Regence

Medical Policy Manual Transplant, Policy No. 05

Liver Transplant

Effective: July 1, 2024

Next Review: March 2025
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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Liver transplantation is now routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain, circulatory or cardiac death, or with a liver segment donation from a living donor. Patients are prioritized for transplant according to length of time on the waiting list, mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network (OPTN) and the United Network of Organ Sharing (UNOS).

MEDICAL POLICY CRITERIA

I. A liver transplant, using a cadaver or living donor, may be **medically necessary** for patients with irreversible, end-stage liver failure due to conditions that include, but are not limited to, the following:

   A. Cholestatic Liver Diseases

      1. Biliary atresia; or
      2. Familial cholestatic syndromes; or
      3. Primary biliary cirrhosis; or
      4. Secondary biliary cirrhosis; or

5. Primary sclerosing cholangitis; or
6. Secondary sclerosing cholangitis when the primary etiology is resolved; or
7. Alagille syndrome; or
8. Nonsyndromic paucity of the intrahepatic bile ducts; or
9. Cystic fibrosis; or

B. Hepatocellular Diseases:
1. Alcoholic cirrhosis; or
2. Viral hepatitis (including A, B, C, or non-A, non-B); or
3. Autoimmune hepatitis; or
4. Cryptogenic cirrhosis; or
5. Alpha-1 antitrypsin deficiency; or
6. Hemochromatosis; or
7. Protoporphyria; or
8. Wilson's disease; or
9. Non-alcoholic steatohepatitis; or

C. Malignancies such as the following:
1. Primary hepatocellular carcinoma confined to the liver; or
2. Rare, non-hepatocellular malignancies originating in the liver such as hemangioepitheliomas in young adults and hepatoblastomas in children, and hemangioendotheliomas; or
3. Fibrolamellar hepatocellular carcinoma; or
4. Unresectable hilar cholangiocarcinoma; or

D. Vascular Diseases:
1. Budd-Chiari syndrome (congenital hepatic vein thrombosis); or
2. Veno-occlusive disease; or

E. Inborn errors of metabolism; or

F. Trauma and toxic reactions; or

G. Miscellaneous Diseases:
1. Polycystic disease of the liver in patients who have massive hepatomegaly causing obstruction or functional impairment; or
2. Familial amyloid polyneuropathy (Corino de Andrade's disease, paramyloidosis); or
3. Amyloidosis; or
4. Disorders of branch chain amino acids (e.g., Maple syrup urine disease (MSUD), branched chain a-ketoacid dehydrogenase (BCKD); or
5. Fulminant hepatitic failure; or

6. Glycogen storage disease type IV; or
7. Hyperoxaluria; or
8. Steatohepatitis; or
9. Tyrosinemia; or
10. Urea cycle defects.

II. Liver transplantation is considered **not medically necessary** in the following patients:
   A. Patients with hepatocellular carcinoma that has extended beyond the liver; or
   B. Patients with active alcohol and/or substance abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of three months is required.)

III. Liver transplantation is considered **investigational** in the following patients:
   A. Intrahepatic cholangiocarcinoma; or
   B. Patients with an extrahepatic malignancy, other than those noted above; or
   C. Patients with neuroendocrine tumors metastatic to the liver.

IV. Liver retransplantation may be considered **medically necessary** in patients with one or more of the following diagnoses:
   A. Primary graft nonfunction; or
   B. Hepatic artery thrombosis; or
   C. Chronic rejection; or
   D. Ischemic type biliary lesions after donation after cardiac death; or
   E. Recurrent non-neoplastic disease-causing late graft failure.

V. Liver retransplantation is considered **investigational** in all other situations not described above in Criterion IV.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Small Bowel/Liver and Multivisceral Transplant, Transplant, Policy No. 18

BACKGROUND

LIVER TRANSPLANTATION

Liver transplantation is routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after a brain or cardiac death or with a liver segment donation from a living donor. Certain populations are prioritized as Status 1A (e.g., acute liver failure with a life expectancy of fewer than seven days without a liver transplant) or Status 1B (pediatric patients with chronic liver disease). Following Status 1, donor livers are prioritized to those with the highest scores on the Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scales. Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, a split graft refers to dividing a donor liver into two segments that can be used for two recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and children from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe, or the left lateral segment can be used for LDLT. In addition to addressing the problem of donor organ scarcity, LDLT allows the procedure to be scheduled electively before the recipient's condition deteriorates or serious complications develop. LDLT also shortens the preservation time for the donor liver and decreases disease transmission from donor to recipient.

RECIPIENTS

In March 2019, OPTN and UNOS published its most recent allocation system.[1]

Status 1A Adults

1. The candidate is at least 18 years old at the time of registration
2. The candidate has a life expectancy without a liver transplant of less than 7 days and has at least *one* of the following conditions:
    a. Fulminant liver failure, without pre-existing liver disease and currently in the intensive care unit (ICU), defined as the onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease, and has at least *one* of the following criteria:
        i. Is ventilator dependent
        ii. Requires dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
        iii. Has an international normalized ratio (INR) greater than 2.0
    b. Anhepatic
    c. Primary non-function of a transplanted whole liver within 7 days of transplant, with aspartate aminotransferase (AST) greater than or equal to 3,000 U/L and at least *one* of the following:
        - International normalized ratio (INR) greater than or equal to 2.5
        - Arterial pH less than or equal to 7.30
        - Venous pH less than or equal to 7.25
        - Lactate greater than or equal to 4 mmol/L

    All laboratory results reported for the tests required above must be from the same blood draw taken 24 hours to 7 days after the transplant.

    d. Primary non-function within 7-days of transplant of a transplanted liver segment from a deceased or living donor, evidenced by at least *one* of the following:
        - INR greater than or equal to 2.5
        - Arterial pH less than or equal to 7.30
        - Venous pH less than or equal to 7.25

- Lactate greater than or equal to 4 mmol/L

e. Hepatic artery thrombosis (HAT) within 7-days of transplant, with AST greater than or equal to 3,000 U/L and at least *one* of the following:
   - INR greater than or equal to 2.5
   - Arterial pH less than or equal to 7.30
   - Venous pH less than or equal to 7.25
   - Lactate greater than or equal to 4 mmol/L

All laboratory results reported for the tests required above must be from the same blood draw taken 24 hours to 7 days after the transplant.

Candidates with HAT in a transplanted liver within 14 days of transplant not meeting the above criteria will be listed with a MELD of 40.

f. Acute decompensated Wilson's disease

Status 1A Pediatrics

1. The candidate is less than 18 years old at the time of registration. This includes candidates less than 18 years old at the time of registration, who remain on the waiting list after turning 18 years old, but does not include candidates removed from the waiting list at any time who then return to the waiting list after turning 18 years old.
2. The candidate has at least *one* of the following conditions:
   a. Fulminant liver failure without pre-existing liver disease, defined as the onset of hepatic encephalopathy within 56 days of the first signs and symptoms of liver disease and has at least *one* of the following criteria:
      i. Is ventilator dependent
      ii. Requires dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
      iii. Has an international normalized ratio (INR) greater than 2.0
   b. Diagnosis of primary non-function of a transplanted liver within 7 days of transplant, evidenced by at least *two* of the following:
      i. Alanine aminotransferase (ALT) greater than or equal to 2,000 U/L
      ii. INR greater than or equal to 2.5
      iii. Total bilirubin greater than or equal to 10 mg/dL
      iv. Acidosis, defined as *one* of the following:
         - Arterial pH less than or equal to 7.30
         - Venous pH less than or equal to 7.25
         - Lactate greater than or equal to 4 mmol/L

   All laboratory results reported for any tests required for the primary non-function of a transplanted liver diagnosis above must be from the same blood draw taken between 24 hours and 7 days after the transplant.

   c. Diagnosis of hepatic artery thrombosis (HAT) in a transplanted liver within 14 days of transplant
   d. Acute decompensated Wilson's disease

Status 1B patients

1. The candidate is less than 18 years old at the time of registration. This includes candidates less than 18 years old at the time of registration, who remain on the waiting

list after turning 18 years old, but does not include candidates removed from the waiting list at any time who then return to the waiting list after turning 18 years old.

