent survival and comparable with the national post-LT survivals of 88.4 %, 80.3 %, and 77.3 %, respectively, for 1-, 3-, and 5-year survival with hazard ratio for death of 0.89. They attributed the low survival in the first period to high number of patients with hepatocellular carcinoma. In this survey, patients with hemochromatosis were more likely to die of cardiovascular disease than other cause of graft failure and infection [23].

Excess iron deposit in other organs like heart and pancreas is a major cause of morbidity in patients with hemochromatosis and iron overload leading to diabetes

and cardiac dysfunction. Cardiac involvement in iron overload may lead to cardiac failure and is a major cause of post-LT morbidity and mortality. In patients with major cardiac involvement, successful combined heart and liver transplantation has been reported [24].

In general, LT is a cure for patients with hemochromatosis and iron overload. Consequences of longstanding excess iron in other organ systems could potentially affect the long-term outcomes. In patients with secondary hemochromatosis, unless the primary disorder is treated, there is a chance for eventual re-accumulation of iron.

9.3.1 Wilson Disease

Wilson's disease is an inherited autosomal-recessive disorder of copper metabolism. The disease is characterized by excessive deposition of copper in the body with predominant involvement of the liver, brain, kidneys, and corneas. The disease mostly presents itself with neurological manifestations in adolescents and young adults with signs of progressive hepatic dysfunction. Remarkable improvements have been achieved with medical therapy with chelating agents in patients with resolution of symptoms, even in more advanced cases of the disease. In situations where medical therapy has failed or in new cases presenting with acute liver failure, liver transplantation has proven to be the accepted treatment. Improvement of neurological manifestations of the disease in the form of dementia, psychosis, extrapyramidal or cerebellar signs after liver transplantation has been a matter of controversy in reported series. In a report from the University of Pittsburgh on 45 patients with an age range of 8–52 years, 30 patients were transplanted for acute or subacute liver failure and the remaining 15 for chronic liver disease. One-, 5-, and 10-year patient survival was 73.3, 73.3, and 68.9 %. Of these patients, 17 had neurological manifestations at the time of transplant. Twelve of these patients survived showing improvement in nine patients [25]. In another multicenter study from France on 121 patients (adults and pediatrics), 89 % of patients survived at 1 year and 87 % at 5, 10, 15, and 20 years. Out of 19 patients with neurological manifestations at transplant, follow-up data were available for 11 patients. Of these 11 patients, 8 patients experienced partial or complete neurological improvement and three remained with stable condition [26].

The US transplant registry of 170 pediatric patients and 400 adults with Wilson's disease showed excellent outcomes after liver transplantation. The overall 1- and 5-year survival was 90.1 and 89 % for children and 88 and 86 % for adults [27].

Liver transplantation is a cure for patients with Wilson disease who failed medial therapy or in those with late initial presentation with complications of the disease, including acute liver failure with excellent long-term outcomes. Over 50 % improvement has been reported in those transplanted with neurological manifestation of the disease.

9.4 Homozygous Familial Hypercholesterolemia

Familial hypercholesterolemia is an autosomal dominant inherited disease and is associated with severe atherosclerosis and early death secondary to cardiovascular complications. The disease is mostly due to a mutation in low density lipoprotein (LDL) receptor gene. The heterozygous form of the disease develops later in life and usually around fourth and fifth decade with an incidence of 1:500. These patients have lower cholesterol levels than homozygotes. The homozygous form occurs rarely, 1:1,000,000, and develops in childhood. Most of the involved patients die before the age of 20 secondary to severe atherosclerosis and cardiovascular complications [28–30].

Medical therapy for these patients consists on low-fat diet with high doses of lipid-lowering agents, though there is low response rate to these medications. Weekly LDL apheresis to lower the cholesterol level is the integral part of therapy in prevention of accelerated atherosclerosis [31–33].

Liver transplantation is the only effective treatment in patients with homozygous familial hypercholesterolemia. The timing of transplant in these patients is a matter of controversy. It is preferable to do LT in childhood before the appearance of cardiovascular complications, however, a preemptive LT has not been considered as the treatment of choice because of the short- and long-term complications including rejection and side effects of immunosuppressive drugs such as renal insufficiency. Patients who received a liver from their living heterozygous parents showed slight reduction of LDL-cholesterol and continued to require life-long lipid-lowering agents after LT [34, 35]. In patients with extensive cardiac disease, combined transplantation of liver and heart is the treatment of choice with excellent survival [36–38].

Liver transplantation for homozygous familial hypercholesterolemia is the only cure for the disease. Emerging therapies such as novel therapeutic agents and LDL apheresis are useful in prevention of development of cardiovascular complications and to delay the need for LT.

9.4.1 Primary Hyperoxaluria Type 1

Primary hyperoxaluria type 1 (PH1) is an autosomal recessive liver disease caused by a deficiency of the enzyme alanine glycoxylate aminotransferase (AGT) found within hepatic peroxisomes [39–41]. It can occur at any age—from birth up to the sixth decade of life with the median age of onset of 5.5 years [42]. This enzyme is involved in the final step of glyoxylate metabolism and its deficiency leads to increased synthesis and excretion of oxalic acid which causes renal oxalate stones, oxalosis of the kidney, and eventually to end-stage renal disease. Renal replacement therapy and other supportive measures cannot take care of this excess oxalate

and as a result oxalate crystals are deposited in many different organs, leading to musculoskeletal, joint, cardiovascular, and peripheral nervous system complications.

The initial trials with kidney transplantation (KT) alone were not successful, other than rare occasions, because of continuous overproduction of oxalate due to defective metabolic pathway in the native liver and re-accumulation of oxalate in the transplanted kidney [43].

Since the liver is the organ responsible for this metabolic disorder, isolated preemptive LT might be considered as the treatment of choice in patients with the disease and before complete failure of their renal function and when the Glomerular filtration rate (GFR) is approaching 40 mL/min/1.73 m^2. Because of the heterogeneity of the disease and advances in conservative management of these patients and also risks involved with LT procedure and outcomes, preemptive LT brings up medical and ethical questions [44].

Dual liver and kidney transplant (LKT) is the treatment of choice for patients with PH1 and end-stage kidney disease when GFR is less than 15 mL/min. Deterioration of renal function to this level results in decrease in clearance and increase in retention of oxalate. These patients should be placed on vigorous hemodialysis and planned combined LKT. Outcomes of solitary KT and combined LKT in patients with hyperoxaluria from the US registry indicates 5-year survival rate of 45 and 14 % for KT alone in adults and pediatric patients and 64 and 76 % for LKT in these patients. Low rate of survival in pediatric patients after KT alone could be a reflection of more severe disease with early onset of the disease [43, 45, 46].

After combined LKT in patients with severe accumulation of oxalate in the system, there is a risk of impairment of function in transplanted kidney with heavy load of oxalate mobilized from different sources in the body. Aggressive dialysis after combined LKT has shown to be an effective way of preventing this complication. Transplantation of liver with delayed KT is another approach for these patients. The theory behind this sequential transplant is to put a halt in production of oxalate after LT and with aggressive dialysis the excess oxalate load be reduced to the level that KT can be done safely with no more risk of oxalate deposition in the new renal allograft. With this approach possibility of expedited transplant using organs from living donors could be considered [47, 48].

There is no recurrence of PH1 after combined LKT and with good management of the patients after the transplant the excess calcium oxalate will be mobilized and excreted through the kidney. This process may take several years depending on the extent of the oxalate deposits before transplantation. Complications of excess oxalate like joint deformities and those of skeletal system may not recover completely; however, there are reports improved quality of life and reversal of certain complications like cardiomyopathy after combined KLT or LT followed by delayed KT in these patients [49–51].

9.5 Porphyria

Porphyrias (hepatic and erythroid) are a group of metabolic disorders that result from enzymatic deficiencies in heme biosynthetic pathway, with predominant defect either in the liver (hepatic), or in the bone marrow (erythropoietic porphyria). The produced protoporphyrin may accumulate in the liver causing hepatocyte and bile duct damage leading to biliary fibrosis, obstruction, portal hypertension, and splenomegaly which may by itself lead to red blood cell sequestration in the spleen resulting in hemolysis and generation of more protoporphyrin, ending in liver failure [52, 53]

Liver transplantation has been the therapy of choice in these patients [54–56]. Reported series have shown good survival for patients with protoporphyria after LT. In a series of 20 patients, transplanted between 1979 and 2004, 1-, 5-, and 10-year survival were 85 %, 69 %, and 47 %, respectively. In the same report, pediatric patients had a 1-, 5-, and 10-year survival of 100 %, 75 %, and 50 %, respectively [56]. Recurrence of disease occurred in 11 of 17 survivors, and three patients required re-transplantation and three other patients died of the disease [56]. The disease recur since LT does not treat the underlying overproduction of protoporphyrin, which originates from the native bone marrow [56], and sequential liver/bone marrow transplantation may be the best option for these patients [57–59].

9.6 Conclusions

Liver-based metabolic disorders account for a good percentage of indications for LT. Over the last 20 years, major advances have been made in the understanding of these disorders, and new therapies have become available. Increased knowledge about these disorders has led to discovery of new drugs and better management guidelines and as a result better selection of patients who can get benefit of LT. Liver transplantation is a cure for the underlying defect in most of these liver-based disorders; however, certain long-term consequences of these diseases may not always respond to LT. Early diagnosis of these diseases and close follow-up of these patients is needed for the optimal post-LT outcomes.

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Chapter 10
Nonalcoholic Fatty Liver Disease Post-Liver Transplantation

Ibrahim Hanouneh and Bijan Eghtesad

Metabolic syndrome, as defined by the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), is a constellation of metabolic risk factors including obesity, diabetes, hypertension, and hyperlipidemia [1]. The prevalence of metabolic syndrome in the Western world is age dependent, with an overall prevalence of 34 %, to a greater than 40 % in individuals over the age of 60 [2].

The global epidemic of obesity and metabolic syndrome has had a great impact on every aspect of medicine, particularly cardiovascular and liver disease. Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are important consequences of obesity and metabolic syndrome. The presence of any of the five features of metabolic syndrome carries a major risk for the development of fatty liver disease; and the concurrence of three or more features of metabolic syndrome in a single individual is associated with over 50 % risk of fatty liver [3].

Along with the global epidemic of obesity, NAFLD and NASH have emerged as common causes of chronic liver disease worldwide. Based on the United Nation of Organ Sharing adult liver transplant database, the number of adults with NASH cirrhosis waiting for liver transplant has almost tripled between 2004 and 2013 [4], Table 10.1. It is estimated that by the year 2025, more than 25 million Americans may have chronic liver disease secondary to NAFLD and NASH [5]. This prevalence

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Table 10.1 Trends in new liver transplant waitlist registrations between 2004 and 2013

	New waitlist registrants 2004	New waitlist registrants 2013	Percentage increase (%)
Hepatitis C	2887	3291	14
Alcoholic liver disease	1400	2024	45
Nonalcoholic fatty liver disease	804	2174	170

Table 10.2 Overall probability of survival among patients awaiting liver transplant in the United States

	30 day survival on transplant list (%)	60 day survival on transplant list (%)	90 day survival on transplant list (%)
Hepatitis C	82	74	68
Alcoholic liver disease	75	65	59
Nonalcoholic fatty liver disease	80	71	64

would greatly exceed the current prevalence of hepatitis C virus-related liver disease [5]. NASH can progress to cirrhosis and liver failure requiring liver transplantation in 3–15 % of patients [3, 5, 6]. Given these current estimates, we would predict increased demand for liver transplantation for NASH cirrhosis, and that would greatly exceed the demand for liver transplantation in hepatitis C over the next two decades, particularly in the light of new development of potent anti-hepatitis C therapy.

Despite increased demands for liver transplantation in patients with NASH, recent study using the US adult liver transplant database showed that patients with NASH are less likely to undergo liver transplantation and more likely to die on the waitlist than patients with other forms of liver disease such as hepatitis C and alcoholic liver disease [4] (Table 10.2). Additionally, patients with NASH are likely to experience recurrence of fatty liver disease following liver transplantation [5]; and a significant proportion of these patients encounter cardiovascular events post-liver transplant as the result of metabolic risk factors including obesity, hypertension, diabetes, and hyperlipidemia [7].

10.1 Fatty Liver Post-Liver Transplantation

Recurrence of NAFLDand NASH after liver transplantation is not uncommon [5]. Prospective analysis of protocol biopsies reported that 60 % of liver transplants performed for NASH cirrhosis developed steatosis—at least grade 2—at 1-year post-transplant [8]. Additionally, steatohepatitis occurred in over 50 % of patients at 2-year post-transplant. In our experience, 32 % of patients who underwent liver

transplantation for NASH-related cirrhosis developed steatosis over a follow-up period of 5.1 (0.69–13.4) months post-liver transplant [9].

Additionally, among liver transplant recipients who underwent liver transplantation for etiologies outside fatty liver disease, ~20 % develop de novo steatosis, and ~10 % de novo steatohepatitis following transplant [10]. This is particularly true in patients with hepatitis C virus infection. Several studies clearly demonstrated a strong relationship between hepatitis C virus infection and the development of insulin resistance and metabolic syndrome [11]. An experimental mouse model transgenic for hepatitis C virus core gene was able to induce insulin resistance and diabetes mellitus [12]. Saab et al. [13] reported that almost 40 % of hepatitis C patients develop new onset diabetes following liver transplantation compared to only 10 % of those transplanted for other indications. A previous publication [14] reported 50 % prevalence of metabolic syndrome in patients with recurrent hepatitis C following liver transplantation. This figure is significantly higher than the prevalence of metabolic syndrome of 22 % in the general US population as reported in the National Health and Nutrition Examination Survey III.

10.2 Risk Factors of Fatty Liver Disease Post-Liver Transplantation

Among the many factors that may potentially predispose to the recurrence or de novo development of fatty liver post-transplant [3, 5, 6], metabolic syndrome is of particular interest. Features of metabolic syndrome are very common and almost universal following liver transplant, Table 10.3 [14–16]. The rate of diabetes after transplant is approximately 40–60 % rising from ~15 % prior to transplant [14]. Summarily, around 60 % of transplant patients develop hypertension. Dyslipidemia occurs in approximately 50 % of patients after transplant. On average, half of liver transplant population reach obesity—defined by body mass index ≥30—by 1 year of liver transplant [14]. Reason is poorly understood but it is believed that lifestyle modifications—namely the return to sedentary normal daily life and free food intake which obviously contribute to the development of weight gain and metabolic risk

Table 10.3 Prevalence of metabolic risk factors following liver transplantation

Authors	Year	N	Diabetes (%)	Hypertension (%)	Dyslipidemia (%)	Metabolic syndrome (%)	Follow-up (months)
Laryea et al. [21]	2007	118	61	62	48	58	58 ± 21
Hanouneh et al. [12]	2008	82	51	64	–	50	24 ± 17
Bianchi et al. [22]	2008	296	40	52	51	45	38

factors following liver transplantation. Consequently, metabolic syndrome is very prevalent in liver transplant patients ranging from 45 to 58 % at just 6–12 month post-liver transplant—leading to the recurrence or de novo development of fatty liver post-transplant. Seo et al. [10] showed that 10 % increase in body mass index is associated with 20-fold increased risk of the development of fatty liver following liver transplantation. Similarly, we observed a significant association between diabetes, hypertension, and metabolic syndrome and the development of fatty liver disease after transplant [9]. These metabolic risk factors carry an increased risk of hepatic fibrosis following liver transplantation.

Immunosuppressive medications used following liver transplantation may play a significant role in the pathogenesis of fatty liver post-transplant. Corticosteroids are traditionally implicated in the development of steatosis and steatohepatitis, and it has been demonstrated that cumulative use of corticosteroids used following liver transplant is associated with recurrence of NASH post-transplant [9]. Additionally, the use of corticosteroids following liver transplantation has been implicated in the development of fibrosis post-transplant; this has been well documented in a recent study [9]. This study suggested that the use of corticosteroids post-liver transplant in NASH carries a risk of developing hepatic fibrosis that rivals the risk in patients with post-transplant recurrent hepatitis C virus infection. Based on these findings, immunosuppressant protocols following liver transplant for NASH patients should minimize and shorten the use of corticosteroids when possible. Calcineurin inhibitors are associated with the development of hypertension and glucose intolerance [14], whereas mammalian target of rapamycin (mTOR) inhibitors may lead to dyslipidemia [14]—all may contribute to the development of fatty liver following transplantation.

10.3 Consequences of Fatty Liver Post-Liver Transplantation

The majority of patients with recurrent or de novo fatty liver post-liver transplantation have benign course; and only a small number of patients may have progressive disease leading to cirrhosis and require second transplant. Hanouneh et al. [9] reported the median (25 percentile, 75 percentile) rate of fibrosis progression in patients with fatty liver post-liver transplantation of 0.0 (0.0, 0.0) fibrosis stage per year, compared to 0.5 (0.0, 1.3) fibrosis stage per year in patients with recurrent hepatitis C following transplant; (Fig. 10.1). Furthermore, over 5-year period approximately 20 % of hepatitis C patients develop advanced hepatic fibrosis (stage 3 or 4) post-liver transplant, compared to only 2 % of patients with fatty liver post-transplant. The use of corticosteroids in the treatment of acute cellular rejection following liver transplantation is associated with an increased risk of fibrosis progression in patients with hepatitis C as well as those with fatty liver. We demonstrated in a previous publication that liver transplant patients with fatty liver are at

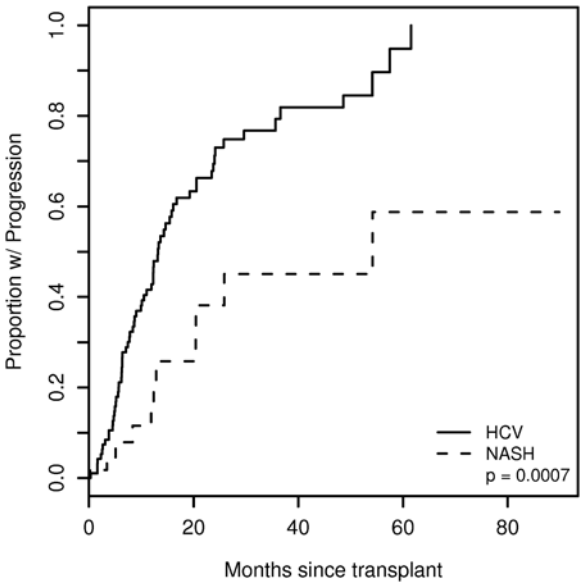

Fig. 10.1 Fibrosis progression post-OLT in patients with HCV and NASH

increased risk of developing hepatic fibrosis following liver transplantation if they received corticosteroids for the treatment of acute cellular rejection, compared to fatty liver patients who did not receive corticosteroids. Interestingly, the risk of developing fibrosis post-transplant in fatty liver patients who received corticosteroids rivals the risk of hepatic fibrosis in patients with recurrent hepatitis C post-liver transplant.

Metabolic risk factors, hypertension, and diabetes mellitus in particular, also contribute to the development of fibrosis post-transplant. Our group identified a significant association between hypertension and metabolic syndrome and the development of fibrosis post-transplant in patients with recurrent fatty liver post-transplant. After adjusting for the use of corticosteroids and indication for liver transplant, subjects with diabetes had twice the hazard of developing fibrosis than those without diabetes [9].

While only a small number of liver transplant patients with fatty liver have progressive disease leading to cirrhosis and require second transplant, the vast majority of these patients suffer complications of cardiovascular events post-liver transplant as the result of obesity, hypertension, diabetes, and dyslipidemia. Several studies reported ~25 % rates of cardiovascular events in liver transplant patients [17]. The risk of coronary artery disease climbs from 7 % before transplantation to 11 % at 1-year post-transplant [18]. Cardiovascular event accounts for at least 6 % of mortality post-liver transplantation [19]. Compared to age-matched non-transplant population, the mortality rate from cardiovascular events is 2.5 time folds higher in the liver transplant recipients [20]. Recent studies concluded that cardiovascular events following liver transplantation are more frequent in NASH recipients compared to other etiologies of liver disease, and that cardiovascular events were the second

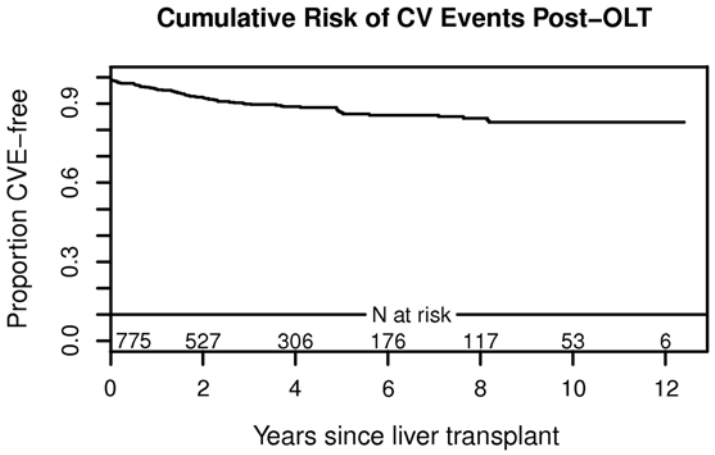

Fig. 10.2 Cumulative incidence of major CV events among liver transplant recipients

cause of death following liver transplantation in these patients, surpassed only by sepsis [21]. The majority of cardiovascular events occur during the immediate perioperative period [22]. Not surprisingly, the majority of NASH patients with cardiovascular events after liver transplantation carry several metabolic risk factors including diabetes, hypertension, dyslipidemia, and obesity. Therefore, patients with NASH cirrhosis should be carefully evaluated and selected for liver transplantation; and metabolic risk factors should be treated aggressively.

In a large study of 775 liver transplant recipients, the cumulative risk of cardiovascular events at 1, 3, and 5 years following liver transplantation were 4.5 %, 10 %, and 13.5 %, respectively (Fig. 10.2). Not surprisingly cardiovascular events were more common in patients with metabolic syndrome [7]. Other factors associated with cardiovascular disease post-transplant in that study were advanced age at the time of transplant (hazard ratio = 1.2), male gender (hazard ratio = 2.0), diabetes mellitus (hazard ratio = 2.0), and hypertension (hazard ratio = 1.8). Although it was more prevalent in patients with metabolic risk factors, recurrence or de novo fatty liver disease per se was not independently associated with the development of cardiovascular events following liver transplantation.

Renal dysfunction is common after liver transplantation and often thought to be secondary to calcineurin inhibitor toxicity, but other factors exist. Parameters of metabolic syndrome—linked to the recurrence of fatty liver following liver transplant—have been also linked with renal function. Diabetes mellitus has been shown to be an independent risk factor for the development of chronic renal insufficiency after liver transplant [23]; and it is not uncommon to observe renal dysfunction in liver transplant patients with fatty liver.

De novo malignancies following liver transplantation is an increasingly common problem [24]. The immunocompromised state in transplant recipients provides a suitable environment for oncogenic viruses to reactivate or infect host, and for

malignant cells to proliferate. Metabolic factors, particularly obesity and diabetes are closely associated with increased risk of malignancies, including hepatocellular carcinoma [25]. Patients with NASH cirrhosis are at 2.6 % risk per year of developing hepatocellular carcinoma compared to 4 % risk per year in patients with hepatitis C cirrhosis [25]. It is yet to be determined whether metabolic risk factors and fatty liver play the same role following liver transplantation.

10.4 Conclusion

Along with the worldwide epidemic of obesity, fatty liver disease has emerged as the leading cause of liver disease, and is approaching the most common indication for liver transplantation in the western world [4]. Given the high prevalence of metabolic risk factors—including obesity, diabetes, hypertension, and hyperlipidemia—in the liver transplant recipients, recurrence of fatty liver disease following transplantation is frequent. From liver graft prospective, the vast majority of these patients have benign course; and only a small number may have progressive disease leading to cirrhosis and require second transplant. However, the vast majority carry serious metabolic risk factors which eventually lead to cardiovascular disease and renal insufficiency—the leading causes of death following liver transplantation. Screening for metabolic risk factors should be incorporated into the routine care of liver transplant recipients in order to identify patients at greater risk for cardiovascular disease and provide preventive and therapeutic interventions as early as possible. Future studies are underway to explore the role of several approaches used to reverse metabolic derangements in the liver transplant patients such as physical activity, diet, weight loss, and insulin-sensitizing agents.

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Chapter 11
Recurrence of Hepatocellular Carcinoma Following Liver Transplantation Within Milan Criteria

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Abbreviations

AFP	Alpha fetoprotein
HCC	Hepatocellular carcinoma
LT	Liver transplantation
RFA	Radio frequency ablation
TACE	Trans Arterial Chemo Embolization
UNOS	United Network for Organ Sharing

11.1 Introduction

Liver cancer (hepatocellular cancer, HCC) is the fifth most common cancer in men and the seventh in women. Approximately, 20,000 new cases of HCC are diagnosed in the United States every year [1, 2]. Major risk factors for hepatocellular carcinoma (HCC) include cirrhosis from any etiology, infection with HBV or HCV,

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Table 11.1 Milan criteria

Milan criteria [5]
• One lesion smaller than 5 cm
• Up to three lesions smaller than 3 cm
• No extrahepatic manifestations
• No vascular invasion

alcoholic liver disease, hemochromatosis, and nonalcoholic fatty liver disease. Worldwide, the highest incidence rates are reported in regions where infection with hepatitis B virus (HBV) is endemic. Chronic HBV infection accounts for approximately 50 % of all cases of HCC worldwide [3]. In the United States, HCV and alcoholic liver disease are the two most common causes.

The optimal curative options for the management of HCC are surgical resection and/or liver transplantation (LT). Recent data may suggest that ablative treatment such as radio frequency ablation (RFA) may be comparable to surgical resection for small tumors. Surgical resection is the optimal treatment in the absence of cirrhosis or less advanced cirrhosis and hence is more common in Asian countries, where HBV-related hepatocellular carcinoma without or minimal cirrhosis is more common. Ideal candidates for surgical resection are patients with a solitary nodule, well-preserved liver function, absence of portal hypertension, without symptoms or signs of extrahepatic spread [4]. The 5-year survival after surgical resection is around 50 %, but tumor-free 5-year survival is less than 50 %, irrespective of the risk factor for HCC. Unlike resection, tumor recurrence rates are lower after LT, and moreover, surgical resection is associated with very high morbidity and mortality in those with cirrhosis and portal hypertension. Therefore, LT is considered the best option in people with cirrhosis and portal hypertension, or those with advanced cirrhosis because of significantly lower surgical mortality rates and lower tumor recurrence rates when patients are selected carefully. However, the shortage of organ donors has been a limiting factor, and this has led to the development of selection criteria to limit LT to patients who are more likely to have very good outcomes. Since the publication of a landmark paper by Mazzaferro et al., the criteria proposed by the group (Milan criteria, Table 11.1) have been used to select people with HCC for LT [5]. Since then, many investigators have confirmed that those transplanted under Milan criteria have lower tumor recurrence rates (less than 10 %) and excellent 5-year tumor-free survival [5]. However, several patients with HCC fall outside the Milan criteria at the time of diagnosis, and several investigators have proposed that Milan criteria could be expanded further with an acceptable risk of tumor recurrence. The proposed extended criteria include the University of California San Francisco (UCSF) [6] criteria, up-to-seven criteria [7], and Hangzhou criteria [8]. The recurrence rates and tumor-free survival rates of patients with HCC when transplanted outside Milan criteria have been discussed in detail in another chapter by Drs. Ganjoo and Schiano. The role of adjuvant and neoadjuvant treatment in the management of HCC is discussed by Dr. Kim. We, therefore, will restrict our discussion to those who were transplanted within Milan criteria, which are the only criteria that have been universally accepted currently.

11.2 Milan Criteria

Prior to the introduction of Milan criteria, the long-term results of liver transplantation in patients with hepatocellular carcinoma have been variable and disappointing, with an overall 5-year survival rate ranging from 30 to 40 % as shown in Table 11.2 [9–16]. However, these studies showed a positive correlation between the tumor burden prior to transplant and post-transplant recurrence rates. In 1996, Mazzaferro et al. reported the outcomes of 48 patients, with cirrhosis and small, unresectable hepatocellular carcinomas, who underwent liver transplantation at the National Cancer Institute in Milan, Italy [5]. This study showed 4-year actuarial survival rates of 73 % and the recurrence-free survival rate of 83 %, and these observations were further corroborated by many other investigators (Table 11.3) [17–25]. These observations were further supported by the outcome data ("real-life data") from the United Network for Organ Sharing (UNOS) database [26]. An analysis of UNOS data suggested that the survival did improve after the publication of Milan criteria in the United States [21]. Based on published literature, 5-year survival of patients transplanted for HCC based on Milan criteria is around 65–78 % whereas it is 68–75 % for non-tumor patients transplanted during the same period [27]. When HCC patients were transplanted outside Milan criteria, 5-year survival rates were 46–60 %. A detailed analysis of studies suggested the hazard ratio is 1.68 when transplanted outside Milan criteria, but hazard ratio was lower (1.28) for live donor liver transplant recipients [27].