2. The candidate has *one* of the following conditions:
    a. The candidate has a biopsy-proven hepatoblastoma without evidence of metastatic disease.
    b. The candidate has an organic acidemia or urea cycle defect and a MELD or PELD exception score of 30 points for at least 30 days.
    c. Chronic liver disease with a calculated MELD greater than 25 for adolescent candidates 12 to 17 years old, or a calculated PELD greater than 25 for candidates less than 12 years old, and has at least *one* of the following criteria:
        i. Is on a mechanical ventilator
        ii. Has gastrointestinal bleeding requiring at least 30 mL/kg of red blood cell replacement within the previous 24 hours
        iii. Has renal failure or renal insufficiency requiring dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
        iv. Has a Glasgow coma score (GCS) less than 10 within 48 hours before the status 1B assignment or extension.
    d. Chronic liver disease and is a combined liver-intestine candidate with an adjusted MELD or PELD score greater than 25 according to *Policy 9.1.F: Liver-Intestine Candidates* and has at least *one* of the following criteria:
        i. Is on a mechanical ventilator
        ii. Has gastrointestinal bleeding requiring at least 10 mL/kg of red blood cell replacement within the previous 24 hours
        iii. Has renal failure or renal insufficiency requiring dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
        iv. Has a Glasgow coma score (GCS) less than 10 within 48 hours before the status 1B assignment or extension.

Following Status 1, donor livers will be prioritized to those with the highest scores on MELD (model for end-stage liver disease) or PELD (pediatric end-stage liver disease). MELD and PELD are a continuous disease severity scale based entirely on objective laboratory values. These scales have been found to be highly predictive of the risk of dying from liver disease for patients waiting on the transplant list. The MELD score incorporates bilirubin, prothrombin time (i.e., INR) and creatinine into an equation, producing a number that ranges from 6 to 40. The PELD score incorporates albumin, bilirubin, INR growth failure, and age at listing. Aside from Status 1, donor livers are prioritized to those with the highest MELD or PELD number; waiting time is only used to break ties among patients with the same MELD or PELD score and blood type compatibility. In the previous system, waiting time was often a key determinant of liver allocation, and yet waiting time was found to be a poor predictor of the urgency of liver transplant, since some patients were listed early in the course of their disease, while others were listed only when they became sicker. In the revised allocation system, patients with a higher mortality risk and higher MELD/PELD scores will always be considered before those with lower scores, even if some patients with lower scores have waited longer.[2]

DONORS

Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, the term “split grafts” refers to dividing a donor liver into two

segments that can be used for two recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and pediatric populations from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe, or the left lateral segment can be used for LDLT. In addition to addressing the problem of donor organ scarcity, LDLT allows the procedure to be scheduled electively, shortens the preservation time for the donor liver, decreases disease transmission and allows time to optimize the recipient's condition pretransplant.

EVIDENCE SUMMARY

Relevant outcomes for studies on liver transplantation (LT) include waiting time duration, dropout rates, survival time, and recurrence. As experience with LT has matured, patient selection criteria have broadened to include a wide variety of etiologies. The most controversial etiologies include viral hepatitis and primary hepatocellular cancer. In the past, the long-term outcomes in patients with primary hepatocellular malignancies were poor (19%) compared to the overall survival of LT recipients. However, recent use of standardized patient selection criteria, such as the Milan criteria (a solitary tumor with a maximum tumor diameter of five cm or less, or up to three tumors that are three cm or smaller and without extrahepatic spread or macrovascular invasion), has dramatically improved overall survival rates. In a systematic review of LT for hepatocellular carcinoma (HCC), Maggs (2012) found five-year overall survival rates ranged from 65% to 94.7% in reported studies.[3] Transplant represents the only curative approach for many of these patients who present with unresectable organ-confined disease and expansion of patient selection criteria. Bridging to transplant, or down-staging of disease, to qualify for LT is frequently studied. Finally, LT cannot be considered curative in patients with locally extensive or metastatic liver cancer, or in patients with isolated liver metastases with extrahepatic primaries.[2]

LIVING DONOR LIVER TRANSPLANTATION: DONOR OUTCOMES

Due to the scarcity of donor organs and the success of living donation, LDLT has become accepted practice. The living donor undergoes hepatectomy of the right lobe, left lobe, or left lateral segment, which is then transplanted into the recipient. Since right hepatectomy involves the resection of 60% to 70% of the total volume of the donor liver, the safety of the donor has been the major concern. The surgical literature suggests that right hepatectomy of diseased or injured livers is associated with mortality rates of about 5%. However, initial reports suggest that right hepatectomy in healthy donors has a lower morbidity and mortality. The Medical College of Virginia appears to have the most extensive experience and has reported the results of their first 40 adult-to-adult LDLTs, performed between June 1998 and October 1999.[4] There were an equal number of related and unrelated donors. Minor complications occurred in seven donors. The outcomes among recipients were similar to those associated with cadaveric donor livers performed during the same period of time. However, in the initial series of 20 patients, four out of five deaths occurred in recipients who were classified as 2A. In the subsequent 20 patients, recipients classified as 2A were not considered candidates for living donor transplant. Other case series have reported similar success rates.[5-7]

Tokodai (2016) published a retrospective review of 56 patients who underwent hepatectomy, between April 2001 and August 2010.[8] Donors were classified as under 50 (average 32) or greater than or equal to 50 (average 58) years of age. The one-, three-, and five-year graft survival rates were 80%, 60%, and 50%, respectively, in the greater than or equal to 50 years of age group compared to the under 50 years of age group with survival rates of 89%, 87%,

and 82%. The authors concluded older patients can undergo hepatectomy safely, but have longer hospital stays and grafts do not survive as long.

Brown (2013) reported on the results of a survey focusing on adult living-related recipients in the United States.[9] The following statistics were reported:

- The survey encompassed 449 adult-to-adult transplantations
- Half of the responding programs already had performed at least one adult-to-adult LDLT, and 32 of the remaining 41 centers were planning to initiate such surgery
- 14 centers had performed more than 10 such transplantations, and these centers accounted for 80% of these transplants
- A total of 45% of those evaluated for living donation subsequently donated a liver lobe; 99% were genetically or emotionally related to the recipient
- Complications in the donor were more frequent in the centers that performed the fewest living-related donor transplantations
- There was one death among the donors, but complications were relatively common (i.e., biliary complications) in 6% and reoperation in 4.5%

Reports of several donor deaths re-emphasize the importance of careful patient selection based in part on a comprehensive consent process and an experienced surgical team.[10-12] In December 2000, the National Institutes of Health convened a workshop on LDLT. A summary of this workshop was published in 2002.[13] According to this document, the risk of mortality to the donor undergoing right hepatectomy was estimated to be approximately 0.2% to 0.5%. Based on survey results, the workshop reported that donor morbidity was common: 7% required re-exploration, 10% had to be re-hospitalized, and biliary tract complications occurred in 7%. The median complication rate reported by responding transplant centers was 21%. The summary report concluded that the incidence and type of complications encountered, and the mortality associated with LDLT in both donors and recipients needs to be determined and compared with that for patients undergoing cadaveric transplantation.

Due to the potential morbidity and mortality experienced by the donor, the workshop also noted that donor consent for hepatectomy must be voluntary and free of coercion; therefore, it was preferable that the donor have a significant long-term and established relationship with the recipient. According to the workshop summary, "At the present time, nearly all centers strive to identify donors who are entirely healthy and at minimal risk during right hepatectomy. As a result, only approximately one third of persons originally interested in becoming a living liver donor complete the evaluation process and are accepted as candidates for this procedure."

Criteria for a recipient of a living-related liver are also controversial, with some groups advocating that living-related donor livers be used only in those most critically ill, while others state that the risk to the donor is unacceptable in critically ill recipients due to the increased risk of postoperative mortality of the recipient. According to this line of thought, living-related livers are best used in stable recipients who have a higher likelihood of achieving long-term survival.[13]

In 2000 the American Society of Transplant Surgeons issued the following statement:[14]

"Living donor transplantation in children has proven to be safe and effective for both donors and recipients and has helped to make death on the waiting list a less common event. Since its introduction in 1990, many of the technical and ethical issues have been addressed and the procedure is generally applied.

The development of left or right hepatectomy for adult-to-adult living donor liver transplantation has been slower. Because of the ongoing shortage of cadaver livers suitable for transplantation, adult-to-adult living donor liver transplantation has been undertaken at a number of centers. While early results appear encouraging, sufficient data is not available to ascertain donor morbidity and mortality rates. There is general consensus that the health and safety of the donor is and must remain central to living organ donation."

LIVING DONOR VERSUS DECEASED DONOR LIVER TRANSPLANT: RECIPIENT OUTCOMES

Few high-quality studies are available regarding recipient outcomes based upon direct comparison of liver transplantation from living and deceased donors.

A systematic review by Gavrilidis (2019) evaluated differences in outcomes between recipients of living-related adult donor and recipients of split liver transplantation from deceased donors.[15] A meta-analysis revealed differences in age distributions for both donors and recipients, with LDLT donors tending to be older than split donors (mean difference 11.12 years, p<0.001) and LDLT recipients tending to be younger than split transplant recipients (mean difference 2.06 years, p<0.001). However, there were no significant differences in postoperative complications, graft survival or overall survival between groups.

Humar (2019) compared outcomes between LDLT (n=245) and DDLT (n=592) at a single center in the U.S. between 2009 and 2019[16] The authors reported superior three-year survival in LDLT recipients (86% vs. 80% for DDLT, p=0.03), as well as shorter hospital stays (11 vs. 13 days, p=0.03) lower likelihood of intraoperative blood transfusion (52% vs 78%, p<0.01) or need for posttransplant dialysis (1.6% vs 7.4%, p<0.01). No significant differences were seen for early reoperation and biliary/vascular complication rates.

Wong (2019) published a retrospective intention-to-treat (ITT) analysis with propensity score matching comparing living and deceased donor LT.[17] The study included data for 375 patients listed for LT between 1995 and 2014: 188 patients in the ITT-DDLT group, and 187 in the ITT-LDLT group. Of these, 122 patients on the DDLT waitlist and 27 on the LDLT waitlist were delisted. Overall survival at one-, three- and five-years was significantly better in the ITT-LDLT group (94.1 vs. 77.5%, 81.4 vs. 48.7% and 75.9 vs. 40.8%, respectively). After propensity score matching, overall and recurrence-free survival were similar between groups.

Przybyszerski (2018) compared outcomes after LDLT and deceased donor liver transplant (DDLT) in a retrospective cohort of pediatric patients.[18] A total of 241 children were included in the study (DDLT n=177, LDLT n=64). Most of the LDLT donors were haplo-identical parents. The study found that LDLT was generally associated with better outcomes than deceased donor LT, including a lower rate of acute cellular rejection (hazard ratio [HR] 0.53, 95% confidence interval [CI] 0.29 to 0.98, p=0.04), chronic rejection (HR 0.12, 95% CI 0.03 to 0.56. p=0.007), and graft loss (HR 0.29, 95% CI 0.10 to 0.88, p=0.03). No difference in mortality by graft type was seen.

Samstein (2017) published a cohort study evaluating complications for recipients receiving DDLT versus LDLT (LDLT).[19] Patients in the study received DDLT (n=471) or LDLT (n=565) from 1998 to 2010 and were followed for up to 10 years post-transplant. The DDLT recipients were found to have higher occurrences of hepatocellular carcinoma, ascites, intra-abdominal bleeding, cardiac complications and pulmonary edema. The LDLT patients had higher biliary-related complications, hepatic artery thrombosis and chronic kidney disease. There was no difference in resolution time, for either group. The authors concluded LDLT outcomes are better than with DDLT, but improvements are needed to lessen complications for both LDLT and DDLT.

Ushigome (2016) published a study evaluating living donor transplants for patients over 60 years of age.[20] Seventy-six adult patients were divided into a greater than 60 years of age group (n=21) or a less than 60 years of age group (n=55). The one-, three-, five-, and 10-year survival rates for the greater than 60 years of age group were 89.9%, 89.9%, 83.0%, and 83.0%, respectively, compared to the less than 60 years of age group with survival rates of 91.1%, 85.2%, 82.8%, and 82.9%. The authors reported no significant differences between the groups' survival rates but noted that the elderly transplant recipients were frailer and needed careful management.

Olthoff (2015) published results from a prospective multicenter National Institutes of Health study comparing recipient outcomes and associated risks from LDLT and DDLT.[21] This was the same cohort evaluated by Samstein (2017), described above. Mortality and graft failure for 1427 liver recipients (963 LDLT and 464 DDLT) enrolled in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study who received transplant between 1998 and 2013, at one of twelve North American centers were analyzed at long-term follow-up (median of 6.7 years). Probability of survival at 10 years was higher for recipients of LDLT then DDLT (70% vs. 64%, respectively). For survival, the adjusted hazard ration for recipients of LDLT was 0.98. LDLT recipients had lower mean model for end-stage liver disease compared to deceased donor recipients (15.5 vs. 20.4, respectively) and had better post-transplant outcomes, regardless of type of donated lobe.

Al Sebayel (2015) published results from a single-center retrospective analysis of survival of recipients of LDLT compared to DDLT in relation to their MELD score.[22] Data was assessed from 222 patients for LDLT and 269 patients with deceased donors. HCV recurrence as a cause of death was significantly higher in recipients of LDLT (p=0.023), but the mortality after one year was significantly higher in recipients of DDLT, (p=0.0072). Overall one, three and five-year survival rates of recipients of LDLT and DDLT were 89%, 85%, and 84%, respectively, for MELD score below 25, and 80%,78%, and 77%, respectively, for MELD score greater than or equal to 25. There were no significant differences in survival of recipients of LDLT and those of deceased donors, regardless of MELD score.

Grant (2013) reported on a systematic review and meta-analysis of 16 studies to compare recipient outcomes between living donor liver transplants and deceased donor liver transplants for HCC.[23] For disease-free survival after living donor liver transplantation, the combined HR was 1.59 (95% CI 1.02 to 2.49) compared to deceased donor liver transplantation. For overall survival, the combined HR was 0.97 (95% CI 0.73 to 1.27). The studies included in the review were mostly retrospective and considered to be of low quality. Further study is needed to determine any differences between living and deceased liver transplantation outcomes for various etiologies.

MALIGNANCIES

The following two issues were the focus of the literature review regarding liver transplant for malignancy: 1) whether selection criteria for hepatocellular carcinoma should be expanded and 2) whether extrahepatic cholangiocarcinoma should be considered an acceptable indication for liver transplantation.