Table 11.2 Outcomes of HCC patients transplanted prior to adaptation of Milan criteria

Author	Number of patients	Recurrence rate post-transplantation	Survival post-transplantation
Iwatsuki et al. [9]	37	72 % (13/18) in Group 2[a]	35 and 30 % at 6 months and 1 year in Group 2 tumor patients
O'Grady et al. [10]	50	65 % in those who survived 3 months post-transplantation	45 and 38 % at 1 and 2 years
Ringe et al. [11]	52	Incidence of recurrence-16 (time period not specified)	36 % at 2 years
Olthoff et al. [12]	16	4—48 % in those who survived 3 months post-transplantation	67 %, 51 %, and 31 %, at 6 months, 1 and 5 years, respectively
Ismail et al. [13]	29	n/a	71 % survived 30 days or longer with median
			Survival of 11.5 months
Penn [14]	637	39 %	30 % and 18 % at 2 and 5 years, respectively
Haug et al. [15]	24	2—25 % in those who survived 3 months post-transplantation	71, 56, and 42 % at 1, 2, and 3 years
Moreno et al. [16]	14	21 % at 13 months follow-up	64 % at 13 months

n/a not available, *HCC* hepatocellular carcinoma

[a]Group 2—consisted of patients who were transplanted for malignant lesions that could not be treated with subtotal hepatectomy

Table 11.3 Outcomes of HCC patients transplanted within Milan criteria

Author	Number of patients	Recurrence rate	Survival
Mazaferro et al. [5]	48	8 % at 4 years	75 % at 4 years
Llovet et al. [17]	79	4 % at 5 years	74 % at 5 years
Bismuth et al. [18]	45	11 % at 5 years	74 % at 5 years
Jonas et al. [19]	120	n/a	71 % at 5 years
Hemming et al. [20]	112	65 % at 5 years in patients with vascular invasion	77 %, 63 %, and 57 % at 1, 3, and 5 years, respectively
		4 % for those without vascular invasion	
Yoo et al. [21]	985	n/a	5-Year patient survival with time—1987–1991, 25.3 %; 1992–1995, 46.6 %; 1996–2001, 61.1 %; ($p < 0.0001$)
Decaens et al. [22]	279 and 184 in the groups based on pre-transplant imaging and explant pathology, respectively	20 % and 9.5 % at 5 years in the groups based on pre-transplant imaging and explant pathology, respectively	60 % and 70 % at 5 years in the groups based on pre-transplant imaging and explant pathology, respectively
Duffy et al. [23]	173 and 126 in the groups based on pre-transplant imaging and explant pathology, respectively	74 % and 72 recurrence-free 5-year survival in the groups based on pre-transplant imaging and explant pathology, respectively	91 %, 85 %, and 79 % at 1, 3, and 5 years, respectively, based on pre-transplant imaging and 96 %,89 %, and 86 % at 1, 3, and 5 years, respectively, based on explant pathology
Adler et al. [24]	145	17 % at 4 years	84 %, 79 %, 72 %, 69 %, and 66 % at 6 months and 1, 2, 3, and 4 years, respectively
Herrero et al. [25]	59	4 % (time period not specified)	83 %, 73 %, 70 %, 70 %, and 43 % actuarial survival rates at 1, 3, 5, 7, and 10 years, respectively

n/a not available, *HCC* hepatocellular carcinoma

11.3 Pitfalls of Milan Criteria

Although Milan criteria are well validated, the cutoff for the size and the number of tumor nodules are rather arbitrary, and are decided by imaging studies, but not based on explant pathology or tumor biology. It has been suggested that Milan criteria are rather stringent, and moreover, imaging studies may underestimate or overestimate the tumor size and tumor numbers depending on pre-transplant radiological imaging techniques, imaging protocols, and more importantly on the interpretation skills of the radiologists. A retrospective analysis of the UNOS/OPTN database confirmed these concerns and showed that radiologic examinations were not very precise, when compared to explant pathology, underestimating tumor load in 27 % and overestimating in 30 % of the population [28]. It has been also suggested that the Milan criteria, based on pre-transplant radiologic criteria, were proposed more than two decades ago, and since then there have been significant improvements in both CT scan and MRI imaging techniques. Nevertheless, a recent review of literature suggested that Milan criteria are very robust in predicting excellent survival, and moreover, those who were transplanted within Milan criteria had more favorable tumor differentiation [27]. When interpreting the excellent outcomes of LT based on Milan criteria, it is important to remember that these results were not reported as "intention to treat" analysis, but based on those who received LT in a timely manner. During the waiting period, tumors do progress and many people may fall outside the Milan criteria and hence do not receive a liver transplantation.

11.4 Predictors and Pattern of Recurrence

Increasing evidence suggests that tumor biology, and not the number and size of tumor nodules, is the most important predictor of favorable outcome. However, until we identify reliable markers of unfavorable tumor biology, we have to depend on other surrogate markers for patient selection. Several risk factors, including significantly elevated alpha fetoprotein (AFP) levels, poor tumor differentiation, and vascular invasion, have been identified that could predict recurrence of HCC even when transplanted within Milan criteria. A higher AFP prior to LT is considered an important predictor of post-LT HCC recurrence in many studies. Higher AFP levels are often associated with more advanced cirrhosis, vascular invasion, higher tumor burden, and poor performance status. An analysis of UNOS database from region 5, where there is a longer waiting period before LT, showed that high AFP was the only pre-transplant variable that predicted post-transplant tumor recurrence and mortality in patients who underwent LT for HCC within Milan criteria [29]. Similarly, in a retrospective cohort study [30] of 313 HCC patients undergoing transplantation—pre-transplant AFP, lens culinaris agglutinin-reactive AFP (AFP-L3), and des-gamma-carboxy prothrombin (DCP) predicted HCC recurrence after transplantation. When compared to LT done within Milan criteria, hazard ratio (HR)

were 2.6 (1.4–4.7, $p=0.003$) for outside Milan, 8.6 (3.0–24.6, $p<0.0001$) for outside Milan, and AFP ≥250 ng/mL and 7.2 (2.8–18.1, $p<0.0001$) for outside Milan and DCP ≥7.5 ng/mL. These findings suggest that using both biomarkers and Milan criteria may be better than using the Milan criteria alone in determining liver transplantation eligibility.

Tumor differentiation and vascular invasion are other important predictors of HCC recurrence. In a study of 155 patients who underwent liver transplants for HCC (84 % within Milan criteria based on the explanted livers), histological grade of differentiation and macroscopic vascular invasion were strong independent predictors of survival [31]. Other investigators have also confirmed that histological differentiation and vascular invasion are independent predictors of survival [32, 33]. It is also important to note that poorly differentiated tumors are more likely to be associated with vascular invasion. Unlike AFP, histological grade of tumor differentiation is unknown before LT as it is not a common practice to do biopsy of HCC, that meet well-established diagnostic criteria of HCC, because of the potential risk for needle track metastases [34, 35]. Studies that have compared contrast-enhanced dynamic imaging of liver with the degree of histopathological differentiation of HCC have reported a good correlation between hypervascular enhancement patterns with higher pathological grades [36–40]. Other investigators, however, have reported a decline in arterial blood supply in the later stages of HCC progression (grade ≥3) [37–39]. A recent Italian retrospective study [41] showed that patients with hypovascular HCC have a lower tendency towards recurrence and a prolonged recurrence-free survival than those with hypervascular HCC. These studies suggest that dynamic imaging findings may not be reliable surrogate markers of tumor differentiation. Although microvascular invasion is a very strong and a consistent predictor for higher recurrence, currently there are no imaging techniques to diagnose microvascular invasion, and when found, it is almost always based on explant pathology.

There are few other predictors that could predict higher HCC recurrence. Recipients of grafts from older donors (≥60 years) or those who received organs through regional sharing have been reported to have significantly higher risk of HCC recurrence, but these data need further corroboration because of many confounding variables [42]. A retrospective Belgian study [43] suggested that FDG positron emission tomography computed tomography with a tumor/liver activity ratios (RSUV max) cutoff value of 1.15 or more is a strong prognostic factor for recurrence and death in patients with HCC treated by LT. In their study, none of the patients outside the MILAN criteria with RSUV max <1.15 suffered from recurrence in the follow-up. Chinese investigators have suggested that pre-transplant platelet to lymphocyte ratio (PLR) ≥125 or preoperative neutrophil-lymphocyte ratio (NLR) ≥4 could be associated with advanced tumor stage and behavior [44] and could be used as a predictor of post-transplant HCC recurrence [44, 45]. These observations need to be corroborated in larger, prospective studies after adjusting for other known confounders. In the future, we may have more refined molecular markers that could be used in association with imaging to better define the LT selection criteria for those with HCC.

11.5 Post-transplant Monitoring

Tumor recurrence is associated with a very poor prognosis, with median survival <12 months. Sites of recurrence include liver alone (16 %), both intra and extra hepatic (31 %), or extrahepatic alone (53 %). Since the introduction of Milan criteria, tumor recurrence rates have dropped from a median of 25.5 % down to 8–11 %. Although one could argue that aggressive surveillance of all patients after LT is probably not cost-effective, most centers do surveillance every 3 months in the first year, every 6 months in the second year, and every 6–12 months from years 3 to 5. Surveillance intervals could be tailored (less frequent if explant pathology is favorable) based on explant pathology to reduce the costs [46]. Although there is no consensus, authors prefer non-contrast CT of chest and contrast-enhanced MRI of abdomen for surveillance purposes. If patients had elevated AFP prior to LT, monitoring of AFP may be helpful. Other options include ultrasound and AFP every 3–6 months for 5 years, but the sensitivity of ultrasound may be less than optimal.

11.6 Immunosuppression

The level and type of immunosuppressive agents may play a role in tumor recurrence and progression after LT as shown in few experimental and clinical studies [47–49]. It has been suggested that a higher level of cyclosporine (CsA) exposure, especially during the first year after LT, may lead to higher tumor recurrence rates [50, 51]. Alternatively, mTOR inhibitors such as sirolimus may have an advantage over tacrolimus or cyclosporine in those who received LT for HCC because of the antiangiogenic properties of the drug [52–54]. mTOR is overexpressed by up to two-thirds in HCC, and in animal models, sirolimus has shown efficacy at reducing tumor growth and longer survival. Zimmerman et al. compared two groups of patients who underwent liver transplantation for HCC: patients on sirolimus and calcineurin inhibitor post-transplant vs. those on cyclosporine or tacrolimus plus mycophenolate mofetil and corticosteroids. The 1- and 5-year survival rates for the sirolimus-treated group were 95.5 % and 78 %, respectively, versus 83 % and 62 % for the non-sirolimus group [55]. In a retrospective case–control study [56], patients who received sirolimus and post-transplant chemotherapy had better recurrence-free survival than patients who were treated with tacrolimus and mycophenolate mofetil along with post-transplant chemotherapy. Although no firm conclusions can be based on these studies, it is perhaps prudent to offer sirolimus-based therapy to those who received LT for HCC.

11.7 Treatment of Recurrence

The optimal treatment for local HCC recurrence is surgical resection, if possible. In one small study, involving 17 patients who had recurrent HCC, overall survival rates of the surgical group were similar to that of the patients without HCC recurrence [57]. If surgical resection is not feasible, as it in majority of cases, other ablative modalities such as radio frequency ablation or chemoembolization may be considered. The role of neoadjuvant and adjuvant treatment for recurrent HCC after transplantation has been discussed in detail in another chapter. Sorafenib is an oral multikinase inhibitor that blocks multiple growth factor pathways including vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor-β (PDGFR-β), and two registration trials (not in transplant recipients) showed that it can prolong life in those with unresectable HCC [58–60]. A retrospective study showed that sorafenib is tolerated by transplant recipients, with recurrent HCC, on sirolimus-based immunosuppressive regimen without any adverse effects on graft function [61]. In this study, common adverse events were diarrhea (46 %), hand-foot skin reaction (27 %), nausea, fatigue, and leucopoenia (18 %), and these adverse events are similar to those reported non-transplant patients. Another retrospective analysis on LT recipients with unresectable HCC recurrence and undergoing combination therapy with everolimus and sorafenib, adverse events led to drug discontinuation and dose reduction of sorafenib in two patients (28 %) and three (43 %), respectively [62]. Recently, a placebo-controlled, double-blind (STORM) trial [63] was designed to evaluate the efficacy and safety of adjuvant sorafenib in patients with HCC who have no lesions after curative resection or ablation. Treatment with sorafenib after curative resection or ablation of HCC did not improve recurrence-free survival when compared with placebo. Additionally, time to recurrence and overall survival showed no differences between the treatment arms. Discontinuation rates with sorafenib were higher (24 % vs. 7 %) compared to placebo. Based on this study, one may conclude that the "preventive" role of sorafenib is unproven.

11.8 Summary

The adoption of the Milan criteria for the selection of HCC patients for LT has improved 5-year post-LT tumor-free survival when compared to pre-Milan era. The recurrence rate of HCC when transplanted within Milan criteria is around 8–11 %. Milan criteria are based on pre-LT imaging findings, but the correlation of the findings on imaging and the explant pathology is not optimal. Imaging techniques, protocols, and interpretations of images are not uniform, and moreover, Milan criteria do not take into consideration the variability of tumor biology. A number of predictors for tumor recurrence have been identified across various studies including biomarkers such as AFP, histological differentiation of the tumor, microscopic vascular

invasion, dynamic imaging findings, and inflammatory markers along with other host factors and the type and degree of immunosuppression. Although tumor recurrence rates are low, it is a common practice to have surveillance protocol for 5 years after LT in order to detect HCC recurrence at an early stage when curative treatment options are feasible. In the future, more reliable and noninvasive molecular markers may be available to predict tumor behavior, and using a combination of imaging and molecular markers, we may be able to redefine the LT selection criteria for patients with HCC, and perhaps offer LT to more people with larger HCC without any negative effects of the outcomes. Until then Milan criteria appear to be a reasonable benchmark for selecting patients for LT. The potential for expanding the criteria is discussed later in this book.

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Chapter 12
Recurrence of HCC When Transplanted Outside Milan Criteria

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Abbreviations

AFP	Alpha fetoprotein
DDLT	Deceased donor transplant
HCC	Hepatocellular carcinoma
LDLT	Live donor liver transplant
LT	Liver transplantation

12.1 Introduction

Hepatocellular carcinoma (HCC) is a cancer with global significance being the fifth most common cancer in men worldwide and seventh among women, with over half a million new cases diagnosed annually. It is presently the second leading cause of cancer-related mortality in the world; the disease burden is highest in Eastern Asian and in sub-Saharan areas with endemic HBV infection. With respect to any available treatment for liver cancer, liver transplantation (LT) retains the potential to cure the disease per se as well as the underlying chronic liver disease [1–3].

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The "Milan criteria" proposed by Mazzaferro et al. in 1996 (a single tumor of 5 cm or less in size or up to a maximum of three HCC, each 3 cm or less in size, with no macroscopic vascular invasion) have been proven to be reliable and easily applicable for the selection of patients with small unresectable hepatocellular carcinomas for LT [4, 5]. The main disadvantage of this set of criteria is that it is relatively restrictive. Several attempts have been made to expand these criteria to include tumors of greater number and size. The model for end-stage liver disease (MELD) prioritization system has utilized the Milan criteria since adopted by UNOS in 2002 and by Eurotransplant in 2006 [6, 7]. The current MELD priority score for T2 HCC (1 lesion of 2–5 cm or 2–3 lesions, each 1–3 cm) is 22 points, and there are quarterly increases corresponding to a 10 % increase in pre-transplant mortality. This system has decreased wait-list time from 1.3 to 0.6 years, and the dropout rate from 25.9 to 6.7 %. The number of LT performed for HCC has risen to 26 %; however, in some UNOS regions the percentage is much higher, as well as there being a parallel increase in the wait-list dropout rate [8–10].

Any macro-morphologic tumor progression beyond the Milan size limits results in loss of MELD prioritization. In such situations, LT centers have looked at downsizing the HCC prior to deceased donor LT (DDLT) or live donor liver transplant (LDLT). Tumor recurrence is a strong predictor for reduced overall post-LT survival. Multiple factors have been looked at in selecting patients to avoid post-transplant recurrence including tumor biology, microvascular invasion, tumor staging, total tumor volume, age and AFP levels [11, 12]. Careful selection of patients outside of Milan criteria disease allows LT of more patients without compromising long-term disease-free and patient survival. What follows is a review of several of the other HCC staging systems that LT centers use to list and prioritize their patients, an outline of specific prognostic variables that may impact post-LT recurrence of HCC, and then data on surveillance strategies to detect post-LT HCC recurrence as well as its treatment.

12.2 Alternative Expanded LT Criteria for HCC

In the pre-MELD era due to lack of any specific criteria of LT for HCC, recurrence rates were high which negatively affected post-LT survival rates [13]. However in 2001, Yao et al. proposed modest expansion of the Milan criteria: solitary HCC $\leq$6.5 cm, or $\leq$3 nodules with the largest lesion being $\leq$4.5 cm and a total tumor diameter $\leq$8 cm (UCSF criteria). With this new set of criteria, a 5-year survival rate of 75 % was demonstrated after LT for HCC. The UCSF criteria were developed based on explant histology and thereafter were validated prospectively using radiology, in contradistinction to the Milan criteria which were based only on radiologically determined tumor burden [14, 15]. A subsequent study from Mount Sinai demonstrated that using the UCSF criteria, there was a potential benefit of transplanting 10 % more patients having HCC without compromising overall patient survival (Table 12.1) [16].

Table 12.1 Other extended criteria for predicting post-LT HCC recurrence

Author/institution	Proposed expanded criteria	Radiology/path	5-year survival
Yao, UCSF [14]	1 nodule ≤6.5 cm, or 2–3 nodules ≤4.5 cm and total tumor diameter ≤8 cm	Pathology	MC—72 % EC—73 %
Herrerro, Pamplona [22]	1 nodule ≤6 cm, or 2–3 nodules each ≤5 cm	Radiology	Not defined comparison Group—79 %
Roayaie, Mt. Sinai [16]	1 or more nodules 5–7 cm	Radiology	EC—55 %
Yao, UCSF [15]	1 nodule ≤6.5 cm, or 2–3 nodules ≤4.5 cm and total tumor diameter ≤8 cm	Radiology	MC—80 % EC—82 %

UCSF University of California, San Francisco, *EC* expanded criteria, *MC* Milan criteria

12.2.1 Up-to-Seven Criteria

This system was developed using data from a retrospective analysis involving 36 centers, enrolling 1556 patients with HCC undergoing LT. It includes seven as the sum of the size of the largest tumor (in cm) and the number of tumors, in the absence of microvascular invasion or extrahepatic disease. The 5-year survival rate for HCC within the up-to-seven criteria system was 71.2 % vs. 53.6 % for patients exceeding it. The survival rates were not very different between Milan criteria and up-to-seven criteria. The "metro ticket paradigm," was developed as a tool to estimate 5-year overall-survival probability according to size of the largest tumor, number of tumors, and the presence or absence of microvascular invasion. On the basis of metro ticket calculations, as the tumor burden increases from the conventional Milan criteria in a patient, the 5-year overall-survival post-LT decreases. An online calculator was devised to predict the survival post-LT at different intervals on the basis of size of the largest tumor and number of tumors (Fig. 12.1) [17, 18].

In light of potential deficiencies of other HCC criteria with regard to difficulties in identifying small lesions accurately in the setting of multifocal HCC, tumor biology not being related to the size and number of the lesions, radiological overstaging, and understaging, the Toronto criteria were designed. In this study, all patients underwent a pre-LT liver biopsy of the dominant lesion. A comparative analysis based on the biopsy results as well as radiologic features of the HCC, and patients were grouped into whether they fell within Milan criteria or within Toronto criteria. Patients with poorly differentiated tumors on biopsy and radiological vascular invasion were excluded and the size and number of tumors did not matter, but AFP more than 400 was considered to be a predictor for recurrence. The 5-year overall-survival rate was 70 % within Toronto criteria vs. 72 % within Milan criteria with similar recurrence-free survival rates. The limitation was sampling error and staging difference at different sites of the tumor [19–21]. Another study performed in a prospective manner utilizing radiological assessment used criteria of 1 tumor nodule ≤6 cm

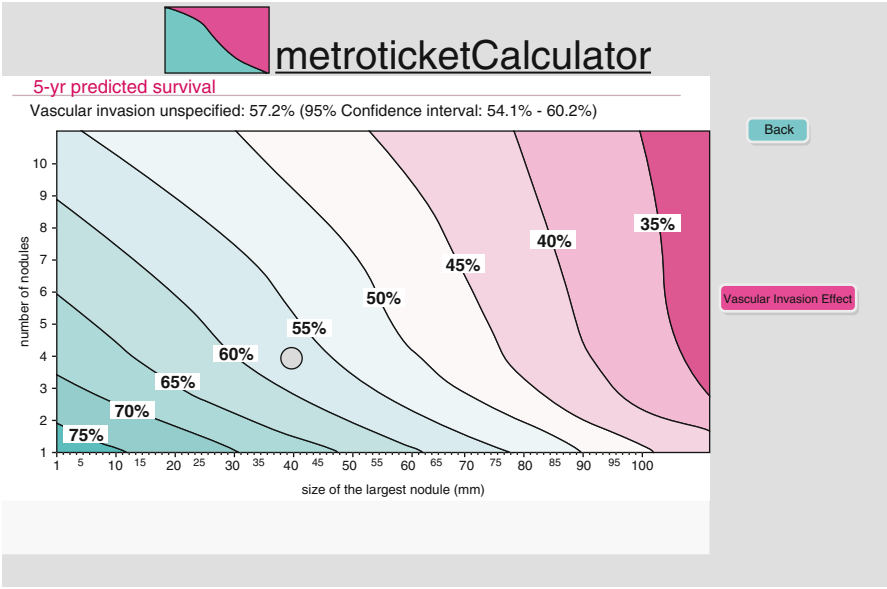

Fig. 12.1 Adapted from metroticket online calculator. Calculated survival is based on size, number of nodules, and the presence of vascular invasion

in diameter or 2–3 nodules of up to 5 cm each; patients with vascular invasion and extrahepatic spread were excluded. Patients underwent regular imaging and locoregional treatment as deemed necessary to prevent wait-list dropout. Intention-to-treat survival of the 26 patients who exceeded the Milan criteria when they were included on the waiting list was comparable to survival of those who fulfilled Milan criteria [22].

The increasing wait time on the LT list due to the severe donor organ shortage has led to progressive tumor burden in many patients. The intent-to-treat approach has been addressed, in that patients with HCC waiting for LT for more than 1 year have been found to have reduced overall survival compared to those waiting for less than 1 year. This reduced survival rate has been attributed to an increase in the number of patients whose tumors progressed beyond Milan criteria, causing the LT center to remove these advanced cases from the waiting list. Estimating progression rates is critical for establishing the patient group that should receive the highest priority on the waiting list [23, 24]. Freeman et al. analyzed United Network for Organ Sharing (UNOS)/OPTN data and found that MELD score at listing, maximum tumor size and alpha-fetoprotein level, in addition to age were the only independent factors associated with increased risk for candidates with HCC, dropping off the list [25].

Most of the Asian literature has revolved around LDLT. Many centers in Asia thus follow different criteria, the most studied criteria of which is the "Kyoto criteria" involving a combination of tumor number $\leq$10, maximal diameter of each

tumor ≤5 cm, and serum des-gamma-carboxy prothrombin (PIVKA II) levels ≤400 mAU/mL. The overall survival rate was 82 %, significantly higher 5-year recurrence rates occur in patients beyond these criteria than within the criteria (9.5 % vs. 7 %). PIVKA II was demonstrated to be more significant than AFP in predicting recurrence [26, 27].

12.3 Patterns and Predictors for Recurrence

A post-LT recurrence may occur when an extrahepatic metastasis has been missed (or was not detectable) during the pre-LT work-up, or it can also be the consequence of circulating HCC cells engrafting and growing in a target organ during the peri-LT period. Given the higher original cancer load of extrahepatic metastasis, such recurrences are expected to appear earlier after transplantation. These two mechanisms may help explain the observed bimodal distribution of recurrences, with most of them appearing during the first 18 months. The time between LT and recurrence is vital in predicting the outcome after recurrence, with worse survival rates occurring when recurrence is diagnosed within 12 months from LT [28–31].

Patients who undergo LT for HCC are always at risk of tumor recurrence. There have been many factors studied that contribute to disease recurrence, and even more so when utilizing the expanded criteria.

Guzman et al. in 2005 utilized immunostaining for p53 and Ki67 in explanted livers and suggested that positive immunostaining of HCC lesions in liver explants was strongly associated with more rapid tumor recurrence after LT. They concluded that patients with staining for both p53 and Ki67 on pre-LT biopsies and who had serum AFP levels >100 ng/mL were particularly at higher risk for early tumor recurrence [32]. Stroescu et al. found that the high labeling index of proliferating cell nuclear antigen (PCNA), p53 nuclear accumulation and high VEGF expression were all associated with a poorer survival in patients with HCC. These data suggest that p53 and VEGF molecular diagnosis along with the expression of proliferating markers (Ki67 and PCNA) may be prognostic markers for recurrence in patients undergoing LT for HCC. It needs to be further studied as to whether these markers can emerge as indicators for vascular invasion and further help in estimation for HCC recurrence [33].

A study from the University of Alberta and University of Geneva used a score for patient selection based on a combination of TTV (Total Tumor Volume) ≤115 cm^3 and AFP ≤400 ng/mL for patients with HCC undergoing LT. It was found that recurrence rates were similar at 10 % vs. 12.8 % for patients within and beyond Milan criteria, respectively, when following these criteria. Their analyses indicated that patients with a TTV greater than 115 cm^3 or an AFP greater than 400 ng/mL had significantly worse survival, with a 50 % survival at 3 years and an overall recurrence rate of 12.8 %. TTV was calculated by adding the maximum volume of each HCC, based on a spherical equation formula ($4/3\pi r^3$) in which r is the maximum tumor radius of each lesion. In following this method of calculating TTV, it

was demonstrated that as tumors increase in size, they frequently deviate from a truly spherical shape, thus more recently an ellipsoid formula has been used that considers diameters in all three dimensions. For example, the volume of a lesion $6.5 \times 5 \times 4$ cm for example would presumably be 144 cm^3 calculated using the maximum diameter only with the spherical equation. Using the three diameters and an ellipsoid formula, the actual volume would be 68 cm^3, which is a more accurate calculation, and may more precisely predict the recurrence risk.

12.4 Predictors of Recurrence

Smoking per se in the pre- and post-LT setting is an independent risk factor for HCC. Pre-LT and continued post-LT smoking has also been shown to be associated with de novo HCC and recurrence [34–38]. HCC recurrence post-LT has been associated with a poor prognosis and decreased survival. Tumor size and number are crude surrogates for the biologic aggressiveness of HCC. Several centers have evaluated expansion of criteria based on tumor differentiation, genetic profile, and alpha fetoprotein levels. Recurrence is largely attributed to micro- or macro-metastasis from the primary tumor [39, 40].

Biological parameters like histopathologic grading and microvascular invasion are generally not assessed pre-transplant. The size of the tumor per se does not rule out higher tumor grades or microvascular invasion. However, tumor diameter and number of nodules in correlation with the histopathologic grading are predictive of vascular invasion only in HCC larger than 5 cm [41, 42]. Apart from the already-mentioned risk factors for recurrence, Hanouneh et al. emphasized that the rate of tumor growth is another important factor that predicts recurrence. It was observed that the recurrence rate of HCC after LT was higher among patients who exceeded both Milan and UCSF criteria compared with those who fell within them (33 % vs. 5.8 %). However, there was no significant difference in post-LT recurrence between patients outside Milan criteria with tumor growth <1.61 cm^3/month from those within it (11 % vs. 5.8 %). Patients beyond Milan criteria with a slow-growing tumor (tumor growth <1.61 cm^3/month) experienced less frequent post-LT recurrence than those who exceeded MC with faster-growing tumors (11 % vs. 58 %). Similarly, there was no significant difference in HCC after LT between slow-growing tumors beyond and those within UCSF criteria (17 % vs. 10 %). The rate of recurrence was significantly higher in subjects beyond Milan criteria and UCSF with faster-growing tumors [43].

In the recent past, there has been a lot of work surrounding the molecular profiling of HCC in order to overcome the discrepancy between tumor morphobiology and post-LT recurrence. Studying short regulatory noncoding RNAs, three major micro-RNA (miRNA) clusters have been identified in a training set of 89 patients with HCC- and HCV-related cirrhosis, within a cohort of 165 patients having different underlying liver diseases. Expression levels of three miRNAs representative at each cluster, miR-520g, miR-516-5p and especially, miR-517a, promoted

tumorigenesis and metastatic spread in vivo. Moreover, low expression of two other miRNAs (miR-26a, miR-26b) was correlated with decreased post-LT survival [44, 45]. Sato et al. analyzed the miRNA expression profiles in paired, tumor and non-tumor tissue samples from HCC liver resections, and found miRNAs associated with recurrence in both the tumor and corresponding non-tumor tissues. They then classified them into tumor-suppressive miR and oncogenic miRs. While the expression of certain miRNAs was suggestive of tumor-suppressive function (13 types), there were relevant miRNAs in non-tumor tissue samples that were also associated with recurrence (56 types). Another group in a multivariate analysis has shown that high expression of miRNA-203 in tumor tissue was an independent factor for a better prognosis and HCC recurrence-free survival [46, 47].

Long noncoding RNAs have also been studied. These RNAs are involved in diverse cellular processes, including cell-cycle regulation, immune surveillance, and stem cell pluripotency. HOTAIR (long noncoding RNA HOX transcript antisense RNA) is one such biologically well-studied, long noncoding RNA [48–50]. Yang et al. studied HOTAIR specifically to predict recurrence in HCC post-LT. Upon clinicopathological correlation analysis, segregation of tumor samples of 60 patients who underwent LT into increased HOTAIR expression and decreased HOTAIR expression groups revealed no significant correlation with any single clinicopathological characteristic, including age, gender, AFP, histopathological grading, tumor number, or tumor size. Furthermore, on univariate and multivariate survival analysis, the 3-year cumulative recurrence-free survival in HCC patients with a high expression level of HOTAIR was significantly lower than those with low HOTAIR expression. Consistently, patients with overexpression of HOTAIR were also prone to earlier recurrence in HCC patients who underwent surgical resection. Lower recurrence-free survival was demonstrated in the patients within Milan Criteria having high expression of HOTAIR, which suggests that size of the tumor alone is not a definitive criterion to exclude patients from LT [51, 52].