Hepatocellular Carcinoma

Selection Criteria for Hepatocellular Carcinoma

The patient selection criteria for liver transplantation for hepatocellular carcinoma (HCC) have focused mainly on the number and size of tumors. An editorial by Llovet (2006) noted that the Milan criteria are considered the gold standard.[24] The Milan criteria specify that patients may either have a solitary tumor with a maximum tumor diameter of five cm or less, or up to three tumors three cm or smaller. Patients with extrahepatic spread or macrovascular invasion have a poor prognosis. UNOS adopted the Milan criteria, combined with one additional criteria (no evidence of extrahepatic spread or macrovascular invasion), as its liver transplantation criteria. A 2001 paper from the University of California, San Francisco (UCSF), proposed expanded criteria to include patients with a single tumor up to 6.5 cm in diameter, three or fewer tumors with maximum size 4.5 cm and a total tumor size of less than or equal to eight cm.[25] It should be noted that either set of criteria can be applied preoperatively with imaging or with pathology of the explanted liver at the time of intended transplant. Preoperative staging often underestimates what is seen on surgical pathology. To apply pathologic criteria a backup candidate must be available in case preoperative staging is inaccurate. Given donor organ scarcity, any expansion of liver transplant selection criteria has the potential to prolong waiting times for all candidates. Important outcomes in assessing expanded criteria include waiting time duration, death or deselection due to disease progression while waiting (dropout), survival time, and time to recurrence or related outcomes such as disease-free survival. Survival time can be estimated beginning when the patient is placed on the waiting list using the intention-to-treat principal or at the time of transplantation. Llovet (2006) stated that one-year dropout rates for patients meeting Milan criteria are 15% to 30%, and five-year survival rates not reported by intention-to-treat should be adjusted down by 10% to 15%.

Guiteau (2010) reported on 445 patients transplanted for HCC in a multicenter, prospective study in UNOS Region 4.[26] On preoperative imaging, 363 patients met Milan criteria, and 82 patients were under expanded Milan criteria consisting of one lesion less than six cm, equal to or less than three lesions, none greater than five cm and total diameter less than nine cm. Patient, allograft and recurrence-free survival at three years did not differ significantly between patients meeting Milan criteria versus patients under the expanded criteria (72.9% and 77.1%, 71% and 70.2%, and 90.5% and 86.9%, respectively). While preliminary results showed similar outcomes when using expanded Milan criteria, the authors noted their results were influenced by waiting times in Region 4 and that similar outcomes may be different in other regions with different waiting times. Additionally, the authors noted that an HCC consensus conference report on liver allocation in HCC patients does not recommend expanding Milan criteria nationally and encourages regional agreement.[27] The report addressed the need to better characterize the long-term outcomes of liver transplantation for patients with HCC and to assess whether it is justified to continue the policy of assigning increased priority for candidates with early stage HCC on the transplant waiting list in the U.S. Overall, the evidence

base is insufficient to permit conclusions about health outcomes after liver transplantation among patients exceeding Milan criteria and meeting expanded UCSF or other criteria.

Schwartz (2008) argued that selection based exclusively on the Milan criteria risks prognostic inaccuracy due to the diagnostic limitations of imaging procedures and the surrogate nature of size and number of tumors.[28] They predict that evolution of allocation policy will involve the following:

1. The development of a reliable prognostic staging system to help with allocation of therapeutic alternatives;
2. New molecular markers that might improve prognostic accuracy;
3. Aggressive multimodality neoadjuvant therapy to downstage and limit tumor progression before transplant and possibly provide information about tumor biology based on response to therapy; and,
4. Prioritization for transplantation should consider response to neoadjuvant therapy, time on waiting list, suitability of alternative donor sources.

A limited body of evidence is available for outcomes among patients exceeding Milan criteria but meeting UCSF criteria (see table below). The largest series was conducted in 14 centers in France including an intention-to-treat total of 44 patients based on preoperative imaging at the time of listing, and a subset of 39 patients meeting pathologic UCSF criteria.[29] The median waiting time was 4.5 months, shorter than the typical six to twelve months in North America. Dropouts composed 11.4%. The post-transplant overall patient five-year survival of 63.6% was more favorable than the intention-to-treat probability of 45.5% but less favorable than among larger numbers of patients meeting Milan criteria. Similar findings were seen for disease-free survival and cumulative incidence of recurrence. Three centers in Massachusetts included ten patients beyond pathologic Milan criteria but within UCSF criteria.[30] Two-year survival post-transplant was 77.1%, with two patients dying and eight alive after a median of 32 months. A group of 74 patients meeting preoperative Milan criteria had a two-year survival probability of about 73%, but it is inadvisable to compare different preoperative and pathologic staging criteria.

From the series of patients from which the expanded UCSF criteria was developed, 14 satisfied those criteria on pathology but exceeded the Milan criteria.[31] UCSF investigators did not provide survival duration data for this subgroup but noted that two patients died. Although the French series suggested that outcomes among patients exceeding Milan criteria and meeting UCSF criteria are worse than for patients meeting Milan criteria, it is unclear if the latter group still achieves acceptable results. A benchmark of 50% five-year survival has been established in the liver transplant community. The French study met this by post-transplant pathologic staging results (63.6%) and fell short by preoperative intention-to-treat results (45.5%). United States centers have published data for only 24 patients exceeding Milan criteria and meeting UCSF criteria; survival and recurrence data are very sparse. Overall, the evidence base is insufficient to permit conclusions about health outcomes after liver transplantation among patients exceeding Milan criteria and meeting expanded UCSF criteria.

Several groups have worked on identifying predictors of survival and recurrence of disease. Ioannou (2008) analyzed UNOS data pre- and post-adoption of the MELD allocation system finding a six-fold increase in recipients with hepatocellular carcinoma and that survival in the MELD era was similar to survival to patients without HCC.[32] The subgroup of patients with larger (three to five cm) tumors, serum alpha-fetoprotein level equal to or greater than 455

mg/mL, or a MELD score equal to or greater than 20, however, had poor transplantation survival. A cancer recurrence prediction scoring system was developed by Chan (2008), based on a retrospective review and analysis of liver transplants at two centers to determine factors associated with recurrence of HCC.[33] Of 116 patients with findings of hepatocellular carcinoma in their explanted livers, 12 developed recurrent hepatocellular carcinoma. Four independent significant explant factors were identified by stepwise logistic regression: size of one tumor greater than 4.5 cm, macroinvasion, and bilobar tumor were positive predictors of recurrence, and the presence of only well-differentiated HCC was a negative predictor. Points were assigned to each factor in relation to its odds ratio. The accuracy of the method was confirmed in two validation cohorts.

Table 1. Outcomes Among Patients with Hepatocellular Carcinoma Exceeding Milan Selection Criteria and Meeting UCSF Criteria

Study	Outcome	Group	Probability (%)			
			n	1yr	2yr	5yr
Decaens (2006)[29] 14 centers in France, Meeting Milan criteria (Milan+). Exceeding Milan criteria, meeting UCSF criteria (Milan-/UCSF+)	Intention-to-treat, preoperative					
	Overall patient survival	Milan+	279			60.1
		Milan-/UCSF+	44			45.5
	Cumulative incidence of recurrence	Milan+				20.2
		Milan-/UCSF+				27.1
	Disease-free survival	Milan+				60.4
		Milan-/UCSF+				47.8
	Post-transplant, pathologic (p)					
	Overall patient survival	pMilan+	184			70.4
		pMilan-/pUCSF+	39			63.6
	Cumulative incidence of recurrence	pMilan+				9.4
		pMilan-/pUCSF+				16.5
	Disease-free survival	pMilan+				7.02
		pMilan-/pUCSF+				62.7
	Milan-/UCSF+ median waiting time 4.5 mo (0.1-20.4); 5/44 dropouts (11.4%)					
Sotiropoulos (2006)[34] Essen, Germany. Unclear if criteria preoperative or pathologic.	Milan-/UCSF+, n=4, 1 patient died at 20 mo, 3 patients alive at median follow-up 57 mo.					
Leung (2004)[30] 3 centers in Massachusetts, Meeting preoperative Milan criteria (Milan+)	Post-transplant overall patient survival	Milan+	74	85.9	~73	50.9
		pMilan-/pUCSF+	10		77.1	
	2 patients died at 3 and 22 months, 8 patients alive after median 32 mo follow-up (6.6-73.5)					
Yao (2002)[31] University of California, San Francisco	Post-transplant overall patient survival	pMilan+	46	91	81	72
	pMilan-/pUCSF+, n=14, 2 patients died, 8 alive but no information on survival duration, 1 patient retransplanted 5 mo after initial transplant					