A recent retrospective analysis of post-transplant patients from two LT centers in the United States with further validation of the analysis using an HCC database from Indiana University assessed the clinical impact of ischemia–reperfusion injury on post-LT HCC recurrence. Apart from AFP >200 ng/mL and macro-microvascular invasion and tumor characteristics, it was found that cold ischemia time (CIT) >10 h and warm ischemia time (WIT) >50 min were statistically significant independent predictors for early HCC recurrence (<12 months). In addition, an increased number of blood transfusions during the surgery were more predictive for tumor recurrence with this being a surrogate marker of a more prolonged and difficult surgery [53–57]. Samoylova et al. demonstrated that the risk of HCC recurrence was significantly lower for patients with a waiting time >120 days versus patients waiting ≤120 days on the LT list. However, the association between HCC recurrence and the wait time lost its significance over time and was not found to be statistically significant 2 years post-transplant. Among the patients receiving ablative therapy for their HCC, those waiting ≤120 days had a significantly higher risk of recurrence than their longer waiting counterparts in the first year after LT [43, 44]. The importance of wait time and HCC recurrence is an emerging concept in DDLT. This has

been the case with LDLT over the years as there practically is no waiting period due to "fast tracking" of living donor cases. In contradistinction, a few recent studies have not shown significant increase in HCC recurrence post-LDLT, so this issue needs further clarification [58–61].

Sharma et al., utilizing a single center retrospective review, demonstrated that the number of HCC lesions and size of the largest lesion were significant predictors for HCC recurrence; they also demonstrated the importance of older donor age in HCC recurrence [62]. Concentrating on the donor factors in tumor recurrence, Parsia et al. reviewed the UNOS database and proposed that along with the tumor factors (microvascular invasion, tumor differentiation), AFP > 500 ng/mL, donor age ≥60 year, and organs of non-local share distribution, when utilized for HCC liver transplant candidates, may convey a higher cumulative incidence of post-transplant HCC recurrence. BMI appears to have no role in disease recurrence [63, 64]. To predict the risk for HCC recurrence after LT, the importance of the vascular invasion in the explant tumor and tumor grade has consistently been demonstrated. Knowing such histological variables is also important in the pre-LT setting [65, 66]. In 2009, Jonas et al., for the first time showed the prognostic significance of DNA index in recurrence of HCC post-LT on pre-LT tissue biopsy. DNA index was determined by Feulgen staining and semi-automatical image analysis of the histograms was obtained from the liver biopsy specimen. Of interest, a group outside Milan criteria ($n = 51$) with a DNA index ≤1.5 (cut off) had 5- and 10-year overall-survival rates of 72 % and 68 %, respectively. In the multivariate analysis, only DNA index and vascular invasion were identified as prognostic variables for overall survival and recurrence-free survival. In contrast, fulfillment of the Milan criteria and histopathological grading did not reach statistical significance [67].

Immunosuppression is known to represent a significant risk factor for tumor growth [68–70]. Lower recurrence-free survival has been observed in patients who received increased doses of cyclosporine in the first post-transplant year. Cyclosporine dosage given in the first 12 months after LT and pathologic tumor stage were independent prognostic factors in multivariate analysis [71, 72]. One of the reasons for early tumor recurrence may be the result of either previously undiagnosed distant metastasis that had been present before LT, or spillage of cancer cells at the time of surgical manipulation, all being aggravated by the effect of immunosuppression post-LT. Recurrence is more aggressive in the setting of post-LT immunosuppression as compared to patients undergoing resection; it is unlikely for de novo tumors to develop in the liver allograft within a span of 1–2 years. Increased AFP and imaging surveillance post-LT were used as markers to detect recurrence. The presence of microscopic extrahepatic foci of disease in lymph nodes or distant organs at the time of LT, as well as hematogenous or peritoneal tumor dissemination during transplantation, are mechanisms leading to disease recurrence. Bone metastasis typically portend have a very poor survival [73–76].

Roayaie et al. studied 1674 patients who underwent LT over a period of 14 years in order to look at the pattern of HCC recurrence and survival after recurrence. Fifty-seven patients out of 311 (18.6 %) were transplanted for HCC with a wide range in the time from LT to the diagnosis of HCC recurrence, the median being

12.3 months (range 1.5–60.3 months). Median survival from the time of LT was 24.5 months for patients having a recurrence. Survival for patients with recurrence was significantly shorter for patients transplanted with HCC that did not recur. Median survival from the time of recurrence was 8.7 months; it was significantly greater in patients who recurred after the first postoperative year after the LT (22 %) [77]. It was demonstrated that intrahepatic disease was identified in the early recurrence group, whereas more extrahepatic recurrences were diagnosed in the late recurrence group. The most common extrahepatic sites of recurrence included lung, bone, abdominal lymph nodes, adrenal glands, and peritoneum, in decreasing order of frequency [78, 79].

In a clinico-radiological assessment of 150 patients looking for patterns and prognostic factors for recurrence of HCC in a univariate analysis, serum α-fetoprotein level >100 ng/mL, Child Pugh class other than C (patients with more advanced cirrhosis fared better than those with better-compensated disease), the presence of intrahepatic portal venous thrombosis more than three tumors, largest tumor greater than 3 cm in diameter, greater than an 8-cm sum of tumor diameter and viable tumor volume ratio after interventional therapy greater than 10 % of the entire tumor volume were all found to be significant [80]. Multivariate analysis found three factors independently significant for recurrence; the presence of intrahepatic portal venous thrombosis, largest tumor greater than 3-cm diameter, and viable tumor volume ratio after interventional therapy greater than 10 % of the original tumor [81]. No survival difference was noted when patients were followed with pre-treatment diagnostic imaging, either within Milan criteria or within UCSF criteria, suggesting that the accuracy of diagnostic imaging at certain centers was comparable to the review of explant pathology [15, 82, 83]. Analyzing data from 865 transplanted patients over 30 years helped in developing a prognostic model to predict recurrence of HCC post-LT. In addition to the radiological features, there were three significant biochemical markers (alpha-fetoprotein, neutrophil–lymphocyte ratio, and cholesterol levels) [84].

12.5 Down-staging

The term “down-staging” can be defined as the use of any sort of treatment prior to LT in patients who have tumors beyond Milan criteria in order to reduce tumor stage to be eligible for LT. Both resection and locoregional therapy can be used to down-stage and as a bridge to LT. Pre-transplant treatments are also used for patients within T2 criteria in order to prevent progression which could lead to increased wait-list dropout. There is, however, no consensus on whether such down-staging of HCC to within the Milan criteria/T2 followed by LT has a beneficial outcome (Table 12.2). Although several published series have shown good post-LT outcomes in down-staged patients, high AFP levels in these patients are considered to be a predictor for poor outcome and HCC recurrence. Locoregional therapy for the tumor during the waiting period helps in the reduction of AFP levels, halting the

Table 12.2 Selected studies on post-LT outcomes after HCC down-staging pre-LT

Group	Treatment	Patients	Inclusion criteria	Transplanted patients	RFS post-LT	Survival post-LT
Chapman et al. [87]	TACE	76	Beyond MC	17	50 % at 5 years	93.8 % at 5 years
Yao et al. [88]	TACE, RFA, resection	61	1 HCC 5–8 cm	35	92 % at 2 years	92 % at 2 years
			2–3 HCCs 3–5 cm			
			Total diameter ≤8 cm			
			4–5 HCCs ≤3 cm			
			Total diameter ≤8 cm			
Otto et al. [98]	TACE	62	Beyond MC	27	68 % at 5 years	73.2 % at 5 years
Cillo et al. [99]	TACE, RFA, PEI, resection	40	Beyond MC	31	No recurrence	>90 % at 3 years
			WD or MD HCC			
Ravaioli et al. [100]	TACE, PEI, RFA resection	48	1 HCC 5–8 cm	32	71 % at 3 years	NA
			2 HCCs 3–5 cm			
			Total diameter ≤8 cm			
			3–5 HCCs ≤4 cm			
			Total diameter ≤12 cm			

HCC hepatocellular carcinoma, *LT* liver transplantation, *RFS* recurrence free survival, *TACE* transarterial chemoembolization, *MC* Milan criteria, *NA* not available, *RFA* radiofrequency ablation, *PEI* percutaneous ethanol injection, *WD* well differentiated, *MD* moderately differentiated

tumor progression and possibly leading to an overall better outcome [85–92]. Change in serum AFP levels (defined as a >50 % decrease compared with baseline) after locoregional therapy is useful in assessing tumor response and survival and for assessing lesions that have progressed on imaging studies. LT recipients having HCC with pre-transplant AFP levels >400 ng/mL have a higher tumor recurrence rate [93, 94].

It is now well understood that patients who undergo LT with HCC beyond Milan criteria after down-staging do quite well, if time is added as a criterion for LT. This strategy now referred to as the "ablate and wait," philosophy is used to assess the response of the tumor to locoregional therapy prior to transplantation [95, 96]. As more patients are waiting longer periods of time on the LT list due to the organ donor shortage and more patients are downsized to meet prioritization criteria, they end up undergoing more frequent locoregional therapy. An increased number of embolization procedures may lead to hepatic artery problems; thus, one should anticipate this post-LT and be keenly aware of the probable complications of ischemic cholangiopathy and hepatic artery aneurysm or stenosis. Patients undergoing therapy with Yttrium [89] radioembolization as well as previous resections for HCC may develop increased adhesions which can lead to a more technically difficult surgery and an increased transfusion requirement. Thus, the clinician should be aware of this especially in patients being downsized [97].

12.6 Management of Recurrence

The incidence of recurrent HCC following LT in different LT centers has ranged from 6 to 56 % [101–104].

Treatment options depend on whether the recurrence of the disease is intrahepatic or extrahepatic. As with HCC of the native liver, the feasibility of surgical resection versus ablation to treat recurrence in the allograft depends on the experience of the team, as well as the size and location of the tumor. While resection may be more applicable to more superficial and larger solitary HCC, ablative techniques may be sufficient and appropriate in the setting of smaller and more deeply situated HCC. While patients who present with disseminated disease are generally not candidates for locoregional therapy, successful surgical salvage has been reported for intrahepatic and/or confined extrahepatic HCC metastasis. Surgical resection has been associated with better survival as compared to nonsurgical approaches with survival of 15.5 vs. 5.5 months, respectively [105]. Chok et al. reported that patients who did not have bone metastasis and who had late HCC recurrence defined as two or more years after LT, had a more favorable 5-year survival with resection of the metastases (71 %) compared with patients who recurred earlier (7 %) [31, 74, 75, 106].

Multi-modality locoregional therapies have been used in the management of HCC recurrence, although the data are lacking on its use in the liver allograft. Ko et al. reported on 28 patients with recurrent HCC who underwent one or more cycles

of TACE after LT; the therapy was well tolerated. However, the long-term outcomes were not reported [107, 108]. Systemic therapies in the management of recurrent HCC have had suboptimal results with limited published data. When HCC progression and tumor burden are not amenable to surgical/ablative/locoregional treatments, sorafenib has proven to increase survival; this modest benefit is similar to that described in patients having advanced HCC in the non-LT setting. Recent studies have confirmed sorafenib to be responsible for a benefit in survival with respect to best supportive care in post-LT unresectable HCC recurrences, with an acceptable safety profile and no apparent drug-to-drug interaction with immunosuppressive medications [107–111].

The role of immunosuppression in the recurrence of HCC post-LT has been a topic of discussion, and there is limited consensus on this topic. Retrospective studies have suggested that the risk of HCC recurrence is increased when calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus are included as part of the post-transplantation immunosuppressive regimen. The exact mechanism for this increased risk is unknown. In contrast, the mTOR pathway is activated in several models of HCC; inhibition of this pathway may reduce cell growth and tumor vascularity. There are data suggesting that immunosuppression regimens that include the m-Tor inhibitor, rapamycin (sirolimus), or its analogs (everolimus) reduce the risk of HCC recurrence as well as the development of de novo malignancies after LT [70, 112–118]. However, recent studies on everolimus (mTORi) show no significant benefit on recurrence of HCC [119]. Sorafenib along with m-TORi was studied as adjuvant therapy for recurrent HCC, but the study reported a few cases of gastrointestinal and cerebrovascular bleeding. Hence, the combination was not advised, whereas sorafenib with other combinations of immunosuppression had no such untoward complication [120–123]. In our experience, the combination of sorafenib with sirolimus has appreciable side effects and is somewhat difficult for post-LT patients to tolerate long term. Although most clinicians try to minimize immunosuppression in the presence of a malignancy, tapering should be judicious and medication levels followed closely, so as to not precipitate acute cellular or chronic ductopenic rejection [124].

Salvage LT is another method of the treatment for post-liver resection recurrence. Limited data suggests the survival rates between the salvage LT and primary LT are similar. In addition, the 1-year, 3-year, and 5-year overall and disease-free survival rates within selected patients were also similar between the LDLT and DDLT in the salvage LT group, which indicates that salvage LDLT is a safe procedure for highly selected patients. HCC recurrence within 8 months after an alpha-fetoprotein level higher than 200 ng/mL and HCC recurrence outside the Milan criteria at salvage LT were independent risk factors for poor recurrence-free survival after salvage LT [125, 126]. Treating the post-LT patient with antivirals for recurrent HBV or HCV may prevent progressive liver disease and the development of cirrhosis. Prevention of the development of allograft cirrhosis will also prevent the development of de novo HCC. Patients with HBV reinfection have been shown to be more likely than patients without HBV to have post-LT HCC recurrence and HCC recurrence itself is a risk factor for HBV recurrence, whereas HBV recurrence is an independent risk factor for recurrence of HCC in the allograft [127, 128].

12.7 The Issue of HCC and LDLT

As the number of patients on waiting lists for LT is increasing, the use of adult-to-adult LDLT may shorten waiting time and possibly decrease wait-list mortality in patients. The offer of living liver donation to adult recipients with HCC has understandably generated controversy with respect to candidate selection, donor risk, and recipient allograft outcomes. In addition, patients with more aggressive tumor biology, who would otherwise drop off the waiting list due to tumor progression, might be "fast-tracked" to transplant without locoregional therapies and this may lead to an increased recurrence rate of HCC post-transplant [129–131]. It has been postulated that the rapidity of liver regeneration can have a stimulatory effect on residual tumor cells, leading to higher HCC recurrence in live donor transplants. A recent animal model supports this hypothesis; this theory of recurrence in LDLT needs more validation however as various transplant groups have noted higher recurrence rates in LDLT as compared to DDLT recipients [132–134].

Bhangui et al. reported no difference in recurrence rates in LDLT vs. DDLT recipients, but did note a trend for poorer outcomes in LDLT recipients whose tumors exceeded Milan criteria. Looking at the survival pattern in LDLT, Vakili et al. reported a significantly improved 5-year survival in LDLT compared to DDLT recipients (81 % vs. 58 %) despite a significantly higher HCC recurrence rate among the LDLT group (29 % vs. 12 %). Improved survival in the LDLT group may be related to the benefits of a superior quality graft due to potentially younger donors and shorter cold ischemia time [135–137]. In a recent report from Korea that studied inflammatory markers in the living donor transplant setting, Neutrophil Lymphocyte ratio (NLR) and CRP (C-reactive protein) were used to assess prognosis post-LT in patients with pre-LT disease exceeding Milan criteria. They developed a scoring system with NLR and CRP, taking into account that inflammation may play a major part in tumorigenesis. In patients exceeding Milan criteria who had an NLR level <6.0 and CRP level <1.0, there was a much higher disease-free survival post-LT [138].

12.8 How HCC in the LT Setting Is Addressed at Our Center

- Non-tumor portal venous thrombus is not considered as a contraindication to LT
- We consider all HCC within Milan criteria
- Multidisciplinary committee including surgeons, hepatologists, radiologists (interventional/diagnostic), and oncologists discuss the patient prior to listing with HCC priority points.
- HCC beyond these limits are treated with locoregional therapy and are observed for >6 months with imaging performed every 3 months.
- Cases identified with a rising trend in AFP or >500 are followed with repeat scans for a minimum of 6 months before transplanting, either prior to listing or while inactive on the list but accruing waiting time.

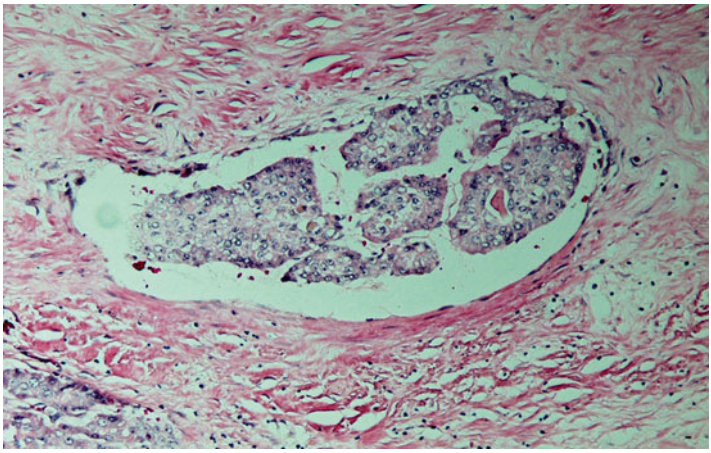

Fig. 12.2 Microvascular invasion in HCC (H&E stain; magnification ×100). This photo demonstrates a thin-walled vessel that contains a thrombus composed of moderately differentiated HCC. Although there is retraction from the vessel wall, the tumor thrombus retains the shape of the vessel lumen (Courtesy of MI Fiel, MD)

- Locoregional therapy is offered to all patients on the waiting list to down-stage or prevent progression of the tumor.
- Liver pathologists thoroughly examine the explant with sagittal dissection of the liver using 5 mm thin cuts to look for sub-centimeter lesions, and specifically assess microvascular invasion (Fig. 12.2), intrahepatic metastasis and differentiation of the tumor (Fig. 12.3) following Edmondson–Steiner classification [139].
- High risk is defined when there is micro- or macrovascular invasion or the tumor burden histologically or grossly exceeds Milan criteria depending on explant pathology. Patients are followed with 3 monthly imaging and biochemical tests for the first year and 6 monthly thereafter post-LT. Conversion from calcineurin inhibitor to m-TOR inhibitor is considered in all patients at the 3-month mark if they are medically well.

12.9 Summary

Although it is known that LT is the best treatment for patients with HCC and the burden of the disease is increasing worldwide, expansion of the present criteria for LT in HCC needs to be addressed on an ongoing basis. Maintaining outstanding post-LT overall and recurrence-free survival rates remains imperative. With the development of the new antiviral agents to treat HCV pre-LT, we hope that in the long term a less number of patients may require transplantation for decompensated liver disease. Thus, the number of patients with HCC needing LT is expected to

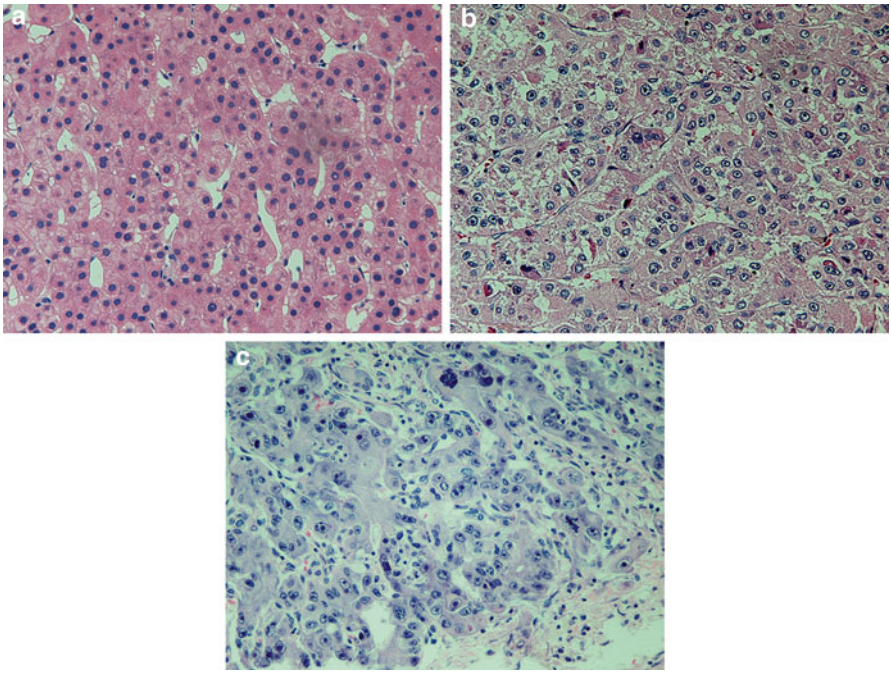

Fig. 12.3 (**a**) Well-differentiated hepatocellular carcinoma (HCC) (Edmonson-Steiner grade 1). (H&E stain; magnification ×100). Tumor cells are arranged in thickened trabeculae (cords) that comprise three- to five-cell thick plates. Each trabeculum is lined by endothelial cells. Tumor cells are easily recognizable to be of hepatocytic origin by the abundant eosinophilic cytoplasm and centrally placed nuclei. Note that the nuclei have minimal pleomorphism, which is an important characteristic to categorize the tumor as a well-differentiated HCC (Courtesy of MI Fiel, MD). (**b**) Moderately differentiated HCC (Edmonson-Steiner grade 2). (H&E stain; magnification ×100). Tumor cells are arranged in thickened trabeculae, similar to the well-differentiated HCC in (**a**). However, note the greater diversity in size and shape of the tumor nuclei, features that characterize the HCC to be moderately differentiated (Courtesy of MI Fiel, MD). (**c**) Poorly differentiated HCC (Edmonson-Steiner grade 3). (H&E stain; magnification ×100). Tumor cells have marked pleomorphism of the nuclei with occasional tumor giant cells and frequent multinucleation. The cytoplasm is basophilic. Tumor cells no longer are arranged in trabeculae but rather are haphazardly arranged in sheets. Mitotic figures are also easily identifiable in this photomicrograph (Courtesy of MI Fiel, MD)

increase in the future, as this becomes the primary indication for LT. It remains to be seen whether HCV eradication may decrease the ultimate development of HCC in cirrhotic patients, as has been seen with HBV and in small studies of interferon treated HCV cirrhotic patients [140]. Thus, ongoing evaluation of the different pre-LT staging systems is necessary along with refinement of prognostic clinical, treatment response, and molecular biologic/genetic variables in order to meet this anticipated transplant need.

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Chapter 13
Role of Neoadjuvant and Adjuvant Treatment in HCC Recurrence After Liver Transplantation

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Abbreviations

CR	Complete response
DEB	Drug-eluting beads
EASL	European Association for the Study of the Liver
EBRT	External beam radiotherapy
HCC	Hepatocellular carcinoma
LRT	Locoregional therapy
LT	Liver transplantation
PR	Partial response
RFA	Radiofrequency ablation
SBRT	Stereotactic body radiation therapy
TACE	Transarterial chemoembolization
TARE	Transarterial radioembolization
UCSF	University of California at San Francisco
UNOS	United Network for Organ Sharing

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13.1 Introduction

Since Mazzaferro et al. reported successful outcomes of LT for HCC with limited tumor loads, LT has become a well-established curative treatment for HCC within the Milan criteria (1 nodule ≤5 cm, 2–3 nodules each ≤3 cm). HCC patients within Milan criteria are given priority to receive deceased donor LT in many developed countries worldwide [1–3]. Even with higher priority given to these patients, usual waiting time for LT can range 6–12 months.

Use of neoadjuvant therapy on HCC patients who are waiting for LT has two objectives. First is to prevent dropout from the waiting list due to tumor progression. The concept of "bridging therapy" prior to LT is accepted in most transplant centers. International consensus recommends bridging strategies for patients with United Network for Organ Sharing (UNOS) T2 (1 nodule 2–5 cm or 2–3 nodules each ≤3 cm) HCC and a likely waiting time longer than 6 months. Another indication of neoadjuvant therapy for possible transplant candidates is down-staging HCC with intermediate stage into the Milan criteria or other acceptable criteria which allows entry to the waiting list for LT. Various locoregional therapies (LRT) for HCC have evolved during the past two decades, and made down-staging feasible with reasonable success rates [4–6]. Multiple studies have proven the efficacy of LRT with transarterial chemotherapy (TACE) and radiofrequency ablation (RFA) for down-staging [7, 8]. Other promising LRT and systemic therapy that have been used in advanced HCC have now been brought into the field of neoadjuvant therapy for transplant candidates. These modalities include TACE using drug-eluting beads (DEB-TACE), transarterial radioembolization (TARE) with Yttrium 90, external beam radiotherapy (EBRT), and sorafenib [9–13]. The goal of down-staging HCC in transplant candidates is to achieve comparable post-transplant outcomes with that of non-HCC patients. Long-term post-transplant survival of 50–60 % at 5 years [14–17] would be a target for outcomes that would justify LT for patients with intermediate staged HCC [14].

Adjuvant therapy after LT to prevent HCC recurrence is rarely performed due to lack of clinical efficacy data. Several small studies have investigated the efficacy of adjuvant chemotherapy after LT; however, clinical outcome with cytotoxic chemotherapy were disappointing. Recently, sorafenib has been introduced as a treatment for recurrent HCC after LT. With the promising result in several series in post-transplant setting for recurrent HCC, sorafenib has gained a great attention as a possible agent for adjuvant therapy. In this chapter, we review the current evidences of neoadjuvant therapy and adjuvant therapy for HCC and its impact on HCC recurrence after LT.

13.2 Conventional LRT with TACE and RFA

The most commonly used LRT in transplant candidates is conventional TACE followed by RFA [4, 18–20]. Most evidence in the field of neoadjuvant therapy for transplant candidates are based on studies mainly using these two modalities. The

concept of LRT prior to LT was first introduced in 1997 with the study using TACE [21]. Successful down-staging rates with TACE have been reported to range from 31 to 61 % [10, 22–24]. RFA has been shown to have a marginal advantage in terms of tumor necrosis. The better indication of RFA comparing transarterial therapies (TACE, TARE) generally include the tumor size ≤3 cm, ≤3 nodules, central location of the lesions in the liver, and no major vascular or biliary structure near the target lesions [25, 26]. RFA has been used mainly as a bridge therapy rather than for down-staging because of its limited efficacy for large tumors.

Mazzaferro et al. [25] reported 50 transplant candidates with HCC, 40 of which are within MC treated with single RFA session. Four patients (8 %) had major complications that required admissions. No dropout was reported with a mean waiting time of 9.5 months. The UCLA group reported another series containing 52 patients, 43 of which are within Milan criteria treated mainly with RFA [26]. Three patients (5.8 %) experienced significant treatment-related complications, and three patients (5.8 %) were reported to dropout due to tumor progression with a mean waiting time of 12.7 months.

13.3 Emerging Locoregional and Systemic Therapies

Recent advance in transarterial and ablative treatments have widened the choice of LRT for intermediate staged HCC. These modalities include DEB-TACE, TARE, and EBRT. Emerging modalities have clinical efficacy that is comparable to TACE but toxicities are more tolerable compared to TACE. These modalities have been used in non-transplant setting and are now introduced to neoadjuvant therapy for transplant candidates.

13.3.1 DEB-TACE

TACE with drug-eluting beads (DEB-TACE) uses beads loaded with chemotherapy agents and release it gradually so that systemic side effects are reduced, and tumor drug delivery is enhanced. The PRECISION study compared DEB with doxorubicin vs. conventional TACE among 212 intermediate staged HCC in non-transplant setting demonstrated comparable disease control rate and comparable adverse events [27]. Subset analyses showed a significantly higher disease control rates in patients with more advanced disease (Child Pugh B, ECOG 1, bilobar, or recurrent disease) treated with DEB-TACE compared to that with conventional TACE. Recent sub-analysis of the trial revealed that liver toxicity and cardiac toxicity were significantly lower in DEB-TACE [28]. In a recent study that compared with DEB and conventional TACE in Asian patients, DEB-TACE showed significantly better treatment response and disease control [29]. In the transplant setting, there is one small study comparing tumor response in explanted livers after DEB-TACE vs. bland

embolization that showed favoring DEB-TACE in CR rate without significant adverse effect [9]. These studies indicate that DEB-TACE is equally effective and safer compared with conventional TACE especially for the patients with advanced liver disease with comorbidity.

13.3.2 Transarterial Radioembolization

Radioembolization with Yttrium-90 is a novel liver-directed brachytherapy using insoluble microspheres. Radiolabeled particles are trapped at the precapillary level within the tumor vasculature, thus limits exposure to the surrounding normal parenchyma. Higher dose delivery with more focused radiation therapy can be done with TARE than with an external beam radiation therapy. TARE has shown a low incidence of post-embolization syndrome, directly supporting its minimally embolic effect [30]. Because of its low embolic effect, TARE may be used for HCC patients with portal vein thrombosis (PVT) [31, 32].

In non-transplant setting, two large cohort studies of TARE for unresectable HCC showed excellent partial response rate of 57–70 % based on European Association for the Study of the Liver (EASL) criteria with acceptable hepatic toxicity [30, 31]. Kulik et al. reported a phase II trial of 108 HCC patients treated with TARE, 37 % with PVT [31]. There was no increased risk of hepatic failure, encephalopathy, or hyperbilirubinemia in patients with PVT compared to no PVT.

Lewandowski et al. [10] compared down-staging efficacy of glass-based TARE ($n=43$) vs. TACE ($n=43$) who are potential LT candidates. Partial response and down-staging from T3 to T2 stage were significantly better in the TARE group (61 % vs. 37 %, 58 % vs. 31 %, respectively) than TACE group. Furthermore, time to progression favored TARE vs. TACE (33.3 months vs. 18.2 months). Barakat et al. used resin-based TARE in their multimodal treatment protocol for down-staging advanced HCC to Milan criteria [33]. TARE was used after TACE in patients with large (>6 cm), multifocal (≥4) lesions or with residual lesions that failed to respond to combined TACE and RFA. Thirty two patients underwent multimodality treatment, and 18 of them (56 %) were successfully down-staged to Milan criteria. Fourteen patients underwent LT after successful down-staging using multimodality therapy.

13.3.3 External Beam Radiotherapy

The relative radiosensitivity of the liver has traditionally limited the use of radiation therapy in HCC. However, the recent development of three-dimensional conformal radiotherapy (3D-CRT) made it feasible to deliver the radiation to large HCC with minimal exposure to the normal liver tissues. More advanced radiation therapy technique, stereotactic body radiation therapy (SBRT) uses fewer fractions of larger

doses with high geometric precision [13]. With these technical advances, EBRT is being recognized as an effective therapy for intermediate/advanced HCC.

EBRT has been reported to have excellent radiological response with mild adverse effect, but it was noted that EBRT alone results in intrahepatic tumor recurrence outside the irradiated volume [34, 35]. Combined use of EBRT with TACE and sorafenib was employed with intent to reduce the intrahepatic recurrence outside the irradiated volume [36, 37]. A recent meta-analysis of 1476 patients comparing TACE in combination with EBRT vs. TACE alone for unresectable HCC showed significant improvement in CR rate and overall survival for combination arm [36].

The experience of EBRT in LT candidates is limited to small single center cohort studies [11, 12, 38, 39]. Neoadjuvant EBRT was performed in Child A/B patients with T2-3 tumors who failed previous LRT. The results showed excellent local control with tolerable adverse effects followed by successful LT. No patients experienced ≥Grade 3 toxicity or radiation-induced liver disease in these series. Pathological CR was reported to be 0–30 % in explant examination [11, 38].

The role of EBRT has been gradually expanded from a palliative intent to a curative intent in intermediate HCC. EBRT is being recognized as an effective therapy for HCC in adjunct to other modalities especially for patients who fail LRT. Although its clinical experience is limited and lack of randomized controlled studies (RCT), EBRT is a viable option for LRT.

13.3.4 Sorafenib

Sorafenib is an oral multikinase inhibitor, with anti-angiogenic activity, that has shown to prolong survival in advanced HCC patients [40, 41]. Sorafenib inhibits tyrosine kinase receptors such as vascular endothelial growth factor (VEGF) receptors and platelet-derived growth factor (PDGF) receptors [42]. Due to its cytostatic effect and low tumor reduction, sorafenib has not been used as a neoadjuvant therapy prior to LT. Combination of TACE and sorafenib represent a potentially powerful therapeutic approach. TACE blocks blood flow, causing necrosis and angiogenic conditions, while sorafenib inhibits angiogenesis and slows tumor progression. At present, there are multiple ongoing clinical trials evaluating outcomes with combining sorafenib and other modalities including EBRT, TACE, and TARE in the neoadjuvant setting or following transplant for high-risk patients [13, 43–45].

13.4 The Role of Neoadjuvant Therapy for HCC Patients Within Milan Criteria

The rate of dropout due to tumor progression at 6 months on the LT wait-list is about 15 % [46]. Since the treatment-related complication is small in modern case series, it is accepted practice to offer neoadjuvant LRT for patients whose waiting time is

longer than 6 months. Use of LRT as a bridging therapy prior to LT can potentially reduce post-transplant HCC recurrence. Austrian cohort study showed that the response to neoadjuvant TACE was associated with better post-transplant survival in patients within Milan criteria [8]. The study included 68 patients within Milan criteria, and a median waiting time was 9 months. Patients with Milan criteria who had radiological CR and PR after TACE had better 1-year post-transplant survival than those with stable or progressive disease (89, 94, and 38 %). However, French multicenter study [47] compared post-transplant HCC recurrence between 100 patients treated with TACE and 100 matched non-treated patients. In both groups, 66 patients were within Milan criteria. Pre-LT TACE did not influence post-LT overall survival and disease-free survival. There were no differences in outcomes of patients within Milan criteria either. These data associated with post-LT recurrence after LRT is still unclear and further randomized control trials are needed to answer if neoadjuvant LRT has an impact on post-LT recurrence.

13.5 Down-Staging Intermediate Stage HCC Before LT

In the Western hemisphere, scarcity of deceased donor and prioritization of HCC patients meeting Milan criteria led to several studies using neoadjuvant therapy as a method of down-staging intermediate HCC (Table 13.1) [8, 19, 24, 48–50]. Otto et al. [22] first reported neoadjuvant therapy using TACE for 62 patients beyond Milan criteria. Thirty four patients (55 %) were down-staged and subsequently listed for LT. This study demonstrated successful down-staging potential of TACE in more advanced HCC who did not meet the Milan criteria.

With the advent of newer LRT, most centers have adopted multimodality approach for down-staging HCC. The University of California at San Francisco (UCSF) group reported their experience in multimodality neoadjuvant therapy [4]. The group limited the inclusion criteria for down-staging and used the UCSF criteria (solitary tumor up to 6.5 cm, or up to three nodules with the largest being up to 4.5 cm and total a tumor diameter up to 8 cm) as a transplant eligible criteria. Neoadjuvant LRT using TACE, RFA, and resection successfully down-staged 43 out of 62 (71 %) enrolled patients. Thirty-five patients underwent LT after median waiting time of 8.2 months. Recurrence-free survival after LT was 92 % at 2 years. Another multimodality approach from Bologna Italy utilized TACE, RFA, percutaneous ethanol injection, and resection [6]. Inclusion criteria for down-staging were also limited to some extension of the Milan criteria and included AFP $\leq$ 400 ng/mL. The down-staging was achieved in 32 (67 %) patients, and all of the 32 patients underwent LT after median waiting time of 6 months. Recurrence-free survival after LT was 71 % at 3 years.

Clinical studies reporting successful down-staging using various approaches are mostly uncontrolled observational studies. Among them, these two prospective studies showed that post-transplant survival in HCC patients with larger tumor load successfully down-staged was similar to that in patients who initially met the

Table 13.1 Selected studies of neoadjuvant therapy for down-staging HCC before liver transplant

Author	Year	*n*	LRT	Inclusion criteria for DS protocol	Successful DS criteria	Mandatory waiting time prior to LT (months)	The role of AFP	DS rate	LT (patients)	Waiting time to LT (months)	Patient survival after LT	Recurrence-free survival after LT
Transarterial therapy alone												
Otto et al. [22]	2006	62	TACE	Beyond MC	30% decrease in size	No	NA	34/62, 55 %	27	5.9 (1.9–19.3)	73 % at 5 years	68 % at 5 years
Chapman et al. [19]	2008	76	TACE	Beyond MC	MC	3–4	NA	17/76, 24 %	17	5.8 ± 3.5	94 % at 5 years	100 %, 50 % at 3, 5 years
De Luna et al. [24]	2009	27	TACI	Beyond MC	MC	No	Not significant	17/27, 63 %	15	10.9 (0.7–114.1)	79 % at 3 years	NA
Lewandowski et al. [10]	2009	43	TACE	UNOS T3	MC	No	NA	11/35, 31 %	11	NA	NA	73 % at 1 year
		43	TARE	UNOS T3	MC	No	NA	25/43, 58 %	9	NA	NA	89 % at 1 year
Multimodal approach												
Yao et al. [4]	2008	61	TACE, RFA, resection	(1) One lesion, 5–8 cm	MC for DDLT	3	AFP >1000 ng/mL predicts DS failure	43/61, 71 %	35	8.2 (3–25)	92 % at 2 years	92 % at 2 years
				(2) 2–3 lesions, 3–5 cm, total diameter ≤8 cm	UCSF criteria for LDLT							
				(3) 4–5 lesions, ≤3 cm, total diameter ≤8 cm								

(continued)

Table 13.1 (continued)

Author	Year	*n*	LRT	Inclusion criteria for DS protocol	Successful DS criteria	Mandatory waiting time prior to LT (months)	The role of AFP	DS rate	LT (patients)	Waiting time to LT (months)	Patient survival after LT	Recurrence-free survival after LT
Ravaioli et al. [6]	2008	48	TACE, RFA, PEI, resection	(1) One lesion, 5–6 cm	MC and AFP ≤400 ng/mL	3	AFP ≤400 ng/mL, listing criteria	32/48, 67 %	32	6	NA	78 %, 71 % at 1, 3 years
				(2) 2 lesions 3–5 cm			AFP >30 ng/mL, predictor of recurrence after LT					
				(3) 3–5 lesions, ≤4 cm, total diameter ≤12 cm								
Barakat et al. [33]	2010	32	TACE, RFA, TARE, resection	Beyond MC	MC	No	Failed vs. successful DS 5670 vs. 799 ng/mL	18/32, 56 %	14	11.2 (4.4–22.6)	92 %, 75 % at 1, 2 years	Two patients recurrence

HCC hepatocellular carcinoma, *LRT* locoregional therapy, *DS* down-stage, *LT* liver transplant, *AFP* alpha-fetoprotein, *TACE* transarterial chemoembolization, *MC* Milan criteria, *NA* not available, *TACI* transarterial chemo-infusion, *UNOS* United Network for Organ Sharing, *TARE* transarterial radioembolization, *RFA* radiofrequency ablation, *UCSF* University of California at San Francisco, *PEI* percutaneous ethanol injection

criteria for LT, justifying the strategy of transplanting high-risk patients following down-staging in the setting of organ shortage [4, 6]. More studies with longer follow-up that can assess the post-transplant tumor recurrence are needed to confirm the current practice of down-staging advanced HCC prior to liver transplant.

13.5.1 Acceptable LT Criteria After Successful Down-Staging

To evaluate the response to neoadjuvant therapy, EASL guidelines suggest that the treatment effect should be assessed based on the amount of viable tumor load, not just a reduction in overall tumor size, and suggested using dynamic CT or MRI to differentiate between viable tumor and necrosis [51]. Overall assessment should include the combined results of target lesions, non-target lesions, and new lesions based on modified Response Evaluation Criteria in Solid Tumors (mRECIST) [52]. Methodologically, a 3-month interval reassessment of radiological image along with AFP sampling is widely accepted in clinical practice [53].

In terms of morphological criteria after the down-stage of intermediate HCC, Milan criteria are the worldwide accepted LT criteria. The UCSF criteria are also being used in some regions in the USA. However, in combination with tumor markers or other surrogate markers, transplant criteria after down-stage may not necessarily be Milan or UCSF criteria as long as tumors respond well to LRT [7, 22]. This area is still a controversial topic in many high volume LT centers.

There is the need to identify surrogate markers for tumor biology in addition to morphological tumor size and number to explore optimal criteria. Because of its association with pathological feature and tumor biology, tumor markers such as AFP and PIVKA-II (protein induced by vitamin K absence) have gained attention. Several studies from Japan suggested that PIVKA-II correlate well with microvascular invasion [54, 55]. AFP is widely recognized as predictive factor for post-transplant recurrence and is proposed to be included for the LT criteria after the down-stage of advanced HCC [1]. Because several studies showed a preoperative AFP level >1000 ng/mL to be a strong independent predictor of post-transplant tumor recurrence, US national conference on liver allocation recommend that for patients who had an initial AFP >1000 ng/mL, successful down-staging should include a decrease to AFP levels <500 ng/mL, and all subsequent AFP levels must also be <500 ng/mL prior to LT [1]. Since there is no biomarker that can predict or prognosticate HCC patients prior to LT, tumor behavior during the waiting time has been considered as a surrogate marker for tumor biology. During period of waiting time after down-stage, the tumor biology is allowed to become apparent by radiological study. This concept "ablate and wait" has recently gained popularity among transplant community [56].

13.6 Adjuvant Therapy Following LT for HCC: Adjuvant Systemic Cytotoxic Chemotherapy

Adjuvant systemic chemotherapy for HCC is given after LT in attempt to treat the micro-metastases that might be present at the time of LT. Table 13.2 summarized selected studies of adjuvant chemotherapy after LT for HCC. Doxorubicin is the most commonly used agent for adjuvant chemotherapy to HCC but newer agents are currently being tested [57, 58].

In 1990s, several uncontrolled trials were conducted to look for outcomes after LT for HCC beyond Milan criteria using doxorubicin-based adjuvant chemotherapy; disease-free survival ranged 46–54 % at 5 years that were considered to be better compared to historical controls [23, 59]. However, the results of these uncontrolled studies are in contrast to recent studies. Pokorny et al. conducted the first prospective RCT to evaluate the efficacy of perioperative doxorubicin chemotherapy for patients with advanced HCC who underwent LT [60]. Thirty-four HCC patients received biweekly doxorubicin pre-, intra-, and postoperatively and were compared with 28 control patients. 5-years OS were 38 and 40 % in the chemotherapy group and in the control group, and 5-years DFS rates were 43 and 53 % without significant difference. Another prospective, randomized, multicenter study was reported from Sweden comparing 17 patients with chemotherapy and 25 control HCC patients. The study showed no significant advantage of adjuvant therapy with weekly systemic doxorubicin administered perioperatively [61].

More recently, some investigators investigated the efficacy of adjuvant FOLFOX in patients who underwent LT for HCC [62]. FOLFOX (5-FU, leucovorin, and oxaliplatin) is a commonly used chemotherapy regimen that has shown clinical activity in metastatic colorectal cancer [63, 64] and was recently reported to be active against HCC [65, 66]. The first RCT from China showed somewhat promising result as there was improvement in OS but not in DFS. More studies are needed to investigate the efficacy of FOLFOX as adjuvant therapy for HCC.

13.7 Sorafenib Use in the Setting of Adjuvant Therapy

With the efficacy of sorafenib in advanced HCC [40, 41], its use in the transplantation field has been tested [67]. Several small series reported data on the safety and efficacy of sorafenib in patients with HCC recurrence after LT [68–72]. These studies showed the safety and preliminary efficacy profile of sorafenib for recurrent HCC after LT. No deterioration of liver graft function was reported, and adverse events were easily manageable with dose reduction of sorafenib. However, dose reduction was needed in 20–73 % of patients in these reports in the post-LT setting, indicating full dose of sorafenib (400 mg twice daily) may not be feasible. In regard to efficacy, the studies showed median time to progression of 2.9–6.8 months and a median OS after the initiation of sorafenib of 5.4–20.1 months [68–70, 72].

Table 13.2 Selected studies of adjuvant chemotherapy after liver transplant for HCC

Author	Year	Patients Tx vs. control	Study design	Stage	Treatment	Completion rate	Pts with recurrence Tx vs. control	OS Tx vs. control	DFS Tx vs. control
Stone et al. [59]	1993	20	Prospective, uncontrolled	6 within MC, 14 beyond MC	20 cycles, every week, Doxorubicin (10 mg/m^2)	17 of 20 (85 %)	8	59 % at 3 years	54 % at 3 years
Roayaie et al. [23]	2002	43	Prospective, uncontrolled	Tumor >5 cm	6 cycles, every 3 weeks, Doxorubicin (50 mg/m^2)	Four received no treatment. 28 of 39 (72 %) completed	17	48% at 5 years	44 % at 5 years
Pokorny et al. [60]	2005	34 vs. 28	RCT	11 within MC, 51 beyond MC	20 cycles, every 2 weeks, Doxorubicin (15 mg/m^2)	Three received no treatment. 25 of 31 (81 %) completed	18 vs. 16	38 vs. 40 % at 5 years	43 vs. 50 % at 5 years
Soderdahl et al. [61]	2006	17 vs. 25	RCT	16 within MC, 26 beyond MC	Every week, Doxorubicin (10 mg/m^2, up to 400 mg/m^2)	10 of 17 (59 %)	4 vs. 10	70 vs. 63 % at 3 years	50 vs. 63 % at 3 years
Zhang et al. [62]	2011	29 vs. 29	RCT	Beyond MC	Six cycles, every 3 weeks, FOLFOX: 5-FU, Luecovorin, oxaliplatin (100 mg/m^2)	28 of 29 (97 %)	15 vs. 14	79 vs. 62 % at 3 years	48 vs. 51 % at 3 years

HCC hepatocellular carcinoma, *Tx* treatment, *Pts* patients, *OS* overall survival, *DFS* disease-free survival, *MC* Milan criteria, *RCT* randomized control study

Better outcomes with response to sorafenib in the transplanted patients compared to non-transplant patients can be explained by smaller metastatic lesions, and preserved liver function of transplanted patients. In addition, mammalian target of rapamycin (mTOR) inhibitors were used with sorafenib in the majority of reported cases and thus a potential synergistic anticancer activity of these two drugs could be postulated.

The data of the good safety profile and efficacy in recurrent HCC after LT suggest potential role of sorafenib as adjuvant treatment in high-risk patients after LT. To date, the data on sorafenib regarding adjuvant therapy are limited with only one small retrospective case-control match study [73]. Currently, a phase II randomized multicenter prospective study to investigate the efficacy of adjuvant sorafenib for high-risk patients is underway (ONC-2010-31). However, with the recent data demonstrating that sorafenib did not improve recurrence-free survival compared with placebo after curative resection or ablation of hepatocellular carcinoma (HCC), it dampens the enthusiasm of the usage of sorafenib after LT [74].

13.8 m-TOR Inhibitor

m-TOR inhibitors have gained a high degree of attention in regard to suppression of tumor activity. These drugs have a potential anticancer effect which has been demonstrated in the experimental setting. The anticancer effect is related to the prevention of angiogenesis by blocking vascular endothelial growth factor-mediated pathways in endothelial cells as well as blockade of downstream for P-I-3-kinase and akt pathways [75].

Kneteman et al. reported the first successful series of 40 HCC patients (19 within Milan criteria, 21 beyond) using sirolimus-based immunosuppressive protocol designed to minimize exposure to calcineurin inhibitor (CNI) and steroids [76]. Only five patients experienced HCC recurrence at 44 months follow-up. Four-years DFS were 81 % and 77 % in patients within Milan criteria and beyond Milan criteria, respectively. Since this satisfactory result, several centers have employed m-TOR inhibitors for immunosuppressive protocol in HCC patients [77, 78].

Recently, a matched case-control study from Bologna showed significant benefits from sirolimus-based immunosuppression compared with CNI-treated patients [79]. Tumor stage and unfavorable HCC pathological features were matched between two cohorts of 31 patients. Three-year DFS was significantly higher in sirolimus group with 86 % vs. CNI group with 56 %.

These results were confirmed by Toso et al. by analyzing data from Scientific Registry of 2491 Transplant Recipients with HCC [80]. Among them 109 patients was on sirolimus and 2382 were treated without sirolimus. Five-year OS was significantly higher in sirolimus group with 83 % vs. non-sirolimus group with 69 %. In a multivariate analysis, sirolimus-based immunosuppressive therapy and anti-CD25 antibody induction were associated with improved survivals. These results suggest that m-TOR inhibition might be important in post-transplant for patients with HCC.

13.9 Conclusion

Neoadjuvant therapy using LRT for liver cancer is effective bridging therapy for the patients with expected waiting time more than 6 months and/or those with high-risk characteristics of HCC. Conventional LRT-like TACE have shown the efficacy in down-staging for intermediate staged HCC to fulfill Milan criteria for LT resulting in acceptable post-transplant outcomes. DEB-TACE, TARE, and SBRT are emerging modalities that are included in the multimodality approach showing clinical efficacy. Due to its acceptance in LT community, it will be difficult to conduct RCT to compare conventional TACE to newer emerging modalities.

Adjuvant therapy is not currently recommended for any patient undergoing liver transplantation for HCC except in the context of a clinical trial. Use of sorafenib and newer chemotherapeutic regimen like FOLFOX may suggest potential role as adjuvant treatment in high-risk patients. With promising result of m-TOR inhibitors for improved post-transplant outcomes in HCC patients, its use as one of immunosuppressant medications is advocated by some investigators.

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Chapter 14
Cholangiocarcinoma

Nicholas Onaco and Göran B.G. Klintmalm

Liver transplantation (LTX) was initially performed more than 50 years ago for patients with liver tumors. While the initial results of transplants for liver tumors were disappointing, LTX is currently the recommended treatment for hepatocellular carcinoma in the cirrhotic patients. Cholangiocarcinoma which makes up 10–20 % of primary liver tumors [1] remains a controversial indication for liver transplantation due to the high rate of tumor recurrence after the transplant [2, 3]. While results of transplantation for cholangiocarcinoma have improved over time [4], recurrent cholangiocarcinoma is still a significant problem leading to inferior posttransplant survival.

14.1 Recurrence Rates After LTX for Cholangiocarcinoma: Pathology, Surveillance, and Diagnosis

Cholangiocarcinomas originate in the biliary duct epithelium. They are classified as intrahepatic or peripheral, arising from intrahepatic bile ducts, and extrahepatic or distal, originating in the bile ducts from the hilar confluence through the hepatic duct or common bile duct [5]. Most extrahepatic cholangiocarcinomas (60 %) are located at the hilar confluence and are known as Klatskin tumors.

Peripheral cholangiocarcinomas in the transplanted liver are almost always recurrent disease, whereas extrahepatic biliary tumors after LTX can represent de novo tumors arising in the native bile duct remnant [6–8]. The latter can occur in patients with primary sclerosing cholangitis (PSC) and inflammatory bowel disease. Of note, although rarely, intrahepatic cholangiocarcinoma can occur de novo years after LTX in the setting of recurrent PSC in patients who did not have

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cholangiocarcinoma in the native liver [9, 10]. Other causes for primary cholangiocarcinoma, such as exposure to thorotrast contrast agent, choledochal cysts, biliary adenomas, and parasitoses such as clonorchiasis, are not specific risk factors for recurrence.

Primary cholangiocarcinoma is sometimes difficult to differentiate from metastatic adenocarcinoma [11], especially when only lymphadenopathy or metastases are found. The tumor can display a histologic appearances of both cholangiocarcinoma and hepatocellular carcinoma [12, 13]. Some tumors are mucin producing, but most tumors are well differentiated.

Recurrent cholangiocarcinoma after LTX follows the pattern similar to the spread of the primary tumors. Local invasion occurs along the hilar structures, into the local lymph nodes. Since most perihilar hepatic lymph nodes are removed at the time of transplant, recurrent cholangiocarcinoma tends to be located in periaortic lymph nodes or other remote intra-abdominal lymph nodes. Most metastases are usually found in the lymph nodes or peritoneum, followed by lung and bone. Compression of vascular structures is encountered with large primary tumors, but it is uncommon with recurrent cholangiocarcinoma. Unlike hepatocellular carcinoma, cholangiocarcinoma rarely invade blood vessels.

Recurrent cholangiocarcinoma lesions are asymptomatic until late in the course, or may cause nonspecific symptoms such as fever, malaise and weight loss. Localized pain is the most common symptom for bone lesions. Intra-abdominal lesions can cause localized pain or, if large, obstructive symptoms such as nausea, vomiting or obstipation. The classic picture of biliary obstruction (jaundice, pruritus, dark urine), with or without cholangitis, is specific for distal biliary lesions or hilar hepatic lesions. Recurrent cholangiocarcinoma can be found as a single lesion or as multicentric at the time of diagnosis.

Tumor markers such as carbohydrate antigen (CA) 19-9, carcinoembryonic antigen, and CA-125, when elevated, can be helpful to make a diagnosis. Of the tumor markers, CA 19-9 is the most specific, but may be falsely elevated in the presence of jaundice. Transplant recipients, even if they have recurrent PSC, rarely display significant cholangitis to have falsely elevated CA 19-9. As most recurrent cholangiocarcinoma lesions are asymptomatic, interval imaging is required for surveillance. There are no current guidelines for imaging. Cross-sectional imaging (computed tomography scans of the chest, abdomen, and pelvis) is advisable every six months posttransplant for the first two years.

Once recurrence is suspected based on surveillance protocol, imaging is tailored to the suspected site of recurrence. Most lesions are detected by computed tomography scans. Magnetic resonance imaging can offer additional detail for intrahepatic lesions. Metastatic intrahepatic lesions can differ in appearance from primary cholangiocarcinoma (Fig. 14.1). Hilar adenopathy is a suspicious finding that can aid in the diagnosis of primary cholangiocarcinoma. Since hilar lymph nodes are removed at the time of transplant, lymphatic spread in recurrent cholangiocarcinoma tends to be more central (Fig. 14.2). In some cases, recurrent cholangiocarcinoma may present as diffuse adenopathy, which is indistinguishable from other malignancies such as posttransplant lymphoproliferative disorders. Bone metastases tend to have a

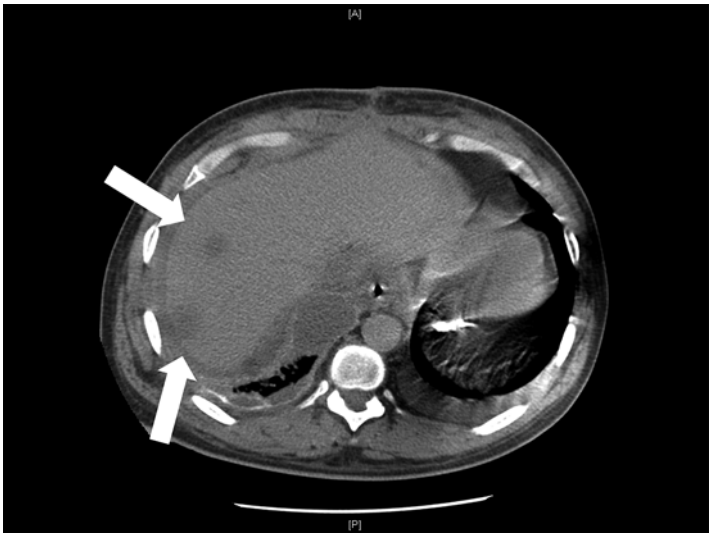

Fig. 14.1 Metastatic cholangiocarcinoma to the liver

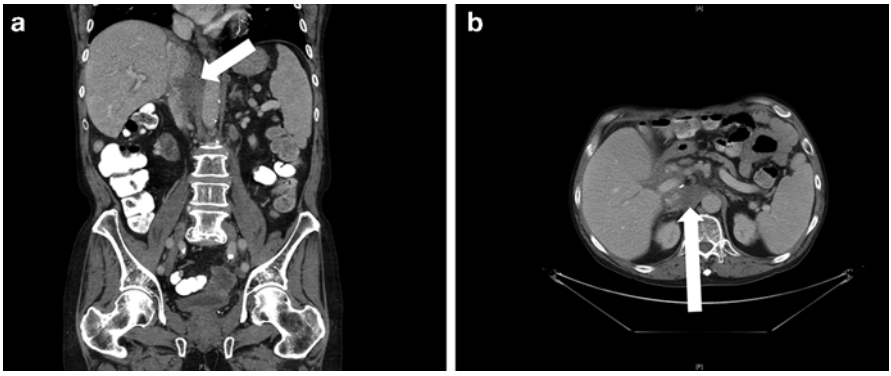

Fig. 14.2 Retroaortic/retrocaval recurrent cholangiocarcinoma

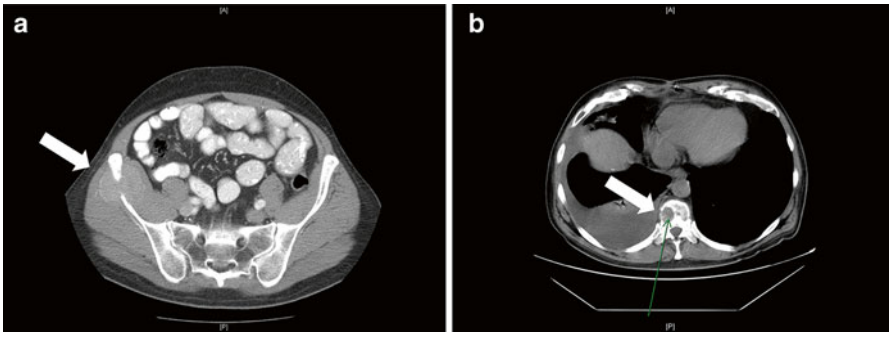

Fig. 14.3 Lytic metastases to the (**a**) iliac bone and (**b**) spine

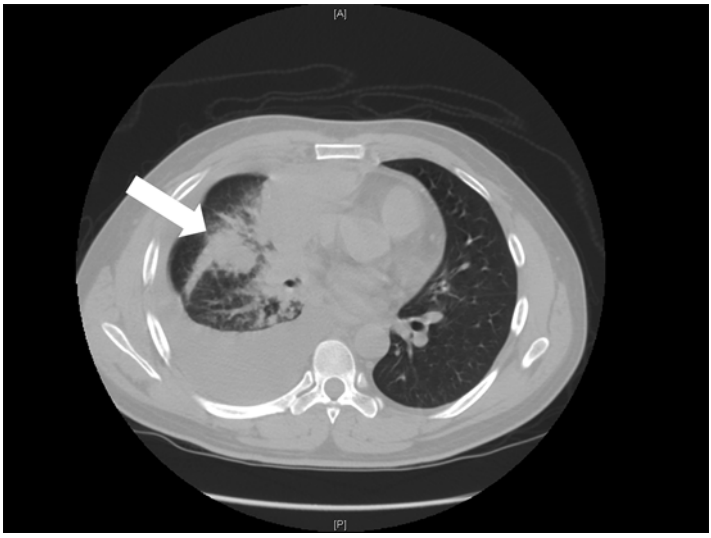

Fig. 14.4 Pulmonary metastatic cholangiocarcinoma

lytic appearance (Fig. 14.3). Pulmonary metastases can be single, with surrounding inflammatory changes (Fig. 14.4), or may appear as multiple nodules. Positron emission tomography scanning is not commonly used in the diagnosis, but it has a role in differentiating metastases from benign, inflammatory processes for post chemotherapy surveillance.