The use of extended Milan criteria, to include other factors, has recently become an area of investigation. Tosco (2015) conducted a prospective study that recruited 233 patients with HCC according to their proposed total tumor volume (TTV, ≤115 cm^3)/alpha-fetoprotein (AFP, ≤400 ng/mL) score.[35] The Milan group was modified to include only patients with AFP <400 ng/mL (n=195); these patients were compared to patients beyond Milan, but within TTV/AFP (n=38), with an average follow-up of 34 ± 25 months. Risk of dropout was higher for patients beyond Milan (42.1%), than for those within Milan (25.1%, p = 0.033), and intent-to-treat survival was lower in patients beyond Milan (53.8% vs. 71.6% at four years, p<0.001). Post-transplant, patients within Milan criteria and those beyond Milan had similar recurrence rates (4.5% vs. 9.4%, p=0.138) and post-transplant survivals (78.7% vs. 74.6% at four years,

p=0.932). The investigators concluded that expanding the Milan criteria may lead to increased risk of drop-out but does not impact overall post-transplant survival.

Liver Transplantation versus Liver Resection for Hepatocellular Carcinoma

Liver transplantation is the gold standard treatment for HCC meeting Milan criteria in decompensated livers such as Child-Pugh class B or C (moderate to severe cirrhosis). Liver resection is generally used for early HCC in livers classified as Child-Pugh class A.[36] Additionally, current UNOS criteria indicate a liver transplant candidate must not be eligible for resection.[1] However, the best treatment approach for early HCC in well-compensated livers is controversial.

Schoenberg (2017) published a systematic review and meta-analysis of 54 retrospective studies (n=13,794) comparing liver resection (n=7,990) with transplantation (n=5,804) in patients with HCC.[37] At one-year follow-up, survival rates were higher in those receiving resection (86.17%) than in those receiving liver transplant (80.58%) (OR 1.19, 95% CI 0.99 to 1.43, p=0.07). At five-year follow-up, survival rates were better for those who received transplantation (61.26%) than for those receiving surgery (51.9%, OR 0.62, 95% CI 0.50 to 0.76, p<0.001). When a subgroup of patients with early HCC (eight studies) was analyzed, one-year follow-up showed comparable survival rates between surgically-treated patients (92.14%), and transplanted patients (90.38%) (OR 0.97, 95% CI 0.63 to 1.50, p=0.89). At five years, transplanted patients had a significantly higher survival rate (66.67%) than surgically treated patients (60.35%, OR=0.60, 95% CI 0.45 to 0.78, p<0.001). Review limitations included a high level of heterogeneity between studies analyzed.

Chapman (2015) conducted a retrospective analysis of outcomes of liver transplant compared to resection in 1765 HCC patients treated across five U.S. centers.[38] There were 884 patients who underwent resection and 881 who underwent transplantation. Of the resected patients, 248 (28.1%) were eligible for transplantation, according to the MILAN criteria; which were compared with 496 transplant patients, matched based on year of transplantation and tumor status. Five- and 10-year survival rates were significantly higher in transplant patients, compared to resected patients eligible for transplant (74% vs. 53% and 54% vs. 22% respectively, p<0.001). The investigators concluded that although transplantation results in better long-term survival, resection will likely remain a standard therapy in selected patients with HCC due to limited donor availability.

Zheng (2013) reported on a meta-analysis of 62 cohort studies (n=10,170 total patients) comparing liver transplantation to liver resection for HCC.[39] Overall one-year survival was similar between procedures (OR 1.08, 95% CI 0.81 to 1.43, p=0.61). However, three- and five-year overall survival significantly favored liver transplantation over resection (OR 1.47, 95% CI 1.18 to 1.84, p<0.001, and OR 1.77, 95% CI 1.45 to 2.16, p<0.001, respectively). Disease-free survival in liver transplant patients was 13%, 29%, and 39% higher than liver resection patients at one, three, and five years, respectively (p<0.001). Recurrence rates were also 30% lower in liver transplantation than resection (OR 0.20, CI 0.15 to 0.28, p<0.001). While liver transplantation outcomes appear favorable compared to liver resection, a shortage of donor organs may necessitate liver resection as an alternative to liver transplantation.

Salvage Liver Transplantation after Liver Resection for Hepatocellular Carcinoma

In patients who have a recurrence of HCC after primary liver resection, salvage liver transplantation has been considered a treatment alternative to repeat hepatic resection,

chemotherapy or other local therapies such as radiofrequency ablation, transarterial chemoembolization percutaneous ethanol ablation or cryoablation. Several systematic reviews have evaluated the evidence on outcomes of salvage transplant compared to primary transplant.

Yadav (2018) published a systematic review and meta-analysis comparing salvage liver transplant (SLT) and primary LT for individuals with hepatocellular carcinoma.[40] Twenty retrospective studies (10 of which were also included in Murali [2017], described below) with a total of 9,879 patients were included in the analysis. One-year overall survival was better for SLT (74.30%) than primary LT (OR 0.86, 95% CI 0.75 to 0.98, p=0.03). SLT also had higher three- (55.69% and 59.07%, respectively; OR 0.85, 95% CI 0.76 to 0.96, p=0.01) and five-year (48.67% and 52.32%, respectively; OR 0.85, 95% CI 0.76 to 0.96, p=0.009) overall survival than primary LT. One- (OR 0.86, 95% CI 0.75 to 0.99, p=0.03), three- (OR 0.56, 95% CI 0.39 to 0.81, p=0.002), and five-year DFS (OR 0.75, 95% CI 0.66 to 0.86, p<0.001) were worse for primary LT (70.03%, 74.08%, and 47.09%, respectively) than for SLT (67.69%, 57.02%, and 41.27%, respectively). There was no significant difference between the two groups for postoperative biliary complications (p=0.19) or sepsis (p=0.68). No limitations to the analysis were reported.

Murali (2017) published a systematic review and meta-analysis comparing primary LT to locoregional therapy with curative intent (CLRT) followed by SLT.[41] Forty-eight studies with 9,835 patients were included in the review, which found that five-year overall survival and disease-free survival were worse for the CLRT compared with primary LT (OR for overall survival 0.59, 95% CI 0.48 to 0.71, p<0.01), but there was no significant difference between primary LT and CLRT followed by SLT. However, only 32.5% of patients who had disease recurrence after CLRT received SLT, so disease-free survival was worse with CLRT-SLT.

A systematic review of 14 non-randomized comparative studies was published by Zhu (2013) (n=1,272 for primary transplant and n=236 for salvage).[42] Overall survival at one, three, and five years, and disease-free survival at one and three years were not significantly different between groups. Disease-free survival, however, was significantly lower at five years in SLT compared to primary transplantation (OR 0.62, 95% CI 0.42 to 0.92, p=0.02). There was insufficient data to evaluate outcomes in patients exceeding Milan criteria but in patients meeting Milan criteria, survival outcomes were not significantly different suggesting SLT may be a viable option in these patients.

Chan (2013) systematically reviewed 16 non-randomized studies (n=319) on SLT after primary hepatic resection for HCC.[43] The authors found overall and disease-free survival outcomes with SLT were similar to reported primary LT outcomes. The median overall survival for SLT patients was 89%, 80% and 62% at one, three, and five years, respectively. Disease-free survival was 86%, 68% and 67% at one, three, and five years, respectively. SLT studies had median overall survival rates of 62% (range 41 to 89%) compared to a range of 61% to 80% in the literature for primary LT. Median disease-free survival rates for SLT were 67% (range 29% to 100%) compared to a range of 58 to 89% for primary liver transplantation. Given a limited donor pool and increased surgical difficulty with salvage liver transplantation, further studies are needed. UNOS criteria indicate LT candidates with HCC who subsequently undergo tumor resection must be prospectively reviewed by a regional review board for the extension application.