Pathologic confirmation is not always necessary for cholangiocarcinoma in the native liver [14]. With recurrent cholangiocarcinoma, however, the differential diagnosis includes metastatic adenocarcinomas of other origins. Brush cytology and fluorescence in situ hybridization are useful tools in the differential diagnosis of primary cholangiocarcinoma [1]. Although these modalities are useful for lesions in the biliary tree, they are rarely of help in the diagnostic work-up of recurrent cholangiocarcinoma elsewhere.

Staging for cholangiocarcinoma was designed to assess outcome with resection. Recurrent cholangiocarcinomas, however, belong to stage IIIB for adenopathy or stage IV for distant metastases.

14.2 Prevention of Recurrence

Initial results with liver transplantation for cholangiocarcinoma, including incidental tumors, were poor due to early recurrence in the lungs, bone, liver, and skin [15, 16, 17]. The 1-year survival was as low as 36 %, and the 5-year survival was 5–38 %, similar to survival rates of patients who underwent palliative treatments [18–23]. Cholangiocarcinoma is extremely rare in the pediatric population with

PSC; in children, as in adults, the posttransplant prognosis is poor [24]. Therefore, known cholangiocarcinoma is still considered a contraindication to liver transplantation [3, 25], unless transplantation is performed as part of a multimodal approach [23, 26]. An analysis from the Cincinnati Transplant Tumor Registry database showed 84 % tumor recurrence rate at 2 years [23]. Results were poor even with incidental tumors, which are often relatively small in size at the time of transplant [27]. The finding of poor survival has recently been disputed, as a small group of patients with solitary intrahepatic tumors <2 cm had excellent post-LTX patient survival in one study (73 % at 5 years) [28]. Mixed hepatocellular carcinoma–cholangiocarcinoma tumors seem to have a slightly better prognosis than cholangiocarcinoma [29, 30], although recurrence rates in mixed tumors are 70 % at 5 years [31]. These tumors should be approached and treated like cholangiocarcinoma; resection and LTX yield comparable results [32].

To improve the outcomes after LTX, every attempt has to be made to minimize tumor recurrence. Protocol driven multimodality therapies have improved the outcomes of LTX for cholangiocarcinoma, but the optimal regimen that provides best outcomes is still in evolution. Pretransplant photodynamic therapy, delivered by an endoscopic intrabiliary approach, may offer local tumor control pretransplant, and this may be an alternative to brachytherapy prior to liver transplant [33]. Multimodality therapies, starting before transplant, have resulted in lower recurrence rates and better survival, equivalent to transplantation for other liver diseases in few reported series [34, 35].

One of the widely used cholangiocarcinoma protocol was developed by the invetsigators from the Mayo Clinic. The Mayo protocol is designed for patients with biopsy-proven cholangiocarcinoma or malignant-appearing strictures by endoscopic retrograde cholangiopancreatography (ERCP) with positive brushings for cytology and/or fluorescence in situ hybridization or with CA 19-9 >100 U/mL or a malignant-appearing stricture and tumor on imaging. Exclusion criteria included intrahepatic cholangiocarcinoma, extrahepatic disease, a history of biopsy, attempt at resection, or percutaneous transhepatic cholangiography [36]. The Mayo protocol starts with external beam radiotherapy combined with chemotherapy (5-fluorouracil) for 4 weeks, followed by brachytherapy via probes introduced by ERCP, followed by oral capecitabine. Exploratory laparotomy is performed at least 2 weeks after brachytherapy and as close as possible prior to transplantation, with sampling of the perihilar lymph nodes to exclude metastasis. In their experience, one fifth of the patients had tumor spread at exploration after utilizing this protocol. If the Mayo protocol is strictly followed, the outcomes are superior when compared with other treatment with other modalities, and similar to transplantation for nonmalignant disease, with a 5-year survival of 72–84 % [37]. These findings have been replicated by other transplant centers using the multimodal treatment approach provided the cholangiocarcinoma lesions were not >3 cm, no transperitoneal biopsy was performed, and there was no extrahepatic spread [2, 35, 38, 39]. An alternative approach is stereotactic body radiation therapy followed by capecitabine in lymph node-negative patients until liver transplantation, but experience with this regimen is limited [40].

Predictors of recurrence of cholangiocarcinoma after LTX using multimodal therapy are recipient age >45 years, pretransplant CA 19-9 >100 U/mL, cholecystectomy prior to transplant, residual tumor in explant >2 cm, mass on cross-sectional imaging before transplant, tumor grade 2 or 3 out of 4 (Edmonson), or perineural invasion. Underlying PSC, percutaneous biliary procedures, gender, and CA 19-9 prior to treatment were not associated with recurrence in the Mayo experience [41].

The University of California Los Angeles group devised a tumor recurrence predictive index, based on multifocality, perineural invasion, infiltrative growth pattern, lack of neoadjuvant therapy, history of PSC, hilar cholangiocarcinoma, and lymphovascular invasion. Recurrence-free 5-year survival was 78 % in the low-risk group, 19 % in the intermediate group, and zero in the high-risk group. Tumor size was not an independent risk factor for recurrence [42]. However, the factors heavily influencing the predictive index were based on explant pathology.

Multimodal treatment of hilar cholangiocarcinoma leads to better patient survival than resection in select patients [43–45]. However, in the Mayo Clinic experience, results were superior with cholangiocarcinoma arising in the setting of PSC but not in de novo cholangiocarcinoma, where recent results with resection have improved [46]. There is increasing evidence to suggest that liver transplantation could offer long term cure to few rigorously selected patients with cholangiocarcinoma after neoadjuvant multimodal therapy [47]. Careful patient selection and protocol driven neoadjuvant treatment are critical for the best outcomes.

Current guidelines from the British Society of Gastroenterology state that "increasing data suggest that liver transplantation for cholangiocarcinoma can be successful in rigorously selected patients undergoing neoadjuvant therapy in highly specialised centres" [47].

14.3 Orthotopic Liver Transplantation for Cholangiocarcinoma: Technical Considerations

There is no documented advantage between the two main technical options for liver transplantation with regard to the recipient cava–caval interposition and caval sparing (piggyback technique). The main difference in the technical approach is in the management of the native bile duct. An attempt should be made to resect as much native bile duct as possible in recipients with cholangiocarcinoma and/or PSC with creation of a Roux hepaticojejunostomy. In patients with known or suspected cholangiocarcinoma, an intraoperative microscopic frozen-section exam of the distal margin of the resected bile duct can confirm full resection of the cholangiocarcinoma. If there is residual disease at the margin, a Whipple pancreaticoduodenectomy can be performed. Although perceived as a major procedure in addition to the transplant, it can be performed without significant additional morbidity [37, 48–51]. We prefer to perform the pancreaticoduodenectomy as a staged procedure the day after the transplant, which seems to significantly lower the postoperative complications.

The multimodal treatment adds technical difficulty to the transplant surgery, including radiation injury from brachytherapy, and inflammatory changes from endoscopic procedures or from a previous exploratory laparotomy (if the latter is part of the protocol). Therefore, LTX as part of multimodal therapy is associated with a significantly higher incidence of vascular complications, both early and late after LTX. However, limited experience suggest that these complications do not adversely impact patient survival [52].

14.4 Immunosuppression and Recurrence of Cholangiocarcinoma

Mammalian target of rapamycin (m-TOR) inhibitors, such as sirolimus and everolimus, inhibits the vascular endothelial growth factor, which may have a role in the development and spread of cholangiocarcinoma tumors. Sirolimus can induce partial remission or stabilization of disease in some patients with cholangiocarcinoma [53]. Based on this preliminary observation, it is perhaps beneficial to use an m-TOR inhibitor as part of the immunosuppression regimen after LTX for cholangiocarcinoma or after the diagnosis of tumor recurrence. In our center, we start the m-TOR the day after transplant, however, no studies to date have compared m-TOR inhibitor-based immunosuppression to other regimens in LTX for cholangiocarcinoma.

14.5 Treatment Options

Recurrent cholangiocarcinoma is associated with a poor prognosis. Treatment options for recurrent cholangiocarcinoma after LTX depend on tumor size, number, and location. Resection of recurrent cholangiocarcinoma is feasible for solitary lesions and resection can be curative for late recurrences with a favorable histology (e.g., well-differentiated tumors on histology). Palliative surgery can be contemplated for obstructive symptoms as most tumors are not amenable to surgical therapy.

External beam radiotherapy has been used for bone lesions with temporary remission. Intrahepatic recurrent lesions can benefit from radiofrequency ablation, similar to some cholangiocarcinoma lesions in the native liver, with up to 18-month posttreatment survival in one series [54]. Ablative therapies can be combined with surgery, for instance, targeted Yttrium 90 microsphere infusion followed by interval hepatic lobectomy of the allograft [55].

Chemotherapy, however, is the principal therapy for recurrent cholangiocarcinoma. Multiple agents have been used in this setting. 5-Fluorouracil was the mainstay of chemotherapy, as a single agent or combined with cisplatin, doxorubicin, epirubicin, lomustine, mitomycin C, and paclitaxel [1]. Gemcitabine is the preferred agent currently, and gemcitabine in combination with cisplatin [56] has shown better tumor control when compared to gemcitabine monotherapy [57].

14.6 Conclusion

Liver transplantation for cholangiocarcinoma remains controversial due to the high risk of tumor recurrence and related mortality. Currently, LTX is reserved for a strictly selected group of patients, where LTX is part of a multimodal treatment including neoadjuvant chemotherapy and/or ablation therapies.

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Chapter 15
Recurrent Non-hepatic and De Novo Malignancies After Liver Transplantation

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15.1 Introduction

This chapter organizes post-transplant malignancy into two categories. The first section describes recurrence of non-hepatic malignancy in those who had pre-LTx history of non-hepatic malignancy. The second section describes "de novo malignancies," encompassing all malignancies not present prior to transplant. In the discussion to follow, primary hepatic malignancies which the recipient had at the time of transplant are excluded as it has been discussed elsewhere in this book.

15.2 Recurrence of Non-hepatic Malignancies in Those with Pre-LTx History of Malignancy

With the growing experience and success of LTx, the indications for transplantation are also expanding. Many patients, not considered candidates for transplantation in the past, are now being evaluated for LTx. Furthermore, with our aging population, the number of transplant candidates above the age of 65 years or even 75 years is growing. Accordingly, the incidence of pre-LTx malignancies can be expected to be higher, and therefore, also the risk of post-LTx malignancy recurrence. For simplicity, we have divided post-LTx malignancy recurrences into four categories; (1) non-hepatic solid malignancy, (2) hematological malignancy, (3) neuroendocrine malignancy, and (4) epidermal cutaneous malignancies.

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15.2.1 Recurrence of Non-hepatic Solid Malignancies

Initial estimates come from the data collected and analyzed through the tumor registry maintained by the late Israel Penn [1]. He found an overall rate of recurrence of 22 %. He observed higher rates of recurrence with soft tissue sarcoma, breast cancer, and symptomatic renal cell carcinoma. The incidence, however, was lower for uterine, testicular, thyroid, and cervical cancer [2–4]. After extensive review of post-transplant tumor recurrence from the registry data, he also suggested, a guideline, for a waiting period between treated cancer and transplantation, in an effort to prevent recurrence of malignancies after transplant.

Penn suggested that in the case of in situ cancer of the colon and kidney, waiting period was not necessary. For most early stage cancers, the recurrence-free survival of 2–5 years was suggested. For lymphoma, breast carcinoma, prostate, colon, and >5 cm renal cell carcinoma, a recurrence-free interval of at least 5 years was advocated [2–4]. Most transplant centers have followed these recommendations and also monitored their patients while awaiting LTx.

Four studies describing the incidences of recurrent malignancies in those with pre-LTx history of cancer from four different centers are summarized in Table 15.1. Kelly et al. gave an account of 888 LTx recipients at their transplant center [5]. Twenty-nine cases with pre-transplant malignancy were identified. Of these, four had a history on non-hepatic malignancy. There were two cases of breast cancer, and one each of palate and thyroid. Their time line of disease before and after LTx with management and survival is given in Table 15.1. Saigal et al. analyzed 1097 LTx recipients [6]. There were 12 cases of solid non-hepatic malignancies before transplant. One of them had recurrence of Non-Hodgkin's lymphoma 31 months post-LTx. Benten et al. examined 606 LTx recipients; 37 of them had pre-transplant extrahepatic malignancies [7]. One of them was found to have carcinoma of the colon at the time of LTx which was resected 3 weeks post-transplant. This patient later, presented with disseminated metastatic lesions 6 months post-transplant. The remaining 36 patients remained recurrence-free during the follow-up period.

We reported our experience from 1128 LTx recipients with mean follow-up of 34.1 ± 35.3 months in 2009 [8]. There were 30 patients with 31 non-hepatic malignancies prior to liver transplant. These consisted of seven colorectal, six breast, three each of prostate, cervical, and bladder cancer, and nine other malignancies. One patient (3.3 %) had squamous cell carcinoma of the retromolar trigone (stage PT3N1M0). She was recurrence-free for 77.3 months prior to LTx. However, 36 months post-transplant she developed oropharyngeal recurrence of the tumor. This was treated with chemotherapy, but she died 11 months after the recurrence.

15.2.2 Recurrence of Hematological Malignancies

Myeloproliferative disorders leading to Budd–Chiari syndrome are not contraindications for LTx according to Saigal et al. [6] and Benten et al. [7]. These can be treated while waiting on the list, or after transplant. Saigal et al. reported six cases

Table 15.1 Recurrent non-hepatic malignancies post-liver transplant

Authors	# of transplant recipients	Total cases with pre-transplant malignancies	# of recurrences post-transplant	Type of cancer and pre-transplant time	Post-transplant recurrence time	Treatment	Last follow-up post-recurrence
Kelley et al. [5]	888	29	4	Breast cancer 5 years	3 years	(1) Chemotherapy	2 years
				Breast cancer 7 years before LTx	1 year		Expired 4 years after recurrence
				Squamous cell carcinoma of the palate, 8 months	1 year	(3) Surgery + radiotherapy	Alive 3 years post-recurrence
				Thyroid carcinoma 4 years	9 months	(4) Surgery	Tumor free 18 months post-recurrence
Saigal et al. [6]	1097	12	1	Non-Hodgkin's lymphoma Stage 3, 10 years pre-LTx, 23 months pre-transplant stage 3	31 months, stage 4B		Alive 31 months post-recurrence
Benten et al. [8]	606	37	1	Stage 3 colon cancer at the time of transplant, colectomy 3 weeks post-transplant**	Disseminated 6 months		Expired
Jain et al. [8]	1127	30	1	Squamous cell carcinoma right retromolar trigone (PT3N1M0), 77.3 months before transplant	Oropharyngeal recurrence 36 months post-transplant	Chemotherapy	Expired 11 months post-recurrence

** = Cancer was discovered at the time of LTx. In true technical terms, not a de novo cancer. However, reported as de novo cancer

of myeloproliferative disorder requiring liver transplant; one patient developed leukemia 6 years after transplant [6]. Benton et al. reported 11 cases of hematological malignancy including seven cases of myeloproliferative disorder with Budd–Chiari syndrome; none had a recurrence of the disease or leukemia within a median follow-up of 66 months [7].

15.2.3 Recurrence of Neuroendocrine Tumor

Post-LTx recurrence in the presence of non-resectable neuroendocrine/carcinoid metastases is very high, and LTx usually should not be considered. However, in highly selected cases, LTx may be justified. Olausson et al. suggested criteria for undertaking LTx in cases with carcinoid and pancreatic endocrine tumor: (1) hepatic tumor recurrence after surgery for cure; (2) non-resectable hepatic, metastatic disease, especially in cases of severe hormonal symptoms; and (3) disease progression after hepatic arterial embolization and medical therapy [9]. He felt that LTx may provide these patients with a favorable prognosis. No doubt, there was a risk of recurrence of tumor; however, due to the relatively indolent nature of neuroendocrine and carcinoid tumor, the LTx could potentially provide substantial years of acceptable quality life.

Serralta et al. reported three cases of LTx done for gastrointestinal stromal tumors [10]. He suggested choosing cases with GI stromal tumors sensitive to Imatinib (antineoplastic drug) that could control the potential recurrence of the tumor. Van Vilsteren et al. described 19 patients who underwent LTx for gastroenteropancreatic neuroendocrine tumors [11]. These included 11 cases of pancreatic islet cell tumor with a recurrence rate of about 23 %, whereas eight patients with carcinoid remained free of disease.

In the last 8 years, European centers have provided more details on the subject. Mazzaferro et al. summarized nine studies consisting of 203 patients, where LTx for metastatic neuroendocrine tumors was performed [12]. Recurrence-free survival up to 50 % at 3 years and 24 % at 5 years was noted. He has proposed the Milan criteria of exclusion and inclusion for LTx with neuroendocrine metastatic disease. De Herder et al. has proposed multidisciplinary surgical approach to treat the condition with hepatic resection and LTx [13]. Recently, Le Treut et al. summarized 213 cases from 35 LTx centers in 11 European countries from 1982 to 2009 with mean follow-up of 56 months [14]. Eighty-six patients (40.4 %) died from recurrence of the disease 4–165 months post-LTx, suggesting that LTx should be considered in highly selective cases with strict criteria.

Usually neuroendocrine with hepatic metastasis may not have liver failure and may not acquire adequate MELD score to get a liver for transplant purpose. United Network for Organ Sharing (UNOS) has developed strict guidelines for MELD exception points for these cases so that they may get a liver in about a year. Given these strict guidelines, live donor liver transplant in this situation could provide a suitable alternative to waiting for standard allocation.

15.2.4 Recurrence of Cutaneous Malignancies

Cutaneous epidermal malignancies (other than melanoma and Kaposi's) prior to LTx are not considered a contraindication, since they are usually locally invasive. Recurrence of these types of skin cancers post-LTx is almost always expected. However, these are not accounted for in the tumor registry data and are not uniformly tracked or reported by transplant centers Routine follow-up with dermatologist is strongly recommended for early detection and timely excision of skin cancers. Epidermal lesions of the skin lying close to bone and cartilage or perianal region could invade and spread if left unattended for too long, and hence needs careful evaluation.

15.3 De Novo Cancer Post-Liver Transplant

One of the most common long-term causes of death after successful LTx is related to de novo cancer, often with a functioning allograft. As alluded to before, incidence increases with the age of the recipient at the time of transplant and length of follow-up [15–19].

Increased incidence of de novo cancers after solid transplant was first predicted in 1968 by Stazal et al. [20]. This was subsequently confirmed by Penn and Starzl [21] and McKhann [22]. Since then, there have been several attempts to organize this data. Initial reports were from the Israel Penn International Transplant Tumor Registry (IPITTR) [23]. Subsequently, the Australia and New Zealand Liver Transplant Joint Registry started reporting their data [24]. Additionally, large transplant centers in Texas, Pittsburg, Berlin, Mount Sinai, London, Baylor, Madrid, Valencia, California, Bacelona, and Korea compiled their own data (Table 15.2) [1, 5, 24–34]. There has been wide variation in the incidence of de novo cancers reported, ranging from 2.3 to 12.3 %. There are few explanations to account for these variations. For one thing, reporting in the literature has remained inconsistent; some have included lymphoid malignancies (post-transplant lymphoproliferative disorder, PTLD) while others have excluded them. Also, a majority of the reports have included locally malignant basal cell and squamous cell carcinoma of the skin along with melanoma and Kaposi's sarcoma of the skin. Meanwhile, others have separated them in calculating the incidence. Additionally, the length of follow-up is different in all citations, and some studies have included children while others have excluded them. The mean age group of the transplant population and the distribution of age groups are different between the studies. Twelve large studies have been summarized in Table 15.2. A total of 10,235 post-LTx recipients had 877 (8.57 %) de novo malignancies. No doubt, these do provide useful information on the incidence of de novo cancer and its impact on post-transplant patients' survival; however, it does not compare the actual standard incidence ratio (SIR), which compares the general population in the same geographical location matched for age, gender, and length of follow-up.

Table 15.2 Rate of de novo malignancies without SIR post-LTx

	Location	Total patients	Total cancers	Mean follow-up (years)	Mean age (years)	Head and neck	Liver	Pancreas	Renal, bladder	Lung, trachea	Breast	Prostate	Gastric	Esophagus	Colorectal	Kaposi's sarcoma	Cervix uteri	Thyroid	Other
Levy et al. [28]	US (Texas)	556	33	2.9*		0 (0)	1 (0.18)	1 (0.18)	0 (0)	3 (0.54)	3 (0.54)	1 (0.18)			3 (0.54)		0 (0)		9 (1.62)
Sheil [24]	Australian and New Zealand	434	13	2					1 (0.23)							3 (0.69)		1 (0.23)	8 (1.84)
Penn [1]	Cincinnati Transplant Tumor Registry	324	329			7 (2.16)	3 (0.93)	4 (1.23)	5 (1.54)	10 (3.09)	7 (2.16)	2 (0.62)	3 (0.93)		18 (5.56)	10 (3.09)	6 (1.85)		254 (78.40)**
Jonas et al. [27]	Berlin, Germany	458	33			2 (0.44)	0 (0)		0 (0)	3 (0.66)	3 (0.66)	0 (0)	1 (0.22)		0 (0)	1 (0.22)	7 (1.53)***	1 (0.22)	3 (0.66)
Kelly et al. [5]	US (Mount Sinai)	888	43	4.36		3 (0.34)		1 (0.11)	1 (0.11)	2 (0.23)	2 (0.23)	4 (0.45)			3 (0.34)	4 (0.45)	1 (0.11)		5 (0.56)
Saigal et al. [6]	Kings College London	1140	30	5.91	51.5	3 (0.26)	1 (0.09)	1 (0.09)	3 (0.26)	0 (0)	2 (0.18)	0 (0)	0	0	1 (0.09)	1 (0.09)	1 (0.09)	0	17 (1.49)
Sanchez et al. [31]	US (Baylor)	1421	125	5.58	49.7	6 (0.42)		2 (0.14)	3 (0.21)	11 (0.77)	7 (0.49)	0 (0)		1	9 (0.63)		2 (0.14)		12 (0.84)
Jimenez et al. [26]	Madrid, Spain	505	62		49.5	8 (1.58)				3 (0.59)				2 (0.40)					49 (9.70)
Benlloch et al. [25]	Valencia, Spain	772	41	4.25*	53*	9 (1.17)	1 (0.13)	1 (0.13)	3 (0.39)	8 (1.04)	2 (0.26)	1 (0.13)			2 (0.26)		2 (0.26)		4 (0.52)
Yao et al. [33]	US (California)	1043	53	6.7		3 (0.29)			2 (0.19)	5 (0.48)	4 (0.38)	0 (0)			6 (0.58)	1	2 (0.19)		30 (2.88)
Sapisochin et al. [32]	Barcelona, Spain	742	71	5		5 (0.67)	1 (0.13)	2 (0.27)	6 (0.81)	9 (1.21)	2 (0.27)	2 (0.27)	3 (0.40)	3 (0.40)	6 (0.81)	1 (0.13)	2 (0.27)		29 (3.91)
Park et al. [29]	Korean	1952	44	3.41	55	2 (0.10)	1 (0.05)	2 (0.10)	1 (0.05)	2 (0.10)	4 (0.20)	1 (0.05)	11 (0.56)	2 (0.10)	9 (0.46)		1 (0.05)	3 (0.15)	5 (0.26)
Total		10,235	877																

*median; **237 lymphoma and epidermal cancers; ***dysplasia grade I-III

An attempt at such comparison was made by us in 1998, when post-transplant patients at risk (matched by age, gender, and person-years; by adding the number years for each patient from LTx to last alive) were compared with national SEER (Surveillance Epidemiology End Results) data [35]. This compared the observed incidence of de novo cancer in the study population with expected occurrence from the SEER data, and a standardized incidence rate (SIR) was developed. The expected occurrence for the study population was calculated using a statistical method described by Marsh et al. [36]. A ratio of observed over expected was generated to arrive at SIR. The SIR of <1.0 signified a lower than expected rate, while a ratio of >1.0 signified an increased rate for given type of cancer in the study population. Since then, there have been many reports where the incidences of de novo cancers have been reported with a 95 % confidence interval (CI). A decade later, Rostgaard described another similar methodology [37]. We feel that this unified system of reporting is more informative and useful, as it eases comparison.

We found a total of 15 studies where SIR had been provided with a 95 % confidence interval for various cancer sites (Table 15.3) [35, 38–51]. Some differences are readily apparent. There is also a difference in the incidence and nature of de novo malignancies in various parts of the world. There are certain geographical, population-related risk factors and disease processes that have been identified which increase the risk for certain types of cancers. For example, the relationship between inflammatory bowel disease (IBD) and colon cancer, Barrett's esophagus and esophageal cancer, and ethanol and/or smoking with oropharyngeal or lung cancer is well known.

The SIR for oropharynx/head and neck cancer varied from lowest in the Canadian study (2.5) to highest in the UK registry data (10). The SIR for lung and tracheal cancer was lowest in Finland (0.00) and highest in the report from Pittsburgh (8). For esophageal and gastric cancers, the lowest SIR of 1.06 was reported from the Pittsburg study, whereas, the SIR in the Italian study for gastric cancers was 23.4, and 16.9 in the Japanese study. For kidney cancers, the SIR from Pittsburg was 0.68, in the Netherlands study it was 30.0, and in the Taiwanese report, it was 10.15. Lastly, for breast cancer, all the studies have observed SIR of ≤1.0, other than Taiwan, where the SIR reported was 2.32.

15.3.1 Colorectal Cancer

Sint Nicolas et al. reported a slightly increased risk of colonic cancer in post-LTx patients in a meta-analysis consisting of 29 studies from pooled data [52]. Furthermore, Brentnall and Marchesa have observed in non-transplant patients an increased incidence of colonic cancer in primary sclerosing cholangitis (PSC) patients with IBD [53, 54]. As would be expected, the incidence of de novo colon cancer after LTx in PSC patients with IBD is higher [55–59].

Table 15.3 De novo cancer post-LTx with standard incidence ratios (95 % confidence interval)

	Location	Total patients	Total cancers	Mean follow-up (years)	Mean age (years)	Person-years	Oropharynx, head and neck	Lung, trachea	Esophagus, gastric, colorectal	Renal	Breast	Melanoma
Standard incidence ratios (95 % CI)												
Jain et al. [35]	Pittsburgh	1000	57	6.4	42.6	4759	7.61 (2.7–15.77)	8 (0.72–3.7)	1.06 (0.34–2.88)	0.68 (0.22–1.84	0.74 (0.15–2.16)	1.94 (0.23–6.7)
Haagsma et al. [43]	Netherlands	174	23	5.1 (median)	43 (median)				12.5 (2.5–5.2)	30.0 (6.1–87.7)		
Oo et al. [51]	England and Wales	1778	141	65.6 (median)	50 (median)			1.96 (1.07–3.29)	4.89 (2.90–7.74)		0.97 (0.49–1.74)	
Serraino et al. [50]	Italy and France	322		5.2		1508	5.5 (1.5–14)	0.5 (0.0–3.1)				
Aberg et al. [38]	Finland, Helsinki	3222	540	6.3			7.63 (14.9–30.2)	0.00 (0.00–3.32)	4.97 (0.60–18.0)	4.17 (0.50–15.1)	0.26 (0.01–1.43)	2.10 (0.05–11.7)
Jiang et al. [46]	Canadian Registry	1770	113			10,556	2.5 (0.5–7.3) oral only	1.4 (0.7–2.6)	2.6 (1.4–4.4)	3.1 (0.8–7.9	0.6 (0.2–1.4)	
Finkenstedt et al. [42]	Austria	779	105	4.1 (median)	53		4.8 (2.5–8.4)	3.1 (1.8–5.0)	2.0 (1.3–3.2)	2.5 (0.7–6.5)	0.9 (0.2–2.7)	

Baccarani et al. [15]	Italy	417	43	4.0- 10.2	52 (median)	2856	7.0 (3.0–13.7)	1.6 (0.4–4.1)	23.4 (7.6–54.7)*		0.6 (0.0–3.4)	4.4 (0.5–16.1)
Collett et al. [40]	UK registry	6846					10.0 (5.9–15.8)	1.6 (1.2–2.2)	2.3 (1.7–3.0)**	1.8 (0.8–3.6)	0.8 (0.5–1.1)	
Herrero et al. [44]	Spain						3.46 (1.49–6.82)	2.17 (0.99–4.12)	7.91 (1.63–23.13)	3.31 (1.51–6.28)		
Krynitz et al. [48]	Sweden	10,476					1.71 (2.39–5.81)	1.8 (0.7–4.0)	2.6 (0.1–15)	1.9 (0.2–6.9)	1.0 (0.4–2.1)	1.5 (0.3–4.5)
Ettorre et al. [41]	South Italy						4.5 (2.7–7.1)	1.1 (0.6–1.9)	0.6 (0.1–2.1)		0.7 (0.1–1.9)	3.1 (0.9–8.1)
Kaneko et al. [47]	Japan	360	27	7.5			3.7 (0.5–26.6)		16.9 (2.4–17.9)***	6.4 (1.6–25.4)	0.9 (0.1–6.4)	
Schrem et al. [49]	Hanover/ Germany	2000	120	7.25	36.7	14,490	1.9	1.85 (1.11–3.10)	1.92 (0.23–6.96)	2.65 (1.10–5.50)	0.83 (0.36–1.64)	
Hsiao et al. [45]	Taiwan	444	24	4.2 (median)	38.5		0	1.91 (0.21–6.89)	0	10.15 (1.1–36.7)	2.32 (0.26–8.36)	0

* = gastric only; ** = colorectal only; *** = esophagus only

15.3.2 Esophageal Cancer

Barrett's esophagus is a known premalignant condition in the non-transplant population. In 1992, Kaiser et al. reported extensive immunological studies in patients with Barrett's esophagus involving T and B cell function, immunosuppressive activity of autologous serum, and interleukin production [60]. They concluded that the immunosuppression observed in patients with Barrett's esophagus was milder than that found in other immunocompromised patients. However, they felt it may be sufficient to encourage malignant transformation of Barrett's mucosa. Caygall et al. in an epidemiological study followed 636 patients over 20 years and found that the rate of esophageal cancer was 0.2–1.6 % with men having twice the risk of women [61]. Bani-Hani et al. in another epidemiological study followed 597 cases of Barrett's esophagus over 13 years [62]. They found 12 cases developed carcinoma of esophagus. Fortunately, there are not many cases of Barrett's esophagus with de novo cancer in the post-LTx population. Casavilla et al. from Pittsburgh reported six cases of esophageal complications after LTx. However, none of them had malignancy [63]. Ilan et al. in 1996 described a case of esophageal malignancy a short time after LTx in a patient who had known Barrett's esophagus before transplant [64]. Trotter et al. reported a case of high-grade dysplasia within 9 months post-LTx in a case with Barrett's esophagus [65]. Other authors have found an increased post-transplantation incidence of esophageal cancer in association with alcohol-induced cirrhosis. Kenngott et al. reported two cases of esophageal cancer with ethanol-induced cirrhosis [66]. Presser et al. gave an account of 1926 LTx patients from 1998 to 2006 [67]. He reported nine cases of esophageal cancer; incidentally all nine patients were transplanted for ethanol-induced cirrhosis. These observations are consistent with an increased rate of aerodigestive de novo cancers post-LTx [68].

15.3.3 Ethanol and De Novo Cancer

An epidemiological study of 1.2 million US adults with alcohol consumption revealed significantly higher risk for oral, esophageal, pharyngeal, laryngeal, and liver cancers in the middle-aged and elderly population [69]. De novo cancers of the esophagus and lungs after LTx appear to have a higher SIR for patients transplanted due to ethanol-related cirrhosis. We initially reported an SIR of 7.61 (95 % CI 2.7–15.7) for oropharyngeal and an SIR of 1.66 (95 % CI 0.72–3.27) for lung cancer for a population of 1000 patients with person-years of 4795.3 [35]. However, when we separated the incidence for patients transplanted due to ethanol-related cirrhosis, we found the SIR to be 25.5 for oropharyngeal and 3.7 for lung cancers [70]. Other groups have also found an increased incidence of esophageal cancer for patients transplanted for ethanol-induced cirrhosis [71, 72]. Liu et al. reported an SIR of 3.8 (95 % CI 2.8–4.9) for head and neck cancers on a meta-analysis performed on post-transplant patients from ten studies consisting of 5607 patients with 129,449

person-years [73]. Moderesi et al. claimed a four times higher risk of skin cancer in LTx patients, where ethanol use was the cause of liver failure [74]. Tallon Aguilar et al. claimed the influence of alcohol consumption as a risk factor in the development of de novo cancer post-LTx [75]. Van der Heide et al. reported a higher incidence of tobacco use in patient with liver disease, with a 10 year cumulative risk of 12.7 % for active smokers compared to 2.1 % for nonsmokers [76]. Furthermore, Dumortier et al., claimed that de novo malignancy had more negative impact on survival than alcohol relapse post-LTx [77].

15.3.4 Recipients' Age and Rate of De Novo Cancers

The rate of non-lymphoid de novo cancers is also higher when the recipient is older at the time of transplant. We observed a rate of 2.1 cases/100 person-years for the <40 years age group, 13.6 cases/100 person-years for patients between 40 and 60 years of age, and 23.9 cases/100 person-years for the >60 years old age group for all non-lymphoid malignancies [78]. Xiol et al. reported a rate of 14.5 (95 % CI 3.1–25.9) for any de novo cancer in the <51 years age group and 34.5 (95 % CI 19.2–49.2) for the >51 years age group in a univariate analysis [79]. Haasgma et al. reported de novo cancer incidences of 0.245 for <40 years old patients and 1.48 for recipients aged >40 years [43]. Meaning, de novo cancer is 8.2 times higher for age >40 compared to age <40 years. Fung et al. showed an inverse relationship of de novo non-lymphoid malignancy with PTLD [17]. The rate of PTLD was shown to decrease with age while non-lymphoid malignancy increased with age. Furthermore, the rate of PTLD decreased after 3 years, while non-lymphoid malignancy continue to increase after that point.

15.3.5 Influence of Length of Follow-Up on the Incidence of De Novo Cancer

We followed 1000 patients with a mean follow-up 77.8 ± 11.1 months, where 4975.3 person-years resulted in 57 de novo malignancies (Table 15.4) [35]. The same population when followed until December 2002, increased the total person-years to 8199. The number of de novo cancers increased from 57 to 87. When non-melanoma, non-Kaposi's skin cancers were omitted, the total cancer count was 37 for 4975.3 person-years. With the increase in follow-up to December 2002 for the same population, it increased to 54 (an increment of 45.9 %) for 8199 person-years. Similar reports have been cited by others in relation to length of follow-up. Haagsma et al. reported an increased relative risk of cancer with length of follow-up [43]. It was 2.0 at 5 years, 6.7 between 6 and 10, and 13.5 at >10 years. Hsiao et al. reported a cumulative risk of 5.1 %, 10.4 %, 12.8 %, and 15.8 % at 1, 3, 5, 10 and 15 years post-LTx, respectively [45]. Xiol et al. reported the risk of de novo malignancy of all types as being 13 % at 5 years and doubling to 26 % by 8 years post-LTx [79].

15.4 Breast Cancer

While there is a considerable disparity in the literature on the standard incidence ratios (SIR) of different types of de novo cancer, for breast cancer, the reports are consistent across the board in all studies except one from Taiwan. Compared to all de novo cancers, the SIR for breast cancer post-LTx are similarly low. This low rate was also observed by Stewart et al. in heart and kidney transplant recipients [80]. They reported on 25,914 transplanted women in a follow-up period of 1–11 years. The observed rate for de novo breast cancer was 86 while the expected was 113.8 (SIR = 0.76). They also observed that the SIR in the first year was 0.49 which rose to 0.84 in subsequent years. We have made similar observations in LTx recipients [35, 81]. Several other studies have also reported a similarly low incidence of breast cancer after LTx (Table 15.3) [35, 78]. The exception to these lower rates comes from a recent report from Taiwan in 2014 [45]. They reported SIR of 2.32.

Table 15.4 Type and number of de novo malignancies for various age groups and person-years

	November 1998: total person-years 4975.3	December 2002: total person-years 8199			
		Divide by age group			
	Total %	≤40, $n=354$	>40 to ≤60, $n=442$	>60, $n=204$	Total %
Skin (non-melanoma, non-Kaposi's)	20 (35.09)	4	18	11	33 (37.93)
Gastrointestinal	5 (8.88)	0	7	1	8 (9.19)
Genitourinary	5 (8.88)	0	4	7	11 (12.64)
Lung	8 (14.04)	0	5	4	9 (10.34)
Oropharyngeal	7 (12.28)	0	7	3	10 (11.49)
Miscellaneous	12 (21.05)	3	6	7	16 (18.39)
Breast	(3)	(1)	(2)	(0)	(3)
Leukemia	(0)	(1)	(0)	(2)	(3)
Unknown primary	(2)	(0)	(1)	(0)	(1)
Kaposi's	(2)	(1)	(0)	(1)	(2)
Thyroid	(1)	(0)	(2)	(0)	(2)
Brain	(1)	(0)	(0)	(1)	(1)
Melanoma	(2)	(0)	(0)	(2)	(2)
Eye	(1)	(0)	(1)	(0)	(1)
De novo liver	(0)	(0)	(0)	(1)	(1)
Total including skin cancers	57	7	47	33	87
		Relative risk in relation to age group			
Excluding non-melanoma, non-Kaposi's skin Cancer	37	3 (0.85 %)		29 (6.9 %)	22 (10.8 %)

The Austria registry has found that the SIR of de novo cancers post-LTx is lower compared to heart transplant and lung transplant recipients [42]. Similarly, the UK registry has found the SIR for post-LTx patient to be lower than the post-kidney transplant patient [40].

15.4.1 Gynecological Cancers

Cervical, uterine, and ovarian cancer rates are also reportedly lower in most studies. However, an unusually high incidence of vulvar cancers has been reported in some studies. The specific nature of the malignancies has not been stated [1, 49]. It appears that these could be epidermal skin lesions or condylomata.

15.5 Summary

In summary, one can make some broad generalizations:

1. The incidence of de novo malignancies increases with the recipient's age at the time of transplant.
2. The incidence of de novo cancer gets higher with a longer length of follow-up.
3. Certain types of cancer are higher in patients transplanted for ethanol-induced cirrhosis, particularly oropharyngeal, lung, and esophageal.
4. An increased rate of colorectal cancer is observed for patients with PSC and IBD.
5. Esophageal cancers are increased in the presence of Barrett's esophagus and also with ethanol-induced cirrhosis.
6. The rate of oral pharyngeal cancer is higher in all the studies.
7. There are geographical differences.

15.6 Conclusions

To avoid recurrence of non-hepatic malignancy after LTx, all transplant centers have exercised good clinical judgment in selecting their candidates for LTx with prior history of malignancy. Fortunately, the rate has been quite low, with an intermediate length of follow-up of 3–7 years. However, the question remains, are we too conservative in our selection? Does the in situ malignancy with wide excision really need to wait for minimum period of 2 years? Does there need to be a delay in the lifesaving transplant for stage 1 renal and colonic cancer and also for some hematological conditions?

There are several reports of de novo cancer after LTx, and the rates have varied from 2.3 to 12.3 %. These differences are likely to be related to length of follow-up and age of the patient group. From single center, there have been inconsistencies in the reporting of de novo malignancies. Some studies have included lymphoid malignancies while others have excluded them. Also, cutaneous epidermal cancers are included by some and not by others. In our experience, it is always very difficult for our patients to report these cancers to the transplant center since many patients do not take them seriously. Universal reporting using surveillance end-result data and calculating the SIR for each cancer type should provide the real risk for that particular cancer type. This would take into account the age, gender, and person-years from transplant. This method eliminates the length of follow-up discrepancy, and we can obtain data from an age- and gender-matched population. It is encouraging to know that so many studies are now reporting the de novo cancers with SIR and 95 % CI for each cancer type based on large study populations from Hanover, Sweden, UK, and Helsinki. In the future, the differences in SIR across the globe may enable epidemiologists to look into environmental issues including the behavior of the population being studied.

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Chapter 16
Recurrence of Disease After Liver Transplantation in the Pediatric Population

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16.1 Introduction

Indications for liver transplantation (LT) in the pediatric population differ from those seen in adults, and disease recurrence in children warrants special consideration. Diseases that frequently recur in adult LT recipients, such as alcoholic liver disease, hepatitis C virus (HCV) infections, primary biliary cirrhosis (PBC), and nonalcoholic steatohepatitis (NASH), are rarely seen in children. The most common etiologies necessitating LT in the pediatric age group as described by the latest annual report from the United Network for Organ Sharing (UNOS) are presented in Fig. 16.1 [1]. Between 2010 and 2012, the most frequent indications were cholestatic liver diseases in 47 % of children. Biliary atresia accounts for the vast majority of cases in this subgroup, which also includes primary sclerosing cholangitis (PSC) and familial cholestasis syndromes. Metabolic disease was the second most common category seen in 14 % of pediatric LTs, followed by primary hepatic malignancies in 13 %. Acute liver failure accounts for another 11 % of transplants in children.

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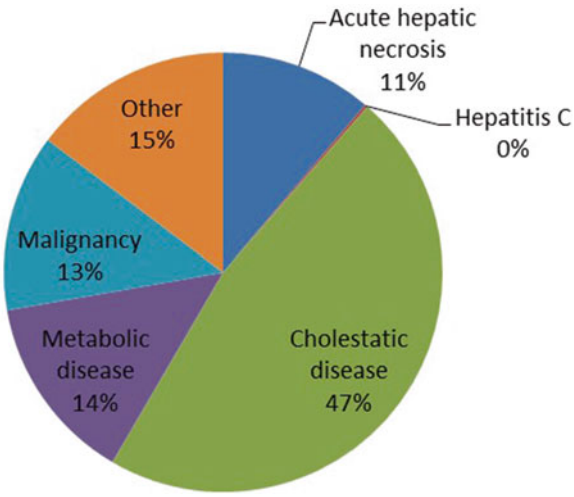

Fig. 16.1 Primary cause of disease in pediatric liver transplant recipients in the United States, 2010–2012

End-stage liver disease related to HCV infections is uncommon in the pediatric population, comprising only 0.2 % of transplants. Autoimmune hepatitis (AIH) was the cause of acute or chronic liver failure in 2 % of LTs. Of all the etiologies listed above, disease recurrence has been reported for primary hepatic malignancies, AIH, HCV, and specific types of cholestatic liver diseases.

16.2 Primary Hepatic Malignancies

The primary liver tumor seen most frequently in children is hepatoblastoma (HBL) followed by hepatocellular carcinoma (HCC). In 2010–2012, these two malignancies are responsible for 7.1 % and 1.1 % of all pediatric LTs, respectively.

16.2.1 Hepatoblastoma

HBL occurs at an incidence of one per one million children and accounts for approximately two-thirds of all liver tumors in the pediatric population [2]. Complete surgical removal of the tumor provides the best chance for cure, and resection has been recognized as the first-line treatment modality. For patients with unresectable HBL without metastatic disease, chemotherapy followed by total hepatectomy with LT has been advocated, and favorable long-term survival rates have been observed [3]. Most studies on outcomes following LT for HBL are small single-center series, and as such the true incidence of tumor recurrence remains poorly defined. Among 12 children who underwent LT for HBL after neoadjuvant

chemotherapy, Reyes et al. reported that two patients (17 %) subsequently died as a result of disease recurrence [4]. Intrahepatic venous invasion, lymph node involvement, and contiguous spread were not associated with significant adverse effects on outcomes. In contrast, pretransplant distant metastases were suspected in both patients who succumbed to recurrent disease. Most deaths attributable to recurrent tumor occurred within 2 years posttransplant [5]. In a review of 15 pediatric patients who underwent LT for HBL, Beaunoyer et al. reported a 67 % recurrence-free survival after a 5-year follow-up [3]. In another single-center analysis, Malek et al. reported a disease recurrence rate of 4 % among 23 children with HBL and 2 children with HCC who underwent LT, which compares favorably with a recurrence rate of 17 % after liver resection [6]. A retrospective review of the Surveillance, Epidemiology, and End Results (SEER) registry identified 318 children diagnosed with HBL between 1998 and 2009. Of all HBL patients, 83 % underwent resection and 17 %, transplantation [7]. Despite having more advanced disease at presentation, with higher incidences of vascular invasion and satellite nodules, transplant patients demonstrated equivalent disease-specific survival rates at 5 years compared with patients who underwent resection. More recently, a single-center retrospective review of 35 children diagnosed with HBL reported 1- and 5-year post-LT survival rates of 86 % and 66 %, respectively. Tumor recurrence was observed in nine cases, with a median time of 6.5 months to recurrence. Significant predictors of patient survival on multivariate analysis include intravascular tumor invasion, the presence of lung metastases, and rescue transplantation after failed resection attempts [8].

16.2.2 Hepatocellular Carcinoma

Although the incidence of HCC is <0.5 per two million children, it constitutes the second most common cause for primary liver tumors after HBL in the pediatric population [6]. Since HCC usually occurs in the setting of preexisting liver disease, and often lesions are quite large at the time of diagnosis; less than 25 % of lesions are amenable to surgical resection [9]. While outcomes following LT for HCC have been extensively studied in adults, less is known about outcomes in pediatric LT recipients with HCC. Reyes et al. reported a 5-year survival rate of 68 % after LT for HCC in children [4]. Six of 19 patients (32 %) died as a result of tumor recurrence, with most recurrences occurring within 3 months posttransplant. Vascular invasion, distant metastases, lymph node involvement, tumor size, and gender were all found to be significant risk factors for recurrence. However, the number of lesions was not associated with posttransplant outcomes in this study. Beaunoyer et al. reported a recurrence-free survival of 83 % at 5 years posttransplantation [3]. In contrast to the earlier study, the number of tumors, size, and gross vascular invasion were not associated with the risk of recurrence. In the SEER registry, a total of 80 children were diagnosed with HCC from 1998 to 2009 [7]. Of all HCC patients, 75 % underwent resection and 25 % received LT. Transplant patients again had more advanced disease as evidenced by a higher prevalence of vascular invasion and

satellite lesions. Nevertheless, disease-specific survival at 5 years was superior for transplant patients (85 %) compared with resection patients (53 %). Venick et al. reported 1-, 5-, and 10-year survival rates of 86, 64, and 64 % for children undergoing LT for HCC [8]. Tumor recurrence was the cause of death in two patients, who were diagnosed with recurrence at 0.4 and 4 years post-LT, respectively.

The published reports presented above demonstrate that childhood HCC is a more aggressive disease than HBL, associated with worse survival and a higher risk for recurrence. Furthermore, children with HCC who undergo surgical resection may develop recurrences more frequently than patients who receive LT. The number of lesions, and perhaps tumor size, are not consistently associated with posttransplant outcomes. As such, the Milan criteria, which has been used to assign Model for End-Stage Liver Disease (MELD) exception points to adult transplant candidates with HCC, are not applicable in the pediatric population [10]. Taken together, the favorable outcomes following LT, even in patients with advanced tumors, suggest that this treatment modality can be used more liberally in children diagnosed with HCC.

16.3 Hepatitis C Infection

HCV infections are uncommon in pediatric patients, occurring in 0.2–0.4 % of children under 19 years of age [11]. The natural history of HCV infections in the pediatric population also differs from that in adults, namely spontaneous clearance of the virus can take place, and progression to end-stage liver disease or HCC as a child is unusual [12]. Accordingly, HCV only accounted for 0.2 % of all LTs performed in children between 2010 and 2012 (Fig. 16.1).

Among adult patients who undergo LT for HCV infections, the persistence of viremia is almost universal, and approximately 50 % of patients will show abnormal liver biopsies by 1 year posttransplant [13]. HCV recurrence has been shown to result in inferior patient and graft survival outcomes and the increased need for retransplantation. Occasionally, a rapidly progressive form of recurrent HCV can occur, resulting in accelerated hepatic decompensation termed “fibrosing cholestatic hepatitis.”

Because of the rarity of HCV infections inpediatric patients, there is limited data on the outcomes and recurrence rates of HCV following LT in this population. Barshes et al. analyzed the UNOS registry to study outcomes of pediatric patients who underwent LT for HCV infections. Overall, the results are similar to those seen in adults, with a 5-year patient survival of 72 % after primary transplantation. The rate of retransplantation due to HCV recurrence was 19 %, slightly higher than the retransplant rates of 8–11 % reported in the adult population [11]. Recurrent disease was the primary indication for the majority of retransplants performed.

In adults, retransplantation for liver allograft failure due to HCV recurrence has been associated with poor outcomes. Posttransplant HCV recurrence is nearly universal, and HCV recipients are at an increased risk of death compared to retransplant patients without HCV [14]. Little is known about outcomes following retransplantation for HCV in the pediatric population. With recent advances in the

use of direct-acting antiviral agents for the treatment of hepatitis C, however, viral clearance can be achieved in cases of post-LT HCV recurrence, and the need for retransplantation may be avoided [12].

16.4 Autoimmune Hepatitis

Autoimmune hepatitis is a progressive inflammatory liver disease characterized serologically by elevated transaminases, the presence of autoantibodies, and age-specific hypergammaglobulinemia, as well as histologically by interface hepatitis. Two types of AIH have been described—AIH type 1 accounts for two-thirds of cases and is associated with the presence of antinuclear antibody (ANA) or anti-smooth muscle antibodies (SMA); AIH type 2 is associated with anti-liver kidney microsomal antibodies and tends to present at a younger age. An overlap syndrome with features of AIH type 1 along with sclerosing cholangitis has also been observed in pediatric patients, a condition termed autoimmune sclerosing cholangitis (ASC) [15].

Although the incidence of AIH in the pediatric population has not been clearly defined, approximately 20–25 % of patients with AIH will die or require LT in childhood [16]. The recurrence of AIH following LT has been documented in both adult and pediatric recipients. The earliest report in the pediatric population described disease recurrence in 5 out of 6 children who underwent LT for AIH after a median of 11 months [17]. Recurrent disease in the grafts appeared to be refractory to augmentations in immunosuppression, and three patients ultimately required retransplantation. Bahar et al. performed a single-center review of 40 patients undergoing LT for AIH and cryptogenic chronic hepatitis and reported a 33 % recurrence rate [18]. African-American children were found to harbor a higher risk of disease recurrence when compared with Caucasian and Hispanic recipients. Patients with AIH type 1 or type 2 demonstrated similar recurrence rates after transplantation. However, LT recipients with ASC have been reported to be at increased risk for recurrence compared with AIH patients [19]. Analysis of the Studies of Pediatric Liver Transplantation (SPLIT) registry found equivalent patient and graft survival outcomes between children transplanted for AIH and those transplanted for other indications [16]. Despite a higher risk for late acute rejection and the need for a greater degree of immunosuppression, infectious and metabolic complications as well as retransplant rates were not elevated for AIH patients. The prevalence of AIH recurrence after LT was not reported in this study.

16.4.1 Giant Cell Hepatitis with Autoimmune Hemolytic Anemia

Giant cell hepatitis (GCH) is a rare form of rapidly progressive liver disease seen mostly in the neonatal period. The presence of giant multinucleated cells is thought to result from the response of immature hepatocytes to stress [20]. An autoimmune

process or immune dysregulation is implicated in the pathophysiology of GCH. GCH often presents with an aggressive and fulminant course requiring intense immunosuppression, bone marrow transplantation, and/or LT. Most LT recipients will show a good initial response to immunosuppressive therapy but followed with frequent relapses.

The association of GCH with autoimmune hemolytic anemia (GCH-AIHA) is a distinct entity and has only been reported in 45 patients in the English literature [20, 21]. In a review of 24 GCH-AIHA cases, five children ultimately went on to require LT [22]. Outcomes following LT were poor, with two deaths secondary to posttransplant lymphoproliferative disease (PTLD)and sepsis; 4 out of the 5 LT recipients also developed recurrent disease. In another single-center report, two of 16 children with GCH-AIHA underwent LT, of which one patient is alive after 9 years of follow-up with normal serum alanine aminotransferase levels. Histologic examination of the liver graft, however, shows the occasional presence of giant multinucleated cells. The other patient died of multiple organ system failure within a few days of transplantation [20]. With these disappointing results and the high risk for recurrence, bone marrow transplantation may be the preferable treatment in children with GCH-AIHA. Nevertheless, in the face of liver failure during a relapse refractory to medical treatment, LT may be the only lifesaving treatment option and may be considered.

16.5 Cholestatic Liver Diseases

16.5.1 Primary Sclerosing Cholangitis

PSC is a chronic and progressive liver disease characterized by insidious inflammation and the obliteration of intrahepatic and extrahepatic bile ducts. This condition has a distinctive appearance on liver biopsy and on cholangiography and is accompanied by the presence of anti-neutrophil cytoplasm antibodies (p-ANCA). PSC is often associated with inflammatory bowel disease (IBD) and can lead to end-stage liver disease and predispose to the development of cholangiocarcinoma. Currently available medical treatments for PSC address the symptoms related to complications but do not necessarily alter the natural history of the disease, and LT may offer the only chance for cure. Recurrence of PSC has been reported in up to one-third of adult patients who undergo LT [23]. Non-anastomotic biliary strictures are more common in PSC patients and are found to be present in 25 % of adult recipients within 3–5 years posttransplant [24].

In children, the incidence of PSC has been estimated at 0.23 per 100,000 person-years, which is only 20 % of the incidence reported for adults. Recurrence rates following LT are similar in children and adults, with reported rates of 0–33 % in the published series. In a single-center review of 12 pediatric LTs for PSC, four patients (33 %) developed disease recurrence after a median duration of 52 months [25].

A review of the UNOS registry reveals a higher proportion of children with PSC requiring retransplantation relative to those transplanted for biliary atresia. The median time to retransplantation for PSC patients was 4.1 years [25]. Analysis of the SPLIT database demonstrates a recurrence rate of 9.8 % at a mean duration of 18.7 months post-LT [26]. PSC patients were more likely to develop intrahepatic strictures by 6 months posttransplant, and experience more cholangitis episodes in the early posttransplant period compared with patients undergoing LT for other indications. Children with concurrent IBD were at a higher risk for PSC recurrence and posttransplant mortality. In adult recipients with IBD, pretransplant colectomy appeared to be protective against recurrent PSC, but it is unclear whether this association also applies to the pediatric population. Data from both the UNOS and SPLIT registries suggest superior survival for PSC patients in the early posttransplant period, but their long-term allograft survival may be worse than patients undergoing LT for other disease etiologies [26].

16.5.2 Progressive Familial Intrahepatic Cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a group of hereditary cholestatic liver diseases categorized by the specific genetic mutations involved (Table 16.1). The incidence of PFIC is estimated to be 1–2 per 100,000 births [27]. All three subtypes of PFIC are inherited in an autosomal recessive fashion. PFIC-1, also called Byler's disease, and PFIC-3 involve mutations of membrane proteins which act as phospholipid flippases. These proteins are integral for the maintenance of membrane asymmetry and the proper function of other transporter proteins responsible for biliary excretion. PFIC-2 is characterized by mutations of the bile salt export pump (BSEP), which is encoded by the ABCB11 gene. BSEP is expressed in the canalicular membranes of hepatocytes and facilitates bile salt excretion into the biliary system. Patients with PFIC-2 typically present in early childhood with jaundice, hepatosplenomegaly, and severe pruritis. Unlike other cholestatic liver diseases, these patients demonstrate normal or low serum levels of gamma-glutamyltransferase (GGT) during episodes of cholestasis.

Recurrence of the PFIC-2 phenotype after LT with cholestasis and refractory pruritis has been reported by several groups recently and has been linked to the de novo development of anti-BSEP antibodies [28–31]. It is estimated that 8 % of

Table 16.1 Subtypes of progressive familial intrahepatic cholestasis (PFIC) and associated genetic mutations

	Affected gene	Protein	Function
PFIC-1 (Byler's disease)	ATP8B1	FIC	Phospholipid flippase
PFIC-2	ABCB11	BSEP	Bile salt export pump
PFIC-3	ABCB4	MDR3	Phospholipid flippase

transplanted PFIC-2 patients will develop anti-BSEP antibodies, targeted against the BSEP protein in the bile canaliculi, thereby impairing bile acid secretion. Recurrent disease may be more common in pediatric LT recipients who are affected by an episode of acute rejection. In a single-center review of 20 children with PFIC-2 who underwent LT, two patients developed a recurrent PFIC-2 phenotype. Recurrent disease has a variable response to immunosuppressive treatment—some authors have reported a favorable response to a regimen of tacrolimus, mycophenolate mofetil, and corticosteroids, while others have documented a failure to respond to any therapy. Lin et al. recently reported the efficacy of the combination of rituximab, intravenous immunoglobulin, and plasmapheresis in managing two patients with recurrent PFIC-2 phenotype after LT [32]. Nevertheless, retransplantation is often required for patients with anti-BSEP antibodies. Of six PFIC-2 patients who developed recurrent disease in a single center, four went on to require retransplantation [31]. All retransplanted patients developed recurrence of cholestasis, suggesting the persistence of anti-BSEP antibodies even after retransplantation.

16.5.3 Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a rare multisystem disorder distinguished by the proliferation and accumulation of histiocytic cells which resemble Langerhans cells in the skin. Involvement of the liver occurs in 20–35 % of cases which often confers a poor prognosis [33]. Severity of liver disease can range from mild hepatomegaly with minimal abnormalities in liver chemistries to sclerosing cholangitis and biliary cirrhosis. It is estimated that LCH represents 15–20 % of sclerosing cholangitis in children [34]. LT has been performed by several centers for children with end-stage liver disease secondary to LCH-associated sclerosing cholangitis, with a reported 87 % patient survival rate after 3.4 years. These LT recipients may be at elevated risk for acute cellular rejection, which necessitates intensification of immunosuppression, leading to a higher reported incidence of PTLD [35].

Zandi et al. reviewed the records of five children who underwent LT for sclerosing cholangitis complicating LCH, and no disease recurrences were recorded [34]. However, a later report by Hadzic et al. documented two cases of recurrent LCH after LT at 5 and 60 months posttransplantation, respectively [16]. The diagnosis of recurrent disease was made based on abnormal biliary enzymes and the appearance of Langerhans cells on histologic examination of the allograft. In one patient, a low-grade cholangiopathy was also evident on subsequent imaging. LCH activity in recurrent cases was controlled with maintenance chemotherapy and increased doses of corticosteroids, which led to regression of inflammation and the disappearance of Langerhans cells on follow-up liver biopsies.

The relapse of LCH in the transplanted allograft has also been described in two adult lung transplant recipients. In both cases, recurrent LCH wasradiographically evident within the first year following lung transplantation [36].