In a meta-analysis, Li (2012) compared primary LT to SLT (liver transplantation after liver resection) for HCC.[44] Included in the meta-analysis were 11 case-controlled or cohort studies totaling 872 primary LTs and 141 SLTs. Survival rates of patients who exceeded the Milan criteria at one, three and five years were not significantly different between the two groups (one-year OR 0.26, 95% CI 0.01 to 4.94, p=0.37, three-year OR 0.41, 95% CI 0.01 to 24.54, p=0.67, and five-year OR 0.55, 95% CI 0.07 to 4.48, p=0.57).

Adenomatosis

Chiche (2016) published a prospective study that evaluated data from the European Liver Transplant Registry (ELTR) for 49 patients who had LT for liver adenomatosis (LA) between January 1, 1986 and July 15, 2013.[45] LA is a rare benign disease that does not affect liver function. It therefore does not increase the MELD score used to determine who should receive a transplant. The most prevalent concern is fear of malignant transformation and severe bleeding. The authors concluded LA is a rare indication for LT and can be handled non-surgically or through other surgical approaches. LT for LA carries an increased risk of morbidity/mortality, and criteria are critical to aid in transplant selection.

Cholangiocarcinoma

Reports on LT for cholangiocarcinoma (CCA), or bile duct carcinoma, generally distinguish between intrahepatic and extrahepatic tumors, the latter including hilar or perihilar tumors. Recent efforts have focused on pretransplant downstaging of disease with neoadjuvant radiochemotherapy. Relevant outcomes included waiting time duration, dropout rates, survival time, and recurrence.

A meta-analysis by Cambridge (2021) assessed survival following neo-adjuvant chemoradiation and orthotopic LT for unresectable perihilar CCA in 20 studies (total n=428).[46] Pooled one-, three-, and five-year overall survival rates following LT for patients who completed neoadjuvant therapy were 82.8% (95% CI 73.0 to 90.8%), 65.5% (95% CI 48.7% to 80.5%), and 65.1% (95% CI 55.1% to 74.5%), respectively. For those without neoadjuvant therapy, survival rates were lower at 71.2% (95% CI 62.2% to 79.4%), 48.0% (95% CI 35.0% to 60.9%), and 31.6% (95% CI 23.1% to 40.7%), respectively. Pooled recurrence at three years with neoadjuvant treatment was 24.1% (95% CI 17.9% to 30.9%), while three-year recurrence without neoadjuvant treatment was 51.7% (95% CI 33.8% to 69.4%).

Lunsford (2018) evaluated neoadjuvant chemotherapy followed by LT in a small, prospective case series of patients with locally advanced, unresectable, intrahepatic CCA at a single center.[47] Of the 21 patients referred between 2010 and 2017, 12 were accepted and six had undergone LT. Three of the transplants were from deceased donors and three were from living donors. All six patients survived to one year after transplant, and five patients survived to three and five years. Three had disease recurrence during follow-up.

Hildebrand (2016) published a multi-center retrospective cohort study to evaluate risk factors, recurrence of biliary strictures, and impact on survival after LT, for patients with primary sclerosing cholangitis (PSC).[48] PSC is a progressive cholestatic disease with inflammation and fibrotic strictures within the hepatic or extrahepatic bile ducts. Progression leads to biliary cirrhosis, recurrent episodes of septic cholangitis, or CCA. The only cure is LT. This study evaluated 2,170 transplant patients with prior PSC. LT was performed at 10 German transplant centers from January 1990 to December 2006. One-, five-, and 10-year recipient survival was 90.7%, 84.8%, and 79.4%, respectively, and one-, five-, and 10-year graft survival was 79.1%,

69.0%, 62.4%. Biliary strictures were found in 36.1% of the recipients after an average of 3.9 years, and recurrent PSC was found in 20.3% of the recipients after 4.6 years post-LT. MELD and Mayo risk score parameters, particularly INR, were higher in patients with biliary stricture after LT. Donor age was also a risk factor for developing strictures after LT.

Gu (2012) reported on a systematic review and meta-analysis of 14 clinical trials on LT for CCA.[49] Overall one-, three-, and five-year pooled survival rates from 605 study patients were 0.73 (95% CI 0.65 to 0.80), 0.42 (95% CI 0.33 to 0.51), and 0.39 (95% CI 0.28 to 0.51), respectively. When patients received adjuvant therapies preoperatively, one-, three-, and five-year pooled survival rates improved and were 0.83 (95% CI 0.57 to 0.98), 0.57 (95% CI 0.18 to 0.92), and 0.65 (95% CI 0.40 to 0.87), respectively.

Darwish Murad (2012) reported on 287 patients from 12 transplant centers treated with neoadjuvant therapy for perihilar CCA followed by LT.[50] Intent-to-treat survival (after a loss of 71 patients before liver transplantation) was 68% at two years and 53% at five years, and recurrence-free survival rates post-transplant were 78% at two years and 65% at five years. Survival time was significantly shorter for patients who had a previous malignancy or did not meet UNOS criteria by having a tumor size greater than 3 cm, metastatic disease, or transperitoneal tumor biopsy. ($p<0.001$).

Panjala (2011) published results from a small case series of 22 patients with CCA treated with neoadjuvant chemoradiotherapy and subsequent LT.[51] Estimated rates of one, two, and three year survival, were 90%, 70%, and 63%, respectively, calculated based upon survival after a median follow-up of 601 days. Smaller tumors and those in the earliest stages of disease were associated with the most promising outcomes.

Among the various publications, the Mayo Clinic in Minnesota had the most favorable results.[52, 53] Between 1993 and 2006, 65 patients underwent LT for unresectable perihilar CCA or had perihilar tumor due to primary sclerosing cholangitis. Unresectable patients underwent neoadjuvant radiochemotherapy. One-year survival was 91% and five-year survival was 76%. In a series of 38 patients from the Mayo Clinic, cumulative recurrence was 0% at one year, 5% at three years, and 13% at five years.

The University of California, Los Angeles (UCLA)/Cedars-Sinai reported on 25 cases of both intrahepatic and extrahepatic CCA.[54] One-year survival was 71% and 3-year survival was 35%. The University of Pittsburgh found one-year survival of 70% and 18% five-year survival among 20 patients with intrahepatic CCA.[55] A German study of 24 patients reported the poorest results.[56]

The European Liver Transplant Registry reported that, among 186 patients with intrahepatic CCA, one-year survival was 58% and five-year survival was 29%.[57] In 169 patients with extrahepatic CCA, the probabilities were 63% and 29%. The Cincinnati Transplant Registry reported on 207 patients with either intrahepatic or extrahepatic CCA, finding a one-year survival of 72% and a five-year survival of 23%.[58] The multicenter report included 36 patients with hilar tumors and 23 with peripheral intrahepatic disease.[59] One-year survival was 82% and 77%, while five-year survival was 30% and 23%, respectively. Crude recurrence rates were 53% and 36% for extrahepatic and intrahepatic CCA, respectively. The German center at Hannover found a crude recurrence rate of 63%.[56]