16.6 Summary

The spectrum of recurrent diseases in pediatric LT recipients differs from that seen in adult patients. Unresectable malignant liver tumors, namely HBL and HCC, demonstrate relatively low recurrence rates and favorable survival outcomes following neoadjuvant chemotherapy and LT. Childhood HCC appears to be a more aggressive tumor than HBL, with higher rates of recurrence particularly after surgical resection. Although an uncommon indication for LT in the pediatric age group, recurrence of HCV infections occurs at a similar frequency as in the adult population. The several reports addressing children with AIH suggest a high relapse rate after LT. GCH-AIHA carries a high risk of post-LT recurrence and confers an exceptionally poor prognosis. Of the cholestatic liver diseases, the recurrence of PSC after LT has been documented in children. An interesting phenomenon is seen in LT recipients with PFIC-2, the familial cholestasis syndrome characterized by BSEP deficiency. The de novo appearance of anti-BSEP antibodies can cause the recurrence of the PFIC-2 phenotype after transplantation. LT has also been advocated for patients with sclerosing cholangitis associated with the rare multisystem disorder LCH. The recurrence of LCH activity in the liver allograft has been described, and disease regression was achieved using maintenance chemotherapy in the reported cases.

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Chapter 17
Disease Recurrence After Liver Transplantation: Quality of Life and Cost of Retransplantation

Vignan Manne and Sammy Saab

17.1 Introduction

Liver transplantation is the definitive treatment for decompensated liver disease and hepatocellular carcinoma [1]. Advances in patient selection, surgical technique, and immunosuppressant therapy have led to improved patient outcomes [1]. Nevertheless, recurrent disease occurs in transplant recipients. This can severely impair health-related quality of life (HRQOL), patient and graft survival, and health care utilization. Currently, over 6000 liver transplantations are successfully performed annually in the United States, and there are over 65,000 recipients believed to be alive today [2].

HRQOL is a multidimensional assessment of a patient's physical, social, emotional, and psychological well-being [3]. Issues of HRQOL are very pertinent in clinical practice given the increasing cohort of transplant survivors [3, 4]. The rate of graft failure from recurrent disease can be substantial. National data from the Organ Procurement and Transplantation Network (OPTN) indicate that the graft failure rate varies depending on the underlying reason for liver disease with rates between 25 and 50 % described with patients transplanted with a diagnosis of liver neoplasm [5]. The approach to recurrent disease is treatment of the underlying liver condition, but can involve retransplantation.

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17.2 Epidemiology of Liver Transplantation and Retransplantation

The most common indications of liver transplantation are demonstrated in Fig. 17.1 [1]. Over the past two decades, nonalcoholic steatohepatitis (NASH) has emerged as an important cause for liver transplantation [1]. Nonalcoholic steatohepatitis has become the second most common etiology of liver transplantation [1]. Patient and graft survival both appear directly related to the indication for liver transplantation. For instance, the 10-year graft survival for patients transplanted for NASH was 80.4 %, but 62.3 % in patients transplanted for the concomitant diagnosis of alcoholic liver disease and hepatitis C (Figs. 17.2 and 17.3) [1].

Over the past decade, approximately 10 % of all liver transplantation has been for graft failure of the original transplant [6]. However, the proportion of all grafts used for retransplantation appears to be decreasing. During the time period 2004–2008, close to 1 of every 12 grafts was being used for the purposes of retransplantation [6]. In contrast, one in over ten grafts was for retransplantation between the year 1999 and 2003 [6]. Although patient survival improved from 1999 to 2008 in retransplant patients, it was still inferior to primary transplant patients only 1 year post-transplant, being close to 90 % for primary transplant recipients and 75 % in retransplant recipients [6].

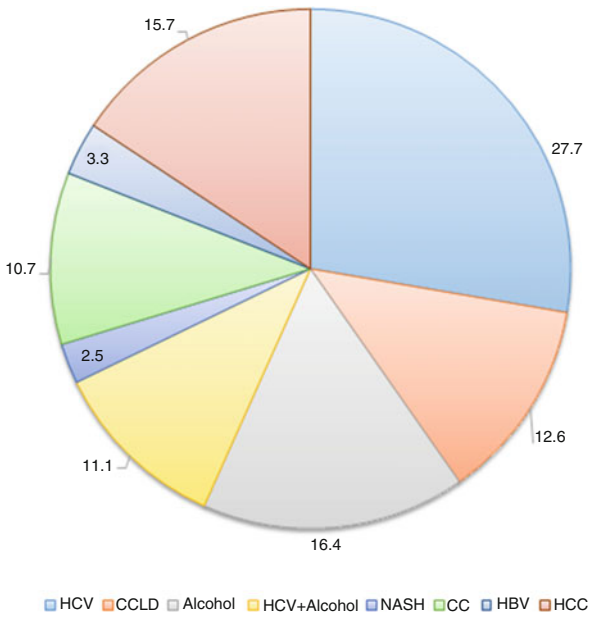

Fig. 17.1 Breakdown of etiology of disease leading to liver transplantation, adapted from Singal et al. [1]. *Abbreviations*: *CC* cryptogenic cirrhosis, *CCLD* chronic cholestatic liver disease, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma; *HCV* hepatitis C virus, *NASH* non-alcoholic steatohepatitis

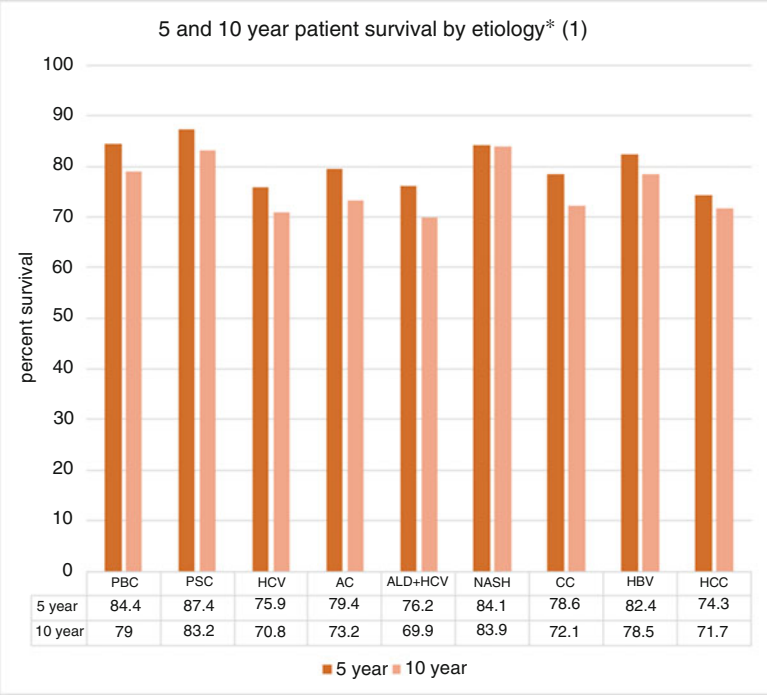

Fig. 17.2 Change in 5- and 10-year survival of patient after liver transplantation by disease etiology, adapted from Singal et al. [1]. *Abbreviations*: *AC* alcoholic cirrhosis, *ALD* alcoholic liver disease, *CC* cryptogenic cirrhosis, *CCLD* chronic cholestatic liver disease, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *NASH* non-alcoholic steatohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis. *Data obtained for transplants done between the years of 1994–2008

17.3 Quality of Life Following Liver Transplantation

17.3.1 Tools to Assess Quality of Life

Although a number of instruments are used to measure HRQOL in liver transplant recipients, none clear standard exists [7]. There has been an attempt at developing a more specific post-liver transplant-specific questionnaire, but this has not yet been validated [3].

One of the commonly used instrument in liver disease is the short-form 36 (SF-36), a generic and validated survey commonly. In a systematic review of long-term HRQOL outcomes, the authors identified 8 of the 23 studies which utilized the SF-36 HRQOL survey [7]. The SF-36 is a self-rated survey that is used to compare

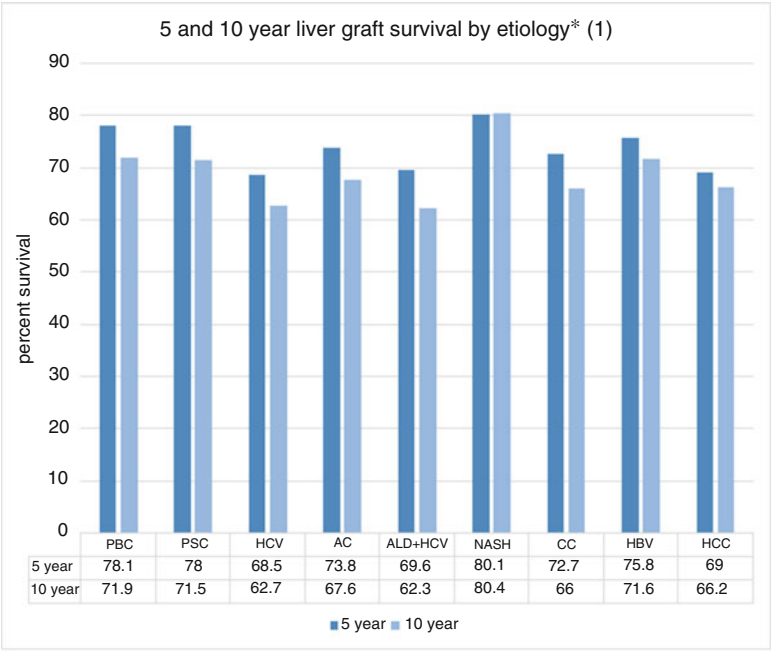

Fig. 17.3 Change in 5- and 10-year survival of liver grafts by disease etiology, adapted from Singal et al. [1]. *Abbreviations*: *AC* alcoholic cirrhosis, *ALD* alcoholic liver disease, *CC* cryptogenic cirrhosis, *CCLD* chronic cholestatic liver disease, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *NASH* non-alcoholic steatohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis. *Data obtained from transplants done between the years of 1994–2008

health status across diverse populations, including different disease processes, and measures 36 items [8, 9]. These items are further divided into eight subscales including general health, physical function, bodily pain, mental health, and four others. A score is then generated for each subscale that can be compared between different populations.

There are a number of limitations understanding HRQOL in liver transplant recipients. For instance, unlike studies assessing HRQOL in patients who undergo primary transplantation, there are few studies measuring HRQOL in patients following liver retransplantation [7]. There is also a paucity of data of HRQOL according to indication for liver transplantation. Most studies on HRQOL provide an overall measure rather than stratification by underlying cause of liver disease [7, 10]. Although it is likely that the etiology of liver disease would have a unique effect on HRQOL, evidence of this effect has so far been less clear [10].

17.3.2 Overall HRQOL of Post-transplantation Recipients

There is strong and convincing evidence of a sustained benefit to HRQOL for post-transplant patients compared to the same patients in the pre-transplant period or an equivalent waiting list group of patients with chronic liver disease [7, 10]. This benefit is found regardless of the whether the instrument used to measure HRQOL and was seen in all categories measured including general health, social interactions [4], emotional, physical well-being, and psychosocial function [11–16]. The sustained benefits in HRQOL ranged anywhere from 3 to 8 years before a significant decrease occurred [14, 17, 18]. Patients that have survived over 10 years post-transplant show a decrease in most HRQOL domains over time, though the rate at which this occurred and after how many years continued to be variable [4, 13, 19–21]. Although there was a decrease in QOL, the HRQOL scores were still consistently higher among post-transplant patients when compared to pre-transplant patients with chronic liver disease [4, 13, 16, 22].

Although post-transplant recipients have much better HRQOL scores as compared to the waiting list population, the comparison of post-transplant patients to a healthy comparison group has conflicting data with regard to HRQOL scores [7, 10]. Several studies have shown that the HRQOL of patients post-transplant can be similar to the general population [4, 15, 17, 18, 23–25]. The magnitude of improvement of scores among the different domains that comprise HRQOL such as general health, mental health, physical role functioning, emotional role functioning, and other domains in transplant recipients can vary according to HRQOL instrument used [7, 10]. However, the domains of general health and mental health were on average found to be similar between the general population and post-transplant patients [4, 15, 17, 18, 23–25]. Increased physical activity may be a good predictor of sustained QOL benefits post-transplant, though this needs further validation [4, 22, 25].

Other studies have shown that the post-transplant population has significant impairment in almost all domains when compared to the general populace [10]. Interestingly, the majority of studies that show poorer QOL for the post-transplant group ranged from 6 months to 10 years with most studies having follow-up times before the 5-year post-transplant mark [10]. Whereas the studies that showed some similarities in certain domains had follow-ups that were usually greater than 5 years [7], one domain that all studies concur on is a poorer performance in physical function, which had consistently lower scores in the post-transplant group when compared to the general population [7].

17.3.3 Functional Status

Functional status has been defined as "…an individual's ability to perform daily activities required to meet basic needs…maintain health and well-being" [26]. The functional status is a valuable predictor of HRQOL; better functional status

correlates with increased HRQOL. Employment status and amount of physical activity are commonly used as surrogates when assessing the functional status of post-transplant patients [7, 10].

There are a number of limitations when assessing employment status and physical activity status in liver transplant recipients. For example, while the majority of post-transplant patients are of working age (28–59 years), the number of patients who were working prior to transplantation is highly variable [7]. Up to half of patients undergoing liver transplant were employed prior to transplant in studies that measured this [27, 28], and 67 % of patients were unemployed or retired by the 8th-year post-transplant [27, 28]. Important factors that can explain the lower rate of employment can be related to pre-transplant factors such as lack of disability prior to transplantation and number of hours worked [29]. Post-transplant factors include the transition into retirement and the disability status that liver transplantation offers after transplantation [10]. Those patients that do stay employed after transplantation have higher HRQOL scores [28, 30, 31].

Encouraging patients to regularly engage in regular cardiovascular exercise (i.e., three times weekly $\geq$30 min per session) has been shown to improve scores in multiple HRQOL domains including physical symptoms, fatigue, social functioning, and general health [14, 25]. Increased physical activity is also associated with decreased surgical complications after transplant [23, 25]. Although encouraging patients to regularly engage in physical activity is beneficial, this may not be possible among all patients. Many patients have multiple comorbid conditions and may not be able to achieve the high level of physical activity that are usually studied [25]. Further study into whether lower levels of activity still offer the same benefit that regular physical activity confers in the future will be useful in this regard.

Sexual function is another measured domain of functional status that did not significantly improve after liver transplantation [7, 10]. There may even be deterioration in sexual function following transplantation [32]. Again this data should be carefully interpreted as there can be multiple confounding factors [10]. Self-assessment questionnaires on sexual health are known to be difficult to interpret, and the presence of encephalopathy prior to transplantation can skew measurement of this domain [10]. In apparent contradiction, one long-term study demonstrated an improvement in sexual function following transplantation, indicating the need for further study [4].

17.3.4 Health-Related Quality of Life of Donors of Liver Transplantation

The number of patients that need lifesaving liver transplantation is much greater than the number of grafts available. This has led to the development of the technique of living donor liver transplantation (LDLT) in which healthy individuals donate a portion of their liver. An estimated 12,000 LDLTs have been performed worldwide [33]. The majority of donors following donation have minimal complications upon

follow-up [34, 35]. The most common short-term complications include bile leaks and other biliary complications, occurring at rates of about 5 %, and abdominal incision-related issues such as pain or incisional hernia, occurring between 9 and 19 % [35]. Other characterized complications include bleeding, ileus, or infections [36]. Due to the short-term complication, there is a transient decrease in HRQOL scores seen that generally lasts for about 3 months [35]. After approximately 6 months, most donors return to a HRQOL similar to the pre-donation period or a healthy comparison group [34, 35]. Of note, anywhere from 7 to 20 % of donors experience a sustained reduction in HRQOL following liver transplantation due to long-term complications of donation such as chronic pain and bile strictures [34]. Other studies have shown a median morbidity rate of 16.4 % following donation [35]. Thankfully, the mortality of donation is low, ranging from 0.28 to 1 % of all donations [35]. Nevertheless, this data indicates that close follow-up is essential to effectively prevent poor outcomes for post-donation patients.

Instruments for assessing HRQOL for donors have not been standardized [35]. The use of the SF-36 form is once again prevalent but still multiple different HRQOL are used [37–42]. The results of most of the studies demonstrate that across all domains, donors have a significant transient decrease in HRQOL followed by a recovery to their baseline HRQOL prior to transplantation [34, 35]. Physical health was an area that showed decline in the immediate post-op period but improved back to a normal level among the majority of patients [34, 35]. Some patients do experience complications related to surgery or have long-term discomfort but overall remain in good physical condition [35]. Mental health did not decline among most post-op studies and remained at preoperative levels, though one study did show a statistically significant lower mental health score but this was still above the norm [35, 43]. Psychosocial function is more complex than previously thought and encompasses multiple domains such as interpersonal, work-related, and financial impact [35]. Work-related impact is generally minimal as the majority of patients return to work [34, 35]. Most studies show a return to work rate of over 90 % within 12 months [35]. Interpersonal and financial impacts are areas that are evolving; financial impact includes immediate post-op follow-up that is generally covered by insurance and long-term postoperative care that is usually an out-of-pocket expense [34]. The mean out-of-pocket expense for patients is estimated around $3660 and $5305 USD [44, 45].

Interpersonal impact is more difficult to assess, but the underlying theme is that patients who freely volunteer to donate instead of feeling coerced into donating have better interpersonal functioning [35]. To address coercion, a five-stage decision-making model has been established to guide patients and professionals through the process although this has not been standardized [46]. There has been no documented detriment or benefit to donating the right or left lobe of the liver, and HRQOL is essentially the same for patients who donate either lobe [35, 43]. Important caveats are that most of the data follow-up are not long term [34, 35]. Studies with longer follow-up times include a 2-year prospective study that corroborates the data from the older studies [47]. Another long-term study with a mean follow-up time of 6.8 years post-donation shows that the HRQOL scores generally

hold either at or above the general population for most domains [43]. One domain that showed a poorer than average score was the role/social composite score (RCS) [43]. This is in line with the complexity that psychosocial function has been discovered to have [34].

17.3.5 Specific Causes for Poor Health-Related Quality of Life

HRQOL scores for the majority of patients are fairly consistent across multiple disease states. Certain disease states have been shown to have worse HRQOL scores and survival as compared to other etiologies [10]. Specific diseases that have shown worse survival outcomes include Hepatitis C virus (HCV) infection and patients who resume drinking following transplant [10]. Patients with HCV cirrhosis that have received a transplant have worse HRQOL scores if the disease recurs post-transplant [10]. Interestingly, the data is conflicted on patients without recurrence of HCV but most studies report a favorable outcome for patients who do not have recurrence of disease in comparison to those who do [7, 10]. Hepatitis B virus infection-related transplant does not have the same drop in HRQOL scores related to disease recurrence and has similar scores to other etiologies of liver transplantation [7, 10] because the rate of recurrence following transplant is less than 5 % when proper post-transplant procedure is followed [48]. Patients who resume alcohol post-transplant also have shown a significant drop in HRQOL scores [49]. Indefinite exposure to immunosuppression and the complications, such as infections, associated with long-term immunosuppression has also been identified as a factor that has led to significant drops in HRQOL scores and even life expectancy [50, 51]. Another less studied factor that leads to drops in HRQOL scores is gender [10]. Women report lower HRQOL scores in comparison to men in most studies following liver transplantation, and the reason for lower scores seen is not well understood but most studies point to psychological or social factors [10]. Other factors that lead to poor HRQOL are less well studied, and as patient survival continues to be longer, more factors will emerge and should be monitored.

17.4 Cost of Retransplantation

17.4.1 Risk Assessment

Risk assessment of retransplant candidates follows a similar algorithm of risk assessment for first-time transplant candidates [52, 53]. Patients with graft failure within 1–2 weeks after transplantation are granted a more urgent status unlike graft failures outside this window [52]. This is an important difference in risk assessment because patients outside this window are assessed as less urgent and basically start over in the process as opposed to patients in this window [52]. Retransplant candidates

Table 17.1 Four major concepts in medical ethics [55]

Ethical principle	Working definition
Patient autonomy	Patient's right to accept or refuse treatment in the form of informed consent on their own behalf
Beneficence	Physician's duty to provide and promote individual patient's best interest while balancing risks of treatment
Non-maleficence	"Do no harm"
Justice	Physician's duty to distribute available scarce medical resources fairly and equally among all of society

are stratified according to their MELD score, and it has been reported that the MELD score may not be as accurate in patients awaiting retransplant [52]. Current MELD allocation rules also have not been shown to significantly change the rate of death for patients awaiting a retransplant or a primary transplant [54]. Other factors that impact whether a candidate is listed for retransplantation include ethical, clinical, and potentially financial concerns.

17.4.2 Ethical Issues in Retransplantation

Liver transplantation in a patient with a prior liver transplant is a controversial subject with ethical, technical, and financial considerations. Four major concepts in medical ethics are patient autonomy, beneficence, non-maleficence, and justice [52, 55] (Table 17.1). These principles form the ethos that guide a physician to perform the best individualized care for patients. Liver retransplantation represents a very complex conundrum for which there is no easy or simple answer. When a patient's graft has reached graft failure, the only available treatment for that patient is retransplantation, but liver grafts are an extremely valuable and scarce resource. Long-term survival after liver retransplantation is not guaranteed, and all-cause liver retransplantation is in fact associated with inferior survival rates when compared to primary liver transplantation [6]. Further retransplantation, a third or greater number of retransplantation, shows even lower survival rates [6]. A single-center study showed a 1-year survival rate of a fourth liver retransplant of 31 % [56]. Thus, the argument that a patient who requires a second or greater liver transplant is not any more deserving than a patient seeking a primary liver transplant has been made and is a serious consideration in the setting of scarce resources [52, 57]. While this argument is theoretically sound, this is not an acceptable explanation for many patients who need a retransplant. Also complicating the matter is the bond that forms between patient and physician. This makes the decision to not implement lifesaving therapy due to a number when clearly the benefits outweigh the risks to the patient very difficult. As currently there is no clear standard on how to treat such patients [52], clinical judgment and a multidisciplinary team approach allow for the burden to be distributed.

Table 17.2 Efficacy of retransplantation from selected studies[a]

Patient group and study	Follow-up time	Survival rate (%)
Elective Re-LT		
Mora et al. [59]	1 and 2 years	82 and 72
Azoulay et al. [60]	1, 5, and 10 years	82, 74, and 67
Bellido et al. [61]	Minimum 6 month follow-up	81
Urgent Re-LT		
Mora et al. [59]	1 and 2 years	40 and 40
Azoulay et al. [60]	1, 5, and 10 years	43, 35, and 35
Bellido et al. [61]	Minimum 6 month follow-up	51.1

Abbreviation: *LT* liver transplantation
[a]Studies were selected based on follow-up and reporting of elective vs. urgent retransplantation

17.4.3 Clinical Issues in Retransplantation

The survival rate after retransplantation is significantly poorer as the number of grafts increase for a patient. One study that had 536 retransplant patients from the years of 1984–2001 showed that 1- and 5-year survival rates were markedly different with a single retransplant recipient survival rate of 59 % and 52 %, respectively [56]. Double retransplant recipient survival rate was 44 and 36 % for 1 and 5 years, with triple retransplant recipient survival rate only having a 1-year survival rate of 31 % [56]. Important considerations that impact survival include the timing of liver transplantation and the age of the patient. In contrast to adults, patient survival among pediatric patients is similar when comparing primary transplant recipients to retransplant recipients, with 5-year survival for both being greater than 70 % [58]. Age clearly has a profound impact on patient survival, and data has shown that this is one of the most important determinants for patient survival [58–60]. Also, other retrospective data has shown that timing of liver retransplantation plays a role in survival [59–61]. Retrospective data shows that patients with emergent retransplantation do significantly worse than patients going for an elective retransplantation with different studies having different survival rates (Table 17.2) [59–61]. The results of a multivariate analysis identified age (RR: 1.04; CI: 1.02–1.07, $p=0.002$), creatinine (RR: 2.44; CI: 1.39–4.28, $p=0.002$), and urgency of transplantation (super-urgent-RR: 3.99; CI: 1.34–11.92, $p=0.01$ and urgent-RR: 3.56; CI: 1.47–8.62, $p=0.005$) as independent factors predicting patient survival after retransplantation [60]. Other studies have also corroborated that recipient age and urgency of retransplantation impact survival after retransplantation [59, 61, 62]. Further research needs to be done to assess whether these survival results can be replicated or improved and to assess and validate those factors that are currently thought to affect survival. Regardless, this data provides evidence for a positive role of retransplantation in a select group of patients.

Table 17.3 Cost of retransplantation and length of hospital stay in hospital following retransplantation in selected studies[a]

Study	Length of stay (days)	Overall cost of transplantation
Primary transplant group		
Mora et al. [59]	29.7 ± 14.9	$122,358 ± 59,782
Azoulay et al. [60]	18.1 ± 29.4	47,307 ± 47,189 euros
Retransplant group[b]		
Mora et al. [59]	58.4 ± 38.9	$289,302 ± 126,907
Azoulay et al. [60]	36.1 ± 58.5	86,933 ± 96,146 euros

[a]Studies based on reporting of both LOS and cost of transplantation of both primary and retransplant patients

[b]Cost is for patients following a second graft transplantation and not more

17.4.4 Health Care Utilization

There is greater health care utilization among patients undergoing retransplantation. Multiple studies have shown that retransplantation is done at an increased cost (Table 17.3) [58, 60, 63]. The economic costs associated with retransplantation are almost double that of first-time transplantation. An important predictor of health care utilization is the length of stay (LOS), which is markedly increased in patients who undergo retransplantation [58–60, 63]. The LOS for patients undergoing retransplantation was double that of patients undergoing a primary liver transplantation (Table 17.3) [60, 63].

17.5 Conclusion

The constant evolution of the methods and medications that are involved in treating patients following liver transplantation has led to increased long-term survival of patients. As survival time lengthens, patients become more concerned with daily HRQOL, and HRQOL becomes increasingly important. Although HRQOL scores are sustained at an acceptable level long-term post-transplant, there is considerable room for improvement as HRQOL scores consistently score below the general population in the long term.

For those patients who fail the initial transplantation, health care utilization of retransplantation can be extremely high. The need for retransplant is decreasing as a proportion of all liver transplants. However, the absolute number of liver retransplants is not decreasing but increasing as more and more liver transplants are being performed. Scarce resources and poorer outcomes in the majority of patients make the decision to list a patient for transplant after they have already received a transplant extremely complex. The cost of retransplantation is not just financial but there is a clinical and ethical component to it as well. Still, retransplantation has been

shown in studies to be helpful for certain patient populations, specifically the young and those patients that undergo elective retransplantation. Further study is needed to elucidate how to better detect and prevent the need for retransplantation. This will hopefully in the future drive down the need for further retransplantation as the more liver retransplantations required, the poorer the outcome.

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ERRATUM

Chapter 14
Cholangiocarcinoma

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Index

A
Ablation, HCC, 198
Acute alcoholic hepatitis, 110, 111
Acute ALD
  liver transplant, 109
Adjuvant systemic cytotoxic chemotherapy
  doxorubicin, 196
  FOLFOX, 196
Adjuvant therapy, 188
Aerodigestive malignancy, 112
Afro-American HCV+ recipients, 41
AIH. *See* Autoimmune hepatitis (AIH)
AIHA. *See* Autoimmune hemolytic anemia (AIHA)
Alanine glycoxylate aminotransferase (AGT), 139
Alcohol relapse risk assessment, 114
Alcoholic cirrhosis, 111
  and alcoholic hepatitis, 106
  eligibility, 107
  MELD score, 107, 109
  prevalence, 106
  transplantation, 107, 111
Alcoholic hepatitis, 105
  acute (*see* Acute alcoholic hepatitis)
  fulminant, 108
  symptomatic, 106
Alcoholic liver disease (ALD), 3, 98
  acute alcoholic hepatitis, 108, 110–111
  alcoholic cirrhosis, 109
  biology, 106
  clinical outcomes, 111, 112
  donor organs, 105
  history of transplant, 107
  medical therapies, 106
  MELD score, 107, 109
  multidisciplinary assessment, 108
  NASH, 109
  post-transplant recidivism, 105
  pretransplant sobriety, 105
  recidivism, 112–116
  6-month rule, 107, 108
  transplantation, 105
Alcoholism
  High Risk Alcoholism Relapse Scale, 114
  multidisciplinary approach, 114–115
  and obesity, 109
  poor lifestyle choices and carries, 107
  treatment, 108, 112
ALD. *See* Alcoholic liver disease (ALD)
Alpha fetoprotein (AFP) levels, 157, 170
Amyloidosis, 135–137
ANA. *See* Antinuclear antibody (ANA)
Anti-BSEP antibodies, 239
Anti-HCV antibodies, 56
Anti-HCV(+) donors, 40
Anti-liver kidney microsomal antibodies, 237
Antilymphocyte agents, 45
Antimitochondrial antibody, 81
Antinuclear antibody (ANA), 237
Anti-smooth muscle antibodies (SMA), 237
Antiviral therapy
  combination prophylaxis, 17
  after histological recurrence, 64
  and HCC, 14
  vs. HCV, 35
  liver transplantation, 56–64
  post-LT prophylaxis, 16
  pre-transplantation, 13
    HBV recurrence, 15, 16
  short-term low-dose IV/IM HBIG, 27
  viral resistance/due to noncompliance, 25

P.J. Thuluvath (ed.), *Disease Recurrence After Liver Transplantation*,
DOI 10.1007/978-1-4939-2947-4

ASC. *See* Autoimmune sclerosing cholangitis (ASC)
Autoimmune aetiology, 98
Autoimmune hemolytic anemia (AIHA)
  GCH-AIAH, 237–238
Autoimmune hepatitis (AIH), 91–98
  adult and pediatric recipients, 237
  age-specific hypergammaglobulinemia, 237
  ASC, 237
  autoantibodies, 237
  corticosteroids, 3
  diagnosis, 3
  disease recurrence, 237
  dnAIH, 98–100
  GCH, 237, 238
  LT, 91
  and PBC, 97
  recurrent (*see* Recurrent AIH)
  SPLIT, 237
  types, 237
Autoimmune sclerosing cholangitis (ASC), 237
AZA. *See* Azathioprine (AZA)
Azathioprine (AZA), 43

B
Barrett's esophagus, 224
Basiliximab, 45
Bile salt export pump (BSEP), 239, 240
  deficiency, 5
Biliary duct epithelium, 205
Bone lesions, 206, 211
Breast cancer
  and gynecological, 5, 227
  after LTx, 226
  palate and thyroid, 216
  SIR, 226
Bridging therapy, 188
British Society of Gastroenterology, 210
Brush cytology, 208
BSEP. *See* Bile salt export pump (BSEP)
Budd–Chiari syndrome, 218

C
CA-125, 206
Calcineurin inhibitors (CNIs), 1, 43, 44, 176
Carbohydrate antigen (CA) 19-9, 206, 209
Carcinoembryonic antigen, 206
Carcinoid endocrine tumor, 218
cccDNA
  and HBV DNA, 15, 25
  in HCC cells, 15
Chemotherapy, 5, 14, 159, 188, 189, 196, 197, 208, 209, 211, 234, 240, 241
Cholangiocarcinoma, 205–212
  immunosuppression, 211
  inferior posttransplant survival, 205
  LT, 5
  orthotopic LT, 210–211
  prevention, recurrence
    ERCP, 209
    guidelines, British Society of Gastroenterology, 210
    Mayo protocol, 209
    minimize tumor, 209
    mixed HCC–cholangiocarcinoma tumors, 209
    multimodality therapies, 209
    palliative treatments, 208
    predictors, 210
    stereotactic body radiation therapy, 209
    University of California Los Angeles group, 210
  primary liver tumors, 205
  recurrence rates (*see* Tumor recurrence, cholangiocarcinoma)
  treatment options, 211
Cholestatic liver diseases, 79
  PSC, 238–240
Chronic HBV infection, 154
Chronic rejection, diagnostic criteria, 123
Cincinnati Transplant Tumor Registry database, 209
Cirrhosis
  AC (*see also* Alcoholic cirrhosis (AC)), 5, 6
  cryptogenic, 246
  diagnosis, 37
  development, 176
  ethanol-induced, 224
  HBV, 14, 16
  HCV, 38, 47–48, 58–60
  HDV, 16
  and liver failure, 2
  liver units, 16
  NASH, 145–147, 150, 151
  PBC (*see* Primary biliary cirrhosis (PBC))
  treatment, 1, 72
CIT. *See* Cold ischemia time (CIT)
CMV. *See* Cytomegalovirus (CMV)
CNIs-based immunosuppression, 85
CNIs. *See* Calcineurin inhibitors (CNIs)
Cold ischemia time (CIT), 171
Collagen proportionate area (CPA), 38
Colorectal cancer, 221
Comorbid conditions, 98

Concurrent cytomegalovirus (CMV) infection, 124–127
Corticosteroids, 3, 98, 100
Cost of RT
clinical issues, 254–255
concepts in medical ethics, 253–254
health care utilization, 255
and length of hospital stay in hospital, 255
risk assessment, 252
CPA. *See* Collagen proportionate area (CPA)
C-reactive protein (CRP), 177
CRP. *See* C-reactive protein (CRP)
Cutaneous epidermal malignancies, 219
Cyclosporine, 66, 70, 85, 96, 99, 100, 159, 172, 176
Cytomegalovirus (CMV), 42, 99, 124, 129

D
Daclizumab, 45
Dasabuvir with/without RBV, 70–71
DCD *vs.* DBD, 41
DDLT. *See* Deceased donor liver transplant (DDLT)
De novo AIH (dnAIH)
allograft dysfunction, 99
AZA, 99
clinical, serological and histological features, 99
cyclosporine, 99
donors, 99
GSST1, 99
immunosuppression, 99
paraffin-embedded sections, 99
plasma cell hepatitis, 99
predominance, 99
and rAIH, 99
and steroids, 99
De novo cancer post-liver transplant
colorectal cancer, 221
esophageal cancer, 224
and ethanol, 224–225
functioning allograft, 219
IPITTR, 219
length of follow-up, 225–226
rates, without SIR post-LTx, 219, 220
recipients' age and rate, 225
SEER data, 221
after solid transplant, 219
SIR, 221–223
type and number, 225, 226
De novo malignancy. *See also* De novo cancer post-liver transplant, 5
DEB-TACE. *See* Drug-eluting beads transarterial chemotherapy (DEB-TACE)
Deceased donor liver transplant (DDLT), 41, 166
Des-gamma-carboxy prothrombin (DCP), 157
Diabetes mellitus, 147, 149, 150
Direct acting anti-viral (DAA) drugs
interferon-free regimens, 58–59
in liver transplant recipients with HCV, 55
severe recurrent HCV, 71
undetectable HCV-RNA, 56
Disease recurrence, 1, 108, 135, 141, 233
after LT (*see* Liver transplantation (LT))
after pediatric LT (*see* Pediatric LT)
spectrum, 241
dnAIH. *See* De novo AIH (dnAIH)
Donor age, 2, 36, 38, 40, 46, 72, 84, 129, 172
Donor age × MELD score (D-MELD), 40
Donor liver steatosis, 40
Donors of LT
HRQOL, 250–252
Down-staging
ablate and wait philosophy, 175
AFP levels, 173
hepatic artery problems, 175
locoregional therapy, 173, 175
pre-transplant treatments, 173
Doxorubicin, 196
Drug-eluting beads transarterial chemotherapy (DEB-TACE), 188–190

E
EBRT. *See* External beam radiotherapy (EBRT)
Elastography (Fibroscan®), 38
Endoscopic retrograde cholangiopancreatography (ERCP), 209
Epidemiology
alcohol consumption, 224
environmental issues, 228
rate of esophageal cancer, 224
SEER, 221
Epstein–Barr virus, 99
ERCP. *See* Endoscopic retrograde cholangiopancreatography (ERCP)
Esophageal cancer, 224
Ethanol
and de novo cancer, 224–225
metabolite, 114
percutaneous ethanol injection, 192
Ethyl glucuronide (hEtG), 114
External beam radiotherapy (EBRT), 190–191

F
Familial amyloid polyneuropathy (FAP), 136
Familial Amyloidotic Polyneuropathy World Transplant Registry, 136
Fatty liver post-liver transplantation
  consequences, 148–151
  etiologies, 147
  HCV, 147
  NAFLD and NASH recurrence, 146
  risk factors, 147–148
FCH. *See* Fibrosing cholestatic hepatitis (FCH)
Fibrosing cholestatic hepatitis (FCH), 28, 36, 236
  classification, 36
  development, 38
  diagnostic, 38
Florid duct lesions, 81, 82, 88
French ANRS CO23 CUPILT study, 71
5-FU, leucovorin and oxaliplatin (FOLFOX), 196
Functional status, HRQOL, 249, 250

G
Gastrointestinal stromal tumors, 218
GCH. *See* Giant cell hepatitis (GCH)
Giant cell hepatitis (GCH)
  AIHA, 237, 238
Glomerular filtration rate (GFR), 140
Glutathione-*S*-Transferase T1 (GSST1), 99
Granulomatous cholangitis, 81, 82
GSST1. *See* Glutathione-S-Transferase T1 (GSST1)
Gynecological cancers, 227

H
HBL. *See* Hepatoblastoma (HBL)
HBV. *See* Hepatitis B virus (HBV)
HBV DNA
  ADV/LAM group, 22
  antivirals before transplantation, 14
  and cccDNA, 15, 25
  creatinine levels, 16
  documented suppression, 25
  HBsAg
    associate, 22
    with/without detectable, 14
  levels pre-transplantation, 27, 29
  negative, 22
  pretreatment bilirubin levels, 16
  prophylaxis, 15
  undetectable, 25
HBV recurrence, 15–27
  ADV-resistant HBV, 28
  antiviral treatments, 27, 28
  characterization, 27
  cirrhosis, 14
  description, 13
  diagnosis, 14, 15
  fibrosing cholestatic hepatitis, 28
  HBsAg, 27
  indications and results, transplantation, 14
  management strategy, 28
  mechanisms, 14, 15
  polymerase mutations, 15
  prevention, (*see also* Prevention of HBV recurrence), 14
  prophylaxis, 14
  risk factors, 14, 15
HCC. *See* Hepatocellular carcinoma (HCC)
HCV. *See* Hepatitis C virus (HCV)
HCV NS5B polymerase inhibitor, 67
Health care costs. *See* Cost of RT
Health care utilization, 255
Health-related quality of life (HRQOL)
  clinical practice, 245
  complications, 252
  donors of LT, 250–252
  functional status, 249, 250
  HCV infection, 252
  immunosuppression, 252
  level long-term post-transplant, 255
  multidimensional assessment, 245
  post-transplantation recipients, 249
  scores, 252
  tools to assess, 247, 248
Hematological malignancies, 216–218
Hemochromatosis gene (HFE), 137–138
Hepatic venous pressure gradient (HVPG)
  and clinical outcomes, 38
  measurement, 37, 38
Hepatitis B immune globulin (HBIG)
  administration, 22, 28
  anhepatic phase, 15
  and antiviral drugs, 17–20
  binding capacity, 16
  combination prophylaxis, 21
  cornerstone of prophylaxis, 16
  discontinuation, 22–25
  dose and duration, 13
  dose reduction, 16
  HBIG-free prophylactic regimens, 25, 26
  high *vs.* low dose, 17
  IV HBIG, 17
  and LAM, 14, 17
  low-dose intramuscular (IM), 17

meta-analyses, 17
monoprophylaxis, 17
and nucleos(t)ide analog, 13, 17
post-LT prophylaxis regimen, 2
post-transplant, 17
prophylaxis, 17
short-term therapy, 16
subcutaneous, 17
treatment, 16
Hepatitis B surface antigen (HBsAg), 15–17, 22
ADV/LAM, 22
HBV DNA, 15, 22
patients development, 25
persistence/reappearance, 15
pre-LT level, 27
pre-transplant viral load with antivirals, 16
selection, escape mutants, 17
in serum, 27
with/without detectable HBV DNA, 14
Hepatitis B virus (HBV), 154
chronic liver failure, 2
management
transplant recipients, 2
post-LT, 2
Hepatitis C infection
pediatric LT, 234, 236, 237
Hepatitis C virus (HCV), 42–45
Afro-American HCV+ recipients, 41
after LT, 36, 37
anti-HCV(+) donors, 40
antiviral treatments, 35
cirrhosis, 35
DCD *vs.* DBD, 41
donor age, 36, 38, 40
donor liver steatosis, 40
factors association with post-transplantation outcome, 39
HCV-infected transplant recipients, 40
HIV coinfection, 42
IL28B polymorphism, 40
immunosuppression (*see* Immunosuppression)
LDLT and DDLT, 41
long-term survival, 3
meta-analysis, 35
MS post-LT, 41
multicenter study (CRUSH-C), 41
post-transplant monitoring, 37, 38
quality of life, 3
RNA negative, 36
RT, 46–48
SVR rates, 35
UNOS/OPTN cohort, 41
viremia, 40
Hepatoblastoma (HBL)
liver tumors in pediatric population, 234
after neoadjuvant chemotherapy, 234–235
outcomes, 234
pretransplant distant metastases, 235
SEER, 235
Hepatocellular carcinoma (HCC), 118, 167–169
adjuvant therapy, 4, 5
childhood, 236
and cirrhosis, 1
comparative analysis, 167
DDLT, 166
free survival, 235
and fulminant liver failure, 2
HBV infection, 165
and HCV-related liver disease, 2
immunosuppression, 159
intent-to-treat approach, 168
LDLT, 166, 168
LT, 154, 177–178, 235
MELD, 166, 236
metro ticket paradigm, 167
Milan criteria, 4, 5, 154–157, 166
and neoadjuvant treatment, 4
optimal curative options, 154
PIVKA II levels, 169
post-transplant monitoring, 159
preexisting liver disease, 235
pre-LT imaging, 160
primary liver tumors, 235
progression rates estimation, 168
radiological assessment, 167
recurrence, 4, 157–158
reliable and noninvasive molecular markers, 161
risk factors, 153
SEER registry, 235
survival rates, 167
treatment, 160
tumor recurrence, 166
UCSF criteria, 166
Hilar adenopathy, 206
Hilar structures, 206
HIV coinfection, 42
HLA. *See* Human leukocyte antigen (HLA)
Homozygous familial hypercholesterolemia, 139–140
HOTAIR. *See* HOX transcript antisense RNA (HOTAIR)
HOX transcript antisense RNA (HOTAIR), 171
Human leukocyte antigen (HLA), 92
Hypertension
transplant patients, 147

I
IAHG. *See* International Autoimmune Hepatitis Group (IAHG)
IBD. *See* Inflammatory bowel disease (IBD)
IL-2 recipient blockers, 45
IL28B polymorphism, 40
Immunosuppression, 96–98, 172, 176
  antilymphocyte agents, 45
  AZA, 43
  cholangiocarcinoma, 211
  CNI, 43, 44
  IL-2 recipient blockers, 45
  international survey, 42
  MMF, 43
  mTor inhibitors, 45
  RAIH
    CNI, 98
    cyclophosphamide, 97
    optimal regimen, 98
    recurrent disease, 98
    treatment, 96
  steroids, 42, 43
Inferior posttransplant
  1-year, 208
Inflammatory bowel disease (IBD), 121, 129, 238
Interferon therapy (IFN), 99
  IFN-based regimen, 56–58
  IFN-free regimens, 58–59
  IFN-treated patients, 35
Intermediate stage
  AFP and PIVKA-II, 195
  down-staging, 192–195
  mRECIST, 195
  multimodality approach, 192
  necrosis, 195
  neoadjuvant therapy, 192
  UCSF, 192, 195
International Autoimmune Hepatitis Group (IAHG), 92
IPITTR. *See* Israel Penn International Transplant Tumor Registry IPITTR)
Israel Penn International Transplant Tumor Registry (IPITTR), 219
Italian AISF-SOFOLT compassionate, 71

K
Kaplan–Meier survival of LT *vs.* medical therapy, 110
Kaplin–Meier plot, 85, 86
Kidney transplantation (KT), 140
Klatskin tumors, 205
Kyoto criteria, 168

L
Langerhans cell histiocytosis (LCH), 240
LCH. *See* Langerhans cell histiocytosis (LCH)
LDLT. *See* Living donor liver transplant (LDLT)
Length of stay (LOS), 255
Liver and kidney transplant (LKT), 140
Liver transplantation (LT), 2, 13, 105, 205, 245
  AIH, 3
  ALD (*see also* Alcoholic liver disease (ALD)), 246, 247
  antiviral therapy, 59–64
  artificial neural network, 2
  bile salt export pump deficiency, 5
  cholangiocarcinoma, (*see also* Cholangiocarcinoma), 5
  concurrent IBD/colectomy, 128
  decompensated liver disease, 245
  de novo malignancy rates, 5
  drug use, 3
  epidemiology, 246–248
  familial amyloidosis, 135–137
  HBV (*see* Hepatitis B virus (HBV))
  HBL, 5
  HCC (*see also* Hepatocellular carcinoma (HCC)), 245
  HCV (*see also* Hepatitis C virus (HCV)), 246, 248
  hemochromatosis, 137–138
  history of obvious, 3
  homozygous familial hypercholesterolemia, 139–140
  IFN-free DAA, 58
  immediate and late outcome, 2
  immunosuppression, 128
  in non-PSC cohort, 123
  indications, 5
  management of hepatitis C, 55
  metabolic disorders, 3, 4, 135
  NAFLD, 4
  nonanastomotic biliary strictures, 122
  non-hepatic rates, 5
  occult alcohol, 3
  outcome, 1
  partial/full liver donor graft, 1
  patients selection, 141
  PBC (*see also* Primary biliary cirrhosis (PBC)), 129
  porphyria, 141
  pre-transplant sobriety and appropriateness, 3
  primary hyperoxaluria type 1, 139–140
  primary liver disease/cancer, 2
  PSC, 3, 122
  QOL (*see also* Quality of life (QOL), 5

short-term and long-term survival, 1
transplant physicians, 1
Wilson disease, 138
Living donor liver transplantation (LDLT), 41, 250
adult-to-adult, 177
aggressive tumor biology, 177
CRP, 177
vs. DDLT, 177
HCC, 166
NLR, 177
recurrence rates, 177
residual tumor cells, 177
tumorigenesis, 177
Locoregional and systemic therapies, 189–191
modalities
DEB-TACE, 189–190
EBRT, 190–191
TARE, 190
sorafenib, 191
transarterial and ablative treatments, 189
Locoregional therapies (LRT), 188
LOS. *See* Length of stay (LOS)
Low density lipoprotein (LDL), 139
LRT. *See* Locoregional therapies (LRT)
Lymphocytic bile duct destruction (florid duct lesion), 82
Lymphoid malignancies, 219

M
Mammalian target of rapamycin (mTOR) inhibitors, 45, 198, 211
Mayo protocol, 209
Medical therapies, ALD, 106
MELD. *See* Model for end-stage liver disease (MELD)
Metabolic liver disease, 3, 5, 137, 139
Metabolic risk factors, 151
Metabolic syndrome (MS) post-LT, 41
Metro ticket paradigm, 167
Milan criteria, 191–192
HCC, 166
HOTAIR, 171
LT, 166, 173
salvage LT, 176
slow-growing tumor, 170
and UCSF, 170, 173
MMF. *See* Mycophenolate Mofetil (MMF)
Model for end-stage liver disease (MELD), 166
Modified response evaluation criteria in solid tumors (mRECIST), 195
mTOR inhibitors. *See* Mammalian target of rapamycin (mTOR) inhibitors
Mycophenolate Mofetil (MMF), 43, 97
Myeloproliferative disorders, 216

N
N-acetyl cysteine (NAC), 106
NAFLD. *See* Non-alcoholic fatty liver disease (NAFLD)
NASH. *See* Nonalcoholic steatohepatitis (NASH)
National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), 145
Native bile duct, 210
Neoadjuvant therapy, 210, 212
LRT, 188
Milan criteria, 191–192
TACE and RFA, 188
Neuroendocrine tumor, 218
Neutrophil lymphocyte ratio (NLR), 177
NLR. *See* Neutrophil lymphocyte ratio (NLR)
Non-alcoholic fatty liver disease (NAFLD), 4
epidemic of, 145
and NASH, 146
Non-alcoholic steatohepatitis (NASH), 246
cirrhosis and liver failure, 146
epidemic of, 145
fibrosis post-transplant, 148
liver transplantation in patients, 146
and NAFLD, 146
Non-hepatic malignancy recurrence
cutaneous, 219
hematological, 216–218
neuroendocrine tumor, 218
non-hepatic solid, 216, 217
post-LTx, 215
pre-LTx, 215
Non-hepatic solid malignancies, 216, 217
Non-lymphoid de novo cancers, 225
Non-Markov analysis, 36

O
Obesity, 109, 146, 147, 150
and diabetes, 151
epidemic of, 145
Ombitasvir, 70–71
OPTN. *See* Organ procurement and transplantation network (OPTN)
Organ procurement and transplantation network (OPTN), 245
Oropharyngeal, 216, 221, 224, 227
Orthotopic LT, cholangiocarcinoma, 210–211

P
Palliative treatments, 208
p-ANCA. *See* Presence of anti-neutrophil cytoplasm antibodies (p-ANCA)
Pancreatic endocrine tumor, 218
Pancreaticoduodenectomy, 210
Paritaprevir/ritonavir, 70–71
Parvovirus, 99
PBC. *See* Primary biliary cirrhosis (PBC)
Pediatric LT
  AIH, 237–238
  cholestatic liver diseases, 238–240
  hepatitis C infection, 234, 236–237
  primary hepatic malignancies, 234–236
  UNOS, 233, 234
Peg IFN/ribavirin, 64–67
Perihilar hepatic lymph nodes, 206
Person-years, 221, 224–226, 228
PFIC. *See* Progressive familial intrahepatic cholestasis (PFIC)
PHOENIX study, 64
Plasma cell hepatitis, 3, 99, 100
Porphyria, 141
Post-transplant lympho-proliferative disorders (PTLD), 206, 225, 238
Post-transplant prevention, HBV recurrence, 16–21
  combination prophylaxis, 17
    antiviral drugs, 17–20
    antiviral therapy, 16
    clinical trials, 16
    HBIG (s*ee* Hepatitis B immune globulin (HBIG))
    low-dose IM HBIG, 17
    meta-analyses, 17, 21
    optimal anti-HBs titre, 17
Presence of anti-neutrophil cytoplasm antibodies (p-ANCA), 238
Pre-transplantation antiviral therapy
  prevention, HBV recurrence, 15–16
Prevention of HBV recurrence, 16–27
  antiviral(s) before and after LT, 26
  guidelines, 27
  post-transplant (s*ee* Post-transplant prevention, HBV recurrence)
  pre-transplantation antiviral therapy, 15–16
Primary biliary cirrhosis (PBC), 3, 80–81, 129
  cholestatic liver disease, 79
  diagnosis, 3
  and LT, 3, 80, 81
  recurrent (*see* Recurrent PBC)
  ursodeoxycholic acid, 79
Primary hepatic malignancies
  HBL, 234, 235
  HCC, 235, 236
Primary hyperoxaluria type 1 (PH1), 139, 140
Primary sclerosing cholangitis (PSC), 3, 205
  adult liver transplantations, 122
  chronic and progressive liver disease, 238
  diagnostic criteria and epidemiology, 122–124
  graft and patient survival, 129–130
  IBD, 238, 239
  inflammatory bowel disease, 121
  LCH, 240
  long-term outcome, 122
  medical treatments, 238
  medical/endoscopic therapy, 131
  non-anastomotic biliary strictures, 238
  outcome, 122, 131
  pathogenesis, 124–129
  PFIC, 239–240
  population-based studies, 121
  recurrence rates, 238
  SPLIT database, 239
  treatment, 130–131
  UNOS registry, 239
Progressive familial intrahepatic cholestasis (PFIC), 239, 240
PSC. *See* Primary sclerosing cholangitis (PSC)
PTLD. *See* Post-transplant lympho-proliferative disorders (PTLD)
Pulmonary metastatic cholangiocarcinoma, 208

Q
Quality of life (QOL), 245
  HCV-positive LT recipients, 3
  HR (*see* Health-related quality of life (HRQOL))
  LT, 5, 247–252

R
Radiofrequency ablation (RFA), 154, 188–189
RAIH. *See* Recurrent AIH (RAIH)
Recidivism, ALD
  abusive drinking, 117
  aerodigestive malignancy, 112
  alcohol consumption, 112, 114, 117
  biochemical testing, 117
  cumulative proportion curve, 114, 115
  excessive drinking and amount of drinking, 117
  graft loss, 117
  heavy-drinking post-transplant, 117
  high-risk alcoholism relapse score, 114, 115
  implantable naltrexone, 118
  Kaplan–Meier survival, 113, 114, 116

living donor LT, 112
measurements, hair samples, 114
monitoring, 114
multivariate logistic regression model, prediction of relapse, 114
pharmacologic approaches, 118
rates, 112, 113
risk stratification scoring systems, 114
self-reporting surveys of LT, 112
transplant centers, 118
zeaxanthin, 118
Recurrence, HCC, 175, 176
ablative therapy, 171
biological parameters, 170
CIT and WIT, 171
cyclosporine, 172
DDLT, 171
diagnostic imaging, 173
discrepancy, 170
DNA index, 172
donor factors, 172
ellipsoid formula, 170
extrahepatic metastasis, 169
high labeling index, 169
histological variables, 172
HOTAIR, 171
immunostaining, 169
immunosuppression, 172
interventional therapy, 173
ischemia–reperfusion injury, 171
management
ablative techniques, 175
allograft cirrhosis, 176
CNIs, 176
immunosuppression, 176
intrahepatic/extrahepatic disease, 175
locoregional therapies, 175
mTOR pathway, 176
salvage LT, 176
sorafenib, 176
median survival, 173
miRNA clusters, 170
pre and post-LT smoking, 170
prognostic markers, 169
retrospective analysis, 171
spherical equation formula, 169
TTV, 169
tumor growth, 170
Recurrence-free survival, 218
Recurrent AIH (RAIH)
autoantibodies, 92
corticosteroids, 95
definition, 100
diagnosis, 91, 92, 95
differential diagnosis, 92
disease and outcome management, 96–98
disease severity, 96
dnAIH, 91
high rates of rejection, 96
HLA-DR3, 96
IAHG, 92
immunosuppression, 92
median reported time, 91
protocol liver biopsy, 92
published series, 91, 93–94
and rejection, 95
risk factors, 95
role of HLA, 96
steroid, 96
TEG, 95
Recurrent hepatitis C, 56–59, 67
antiviral therapy (*see* Antiviral therapy)
DAA
drugs, 55
interferon-free regimens, 58–59
regimens in severe recurrent HCV, 71
dasabuvir with/without ribavirin, 70–71
HCV RNA PCR positive, 55
interferon-based regimen, 56–58
in liver transplant recipients, 55
ombitasvir, 70–71
paritaprevir/ritonavir, 70–71
Peg IFN/RBV, 64–66
Peg IFN/RBV+ first generation protease inhibitors, 66–67
real-world experience, 69–70
retransplantation, 72–73
SOF (*see* Sofosbuvir (SOF))
treatment, 71–72
Recurrent PBC
cumulative incidence, 83, 84
diagnosis, 81–83
natural history, 86–87
prevalence, 83, 84
recipient and donor risk factors, 84–86
short- and median-term outcomes, 81
treatment, 87–88
Reduction in the rate, 16
Retransplantation (RT)
cost
clinical issues, 254–255
ethical issues, 253–254
health care utilization, 255
risk assessment, 252–253
epidemiology, 246
HVC(+) recipients, 46–48
HCV-infected recipients, 37
PSC, 239
recurrent hepatitis C, 72–73

RFA. *See* Radiofrequency ablation (RFA)
Risk factor, PSC, 124–129
Role/social composite score (RCS), 252
Roux hepaticojejunostomy, 210

S
Severe recurrent HCV, 71
SF-36 HRQOL survey, 247
Short-form 36 (SF-36), 247, 251
Sirolimus, 45, 97, 159, 160, 176, 198, 211
SMA. *See* Anti-smooth muscle antibodies (SMA)
Sofosbuvir (SOF)
  and daclatasvir, 67–68
  with interferon, 67
  and ledipasvir, 68–69
  ribavirin, 67
  simeprevir regimens, 69
Sorafenib, 5, 160, 176, 188, 191, 196–198
Standard incidence ratios (SIRs)
  breast cancer, 226
  de novo cancer post-LT, 221–223
  oropharynx/head and neck cancer, 221
  ratios, 221
  and SEER data, 221
Stereotactic body radiation therapy, 209
Steroid therapy, 100, 106, 124
Studies of Pediatric Liver Transplantation (SPLIT) registry, 237
Surveillance, epidemiology and end results (SEER) registry, 221, 235
Survival
  18-month posttreatment, 211
  5-year, 209, 210
  inferior posttransplant, 205
  post-LTX patient, 209
  resection in select patients, 210
Sustained viral response (SVR), 35, 37, 56, 64, 67–72
SVR. *See* Sustained viral response (SVR)

T
TACE. *See* Transarterial chemotherapy (TACE)
Tacrolimus, 85, 92, 96, 97, 99
TARE. *See* Transarterial radioembolization (TARE)
TDF, 16
TEG. *See* Transient elastography (TEG)
Total tumor volume (TTV), 169
Transarterial chemotherapy (TACE), 188–189
Transarterial radioembolization (TARE), 190
Transient elastography (TEG), 95
Transplant outcomes
  ALD, 107
  clinical, 106, 107, 110–112
  graft, 105
  long-term, 105
  social, 107
Transthyretin (TTR), 135, 136
Tumor markers, 206
Tumor recurrence, cholangiocarcinoma
  asymptomatic symptoms, 206
  biliary duct epithelium, 205
  de novo tumors, 205
  diagnosis, 206
  and hepatocellular carcinoma, 206
  hilar structures, 206
  inflammatory bowel disease, 205
  Klatskin tumors, 205
  lytic metastases, 207, 208
  metastatic adenocarcinoma, 206
  metastatic intrahepatic lesions, 206
  metastatic to liver, 207
  nonspecific symptoms, 206
  pathology, 208
  perihilar hepatic lymph nodes, 206
  PSC, 205
  pulmonary metastatic, 208
  retroaortic/retrocaval, 206, 207
  staging, 208
  surveillance protocol, 206
  tumor markers, 206
  vascular structures, 206
Tyrosine kinase receptors, 191

U
United Network for Organ Sharing (UNOS) database, 129, 218, 233
University of California at San Francisco (UCSF), 192
University of California Los Angeles group, 210
University of California San Francisco (UCSF), 154, 166
UNOS. *See* United Network for Organ Sharing (UNOS)
Unresectable hepatocellular carcinomas, 155
Ursodeoxycholic acid (UDCA), 79, 87, 129, 130

V
Viremia
  CMV, 129
  HCV, 56
  monoclonal antibodies OKT3, 45

positive, 36
post-transplantation levels, 40
pre-transplantation levels, 40

W
Warm ischemia time (WIT), 171
Wilson disease, 138
WIT. *See* Warm ischemia time (WIT)

X
Xenotransplantation, 1

Z
Zeaxanthin, 118