Table 2. Outcomes Among Patients with Cholangiocarcinoma

Study	Outcome	Group	n	Probability (%)			
				1yr	2yr	3yr	5yr
Pascher (2003)[30] European Liver Transplant Registry	Overall patient survival	IH-CCA	186	58		38	29
		EH-CCA	169	63		38	29
Meyer (2000)[31] Cincinnati Transplant Registry unresectable CCA, cholangiohepatoma, incidental median follow-up 23 mo (<1-96)	Overall patient survival	IH/EH-CCA	207	72	48		23
Robles (2004)[34] Multiple Centers in Spain 03/88-09/01; hilar or peripheral CCA; unresectable, postoperative recurrent, or incidental	Overall patient survival	Hilar CCA	36	82		53	30
		Peripheral CCA	23	77		65	23
	Crude recurrence rate: EH-CCA: 19/36 (53%); IH-CCA: 8/23 (35%)						
Heimbach (2006)[52]; Rea (2006)[53] Mayo Clinic, Rochester MN, USA 01/93-01/06, aggressive neoadjuvant radiochemotherapy, unresectable perihilar CCA or perihilar CCA from primary sclerosing cholangitis mean follow-up 32 mo (2 d-13 yr)	Overall patient survival	Perihilar CCA	65	91			76
	Cumulative recurrence		38	0		5	13
	Crude recurrence rate: 11/65 (17%) median onset 22 mo (7-65)						
Shimoda (2001)[54] UCLA/Cedars-Sinai, Los Angeles, CA, USA 1984-2000; IH or EH CCA median follow-up 22.3 mo	Overall patient survival	All	25	71		35	
		IH-CCA	16	62		39	
		EH-CCA	9	86		31	
	Disease-free survival	All	25	67		42	
		IH-CCA	16	70		35	
		EH-CCA	9	57		57	
Casavilla (1997)[55] University of Pittsburgh, PA, USA 1981-1994	Overall patient survival	IH-CCA	20	70		29	18
	Tumor-free survival		20	67		31	31
Weimann (2000)[56] Hannover, GER 07/78-12/96; unresectable CCA	Overall patient survival	IH-CCA	24	21	8	4	0
	Crude recurrence rate: 15/24 (63%)						

CCA: cholangiocarcinoma; EH: extrahepatic; IH: intrahepatic

Heimbach (2018) reviewed the published outcomes of the combined protocol in the context of data on outcomes for surgical resection, and concluded that outcomes of neoadjuvant chemoradiotherapy with subsequent LT for patients with early-stage hilar CCA, which is unresectable, or arising in the setting of PSC are comparable to outcomes for patients with hepatocellular carcinoma and other chronic liver diseases, and superior to resection.[60] Intraoperative challenges attributable to the neoadjuvant therapy were described, including severe inflammatory changes and dense fibrosis. The author suggested that key principles for centers considering use of the combined protocol include a multidisciplinary approach, pretransplant staging, inclusion of only patients without lymph node metastasis, replacement of irradiated vessels (when possible), and monitoring for postoperative vascular complications.

Wu (2008) described an extensive surgical procedure combined with radiotherapy.[61] The authors retrospectively reviewed their experience with surveillance and early detection of CCA

and en bloc total hepatectomy-pancreaticoduodenectomy-orthotopic liver transplantation (OLT-Whipple) in a small series of patients with early-stage CCA complicating PSC. Surveillance involved endoscopic ultrasound and endoscopic retrograde cholangiopancreatography and cytological evaluation. Patients diagnosed with CCA were treated with combined extra-beam radiotherapy, lesion-focused brachytherapy, and OLT-Whipple. CCA was detected in eight of the 42 patients followed up according the surveillance protocol between 1988 and 2001, and six patients underwent OLT-Whipple. One died at 55 months after transplant of an unrelated cause without tumor recurrence, and five are without recurrence at 5.7 to 10.1 years.

Section Summary

Treatment benefit of liver transplant has been demonstrated for select patients with CCA and evidence on patients with perihilar CCA have shown reasonable survival rates at five years. However, current evidence regarding five-year survival rates for intrahepatic CCA are less certain as most studies which demonstrated lower overall survival rates reported on a combined intra- and extra-hepatic patient population.

Pediatric Hepatoblastoma

Hepatoblastoma is a rare malignant primary solid tumor of the liver that occurs in children. Treatment consists of chemotherapy and resection; however, tumors aren't often discovered until they are unresectable. In cases of unresectable tumors, LT with pre- and/or post-chemotherapy is a treatment option with reports of good outcomes and high rates of survival.[62] UNOS guidelines list non-metastatic hepatoblastoma as a condition eligible for pediatric LT.[1]

Hamilton (2017) reported on 376 children with hepatoblastoma requiring liver transplantation; this was part of a larger cohort of 544 children receiving a liver transplant from 1987 to 2012, as recorded in the United Network for Organ Sharing database.[63] The five-year patient survival rate after liver transplant for hepatoblastoma was 73%, with five-year graft survival rate of 74%. Recurrent or metastatic disease was the most common (57%) cause of death for this population.

Barrena (2011) reported on 15 children with hepatoblastoma requiring LT.[64] Overall survival after liver transplant was 93.3 (±6.4%) at one-, five- and 10-years. Malek (2010) reported on liver transplantation results for 27 patients with primary liver tumor identified from a retrospective review of patients treated between 1990 and 2007.[65] Tumor recurrence occurred in one patient after LT and overall survival was 93%. Browne (2008) reported on 14 hepatoblastoma patients treated with LT. Mean follow-up was 46 months with overall survival in 10 of 14 patients (71%).[66] Tumor recurrence caused all four deaths. In the 10 patients receiving primary LT, nine survived while only one of four patients transplanted after primary resection survived (90% vs. 25%, p=0.02).

Metastatic Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are relatively rare neoplasms that are generally slow growing but rarely cured when metastatic to the liver. Treatment options to control or downstage the disease include chemotherapy and debulking procedures, including hepatic resection. In select patients with non-resectable, hormonally active liver metastases refractory to medical therapy, LT has been considered as an option to extend survival and minimize endocrine symptoms.

Moris (2017) published a systematic review on LT for the treatment of NETs with liver metastases.[67] There were 64 studies deemed eligible for inclusion in the review, including four studies using registry data and three multicenter studies. The authors reported an overall recurrence rate ranging from 31.3% to 56.8%, with a five-year survival of 63%. Factors that were associated with worse survival included >50% liver tumor involvement, higher Ki67 (a disease marker) and pancreatic NETs (compared to gastrointestinal NETs).

Sher (2015) conducted a retrospective analysis on LT outcomes of 85 patients with NETs, assessing data from a North American multicenter database.[68] One, three, and five-year patient survival rates were 83%, 60%, and 52%, respectively. These rates are similar to those reported in larger studies. Overall, 40 of 85 patients died, with 20 of 40 deaths due to recurrent disease. In multivariable analysis, predictors of poor overall survival included large vessel invasion (p=0.001), and extent of extrahepatic resection at liver transplant (p=0.015). The investigators reported that the survival outcomes are high enough to merit LT in this patient population.

Fan (2014) reported on a systematic review of 46 studies on LT for NET liver metastases of any origin.[69] A total of 706 patients were included in the studies reviewed. Reported overall five-year survival rates ranged from 0 to 100%, while five-year disease-free survival rates ranged from 0% to 80%. In studies with more than 100 patients, the five-year overall survival rate and disease-free survival rate averaged about 50% and 30%, respectively. Frequent and early NET recurrences after LT were reported in most studies.

Mathe (2011) conducted a systematic review of the literature to evaluate patient survival after LT for pancreatic NETs.[70] Data from 89 transplanted patients from 20 clinical studies were included in the review. Sixty-nine patients had primary endocrine pancreatic tumors, nine patients had carcinoids, and 11 patients were not further classified. Survival rates at one-, three-, and five-years were 71%, 55%, and 44%, respectively. The mean calculated survival rate was 54.45 (±6.31) months, and the median calculated survival rate was 41 months (95% CI 22 to 76 months).

Gedaly (2011) reported on a retrospective analysis of LT conducted on 150 patients with metastatic NETs.[71] Survival rates at one-, three-, and five-years were similar to those reported in the systematic analysis above: 81%, 65%, and 49%, respectively. No significant differences were seen in rates of patient survival between patients with metastatic NETs compared with those with hepatocellular carcinoma. Because longer wait times were associated with improved health outcomes, the authors suggested allowing for disease stabilization before attempting transplantation.

Mazzaferro (2007) performed a literature review to establish transplant selection criteria for patients with metastatic neuroendocrine tumors.[72] Eight studies were reviewed between 1970 and 2006, and all but one study reported either poor or limited five-year survival outcomes. Suboptimal patient selection was reported as the cause for the lower rates of long-term survival. However, the authors reported outcomes for 24 patients who were selected for transplant using the Milan criteria,[73] and found a high five-year survival rate of 77%. Although, the utilization of these criteria to select optimal transplantation candidates in patients with non-resectable metastatic neuroendocrine tumors is promising, the data is limited to a small sample (n=24), from a single study. Larger, long-term studies are required to validate the usefulness of the Milan criteria in improving five-year survival rates for this unique patient population.

Section Summary

While there may be centers that perform LT on select patients with NETs, further studies are needed to determine appropriate selection criteria. Few studies are available, and the quality is limited by their retrospective nature and heterogeneous populations.

HIV POSITIVE RECIPIENTS

The subgroup of HIV positive LT recipients was historically controversial due to the long-term prognosis for HIV positivity, and the impact of immunosuppression on HIV disease. HIV candidates for LT are frequently co-infected with hepatitis B (HBV) or HCV, and viral co-infection can further exacerbate drug-related hepatotoxicities.

Cooper (2011) conducted a systematic review to evaluate LT in patients co-infected with HIV and hepatitis.[74] The review included 15 cohort studies and 49 case series with individual patient data. The survival rate of patients was 84.4% (95% CI 81.1% to 87.8%) at 12 months. Patients were 2.89 (95% CI 1.41 to 5.91) times more likely to survive when HIV viral load at the time of transplantation was undetectable compared to those with detectable HIV viremia.

Terrault (2012) reported on a prospective, multicenter study to compare LT outcomes in three groups: patients with both HCV and HIV (n=89), patients with only HCV (n=235), and all transplant patients age 65 or older.[75] Patient and graft survival reductions were significantly associated with only one factor: HIV infection. At three years, patient and graft survival rates were significantly better in the HCV-only group (79%, 95% CI 72% to 84%, and 74%, 95% CI 66% to 79%, respectively) than in the group with both HIV and HCV infection (60%, 95% CI 47% to 71%, and 53%, 95% CI 40% to 64%, respectively).

Current, OPTN policy permits HIV-positive transplant candidates.[1]

The American Society of Transplantation (2019) published a guideline on solid organ transplantation in HIV-infected patients.[76] For liver transplants, the following criteria for transplantation are suggested:

- Cluster of differentiation 4 (CD4) count >100 cells/mL with no history of AIDS-defining illnesses such as opportunistic infection or malignancy or CD4 count >200 cells/mL for at least 3 months
- Undetectable HIV viral load while receiving antiretroviral therapy or a detectable HIV viral load in patients with intolerance to antiretroviral therapy that can be suppressed posttransplant
- Documented compliance with a stable antiretroviral therapy regimen
- Absence of active opportunistic infection and malignancy
- Absence of chronic wasting or severe malnutrition
- Appropriate follow-up with providers experienced in HIV management and ready access to immunosuppressive medication therapeutic drug monitoring

The guideline authors note that patients with a previous history of progressive multifocal leukoencephalopathy, chronic interstitial cryptosporidiosis, primary central nervous system lymphoma, or visceral Kaposi's sarcoma were excluded from studies of solid organ transplantation in HIV-infected patients. Patients with HIV and concomitant controlled HBV

infection may be considered for transplant. Caution is recommended in HCV-coinfected patients who have not been initiated on direct acting antiviral therapy.

Section Summary

While HIV infection reduced three-year survival rates after liver transplantation in patients also infected with HCV, there were still a majority of patients experiencing long-term survival. Overall, survival rates are relatively high for patients with viral loads are low at the time of transplantation.

NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic steatohepatitis (NASH) is a condition where fat build up in the liver causes inflammation of the liver. LT is a treatment option for patients with NASH who progress to liver cirrhosis and failure.

In a systematic review and meta-analysis, Wang (2014) evaluated nine studies comparing LT outcomes in patients with and without NASH.[77] Patients with NASH had similar one-, three- and five-year survival outcomes after liver transplantation as patients without NASH. Patients with NASH also had lower graft failure risk than those without NASH (OR 0.21, 95% CI 0.05 to 0.89, p=0.03). However, NASH LT patients had a greater risk of death related to cardiovascular disease (OR 1.65, 95% CI 1.01 to 2.70, p=0.05) and sepsis (OR 1.71, 95% CI 1.17 to 2.50, p=0.006) than non-NASH liver transplant patients. Given the relatively equivocal survival rates compared to transplant patients without NASH, transplant in patients with NASH appear to be of benefit.

Cholankeril (2017) published a retrospective cohort analysis of records from 2003 to 2014 in the United Network Organ Sharing and Organ Procurement and Transplantation Network database to evaluate the frequency of NASH-related liver transplantation.[78] In all, 63,061 patients underwent liver transplant from 2003 to 2014. NASH accounted for 17.38% of liver transplants in 2014. During the observation period, liver transplants secondary to NASH increased by 162.0%, a greater increase than either HCV (33.0% increase) and alcoholic liver disease (55.0% increase). Five-year survival posttransplant in patients who had NASH (77.81%, 95% CI 76.37% to 79.25%) was higher than patients who had HCV (72.15%, 95% CI 71.37 to 72.93, p<0.001). Patients with NASH also demonstrated significantly higher posttransplant survival than patients with HCV (HR 0.75, 95% CI 0.71 to 0.79, p<0.001).

Section Summary

The evidence on LT for hepatocellular disease includes case series, registry studies, and systematic reviews. Long-term survival rates in patients with viral hepatitis are significant in a group of patients who have no other treatment options. Also, survival can be improved by eradication of hepatitis virus before transplantation. For patients with NASH, a 2013 systematic review has indicated that overall survival rates are similar to other indications for LT.

VIRAL HEPATITIS

The presence of HBV and HCV have been controversial indications for liver transplantation because of the high potential for recurrence of the virus and subsequent recurrence of liver disease. However, in a review of registry data, Belle (1995) have indicated a long-term survival rate (seven years) of 47% in HBV virus-positive transplant recipients, which is lower than that seen in other primary liver diseases such as primary biliary cirrhosis (71%) or alcoholic liver

disease (57%).[2] Recurrence of HCV infection in transplant recipients, who are not treated pretransplant, has been nearly universal, and 10% to 20% of patients will develop cirrhosis within five years.[79]

Historical data demonstrating inferior survival in transplant recipients with HCV is not applicable to the current treatment landscape with the availability of direct acting antiviral agents, which are associated with sustained virological response rates over 95%.[80] Timing the receipt of direct acting antiviral agents either before or after transplantation is still controversial and the decision should be individualized based the presence of compensated or decompensated disease, Model for End-Stage Liver Disease (MELD) score, current quality of life, and the proportion of HCV-positive donors in the local and regional areas.

ELDERLY DONORS AND RECIPIENTS

Elderly Donors

Gao (2019) evaluated trends in long-term outcomes for LT with donors aged 60 years and above, using data from the OPTN/UNOS database.[81] There were 14,796 adult LT between 1990 and 2014 included in the analysis. There was a steady increase in the number of transplants from older donors found during the first 15 years of period, followed by a leveling off. There were significant improvements in the unadjusted five-year graft and patient survival over time ($p<0.0001$), as well as a reduction in the survival difference between older and younger grafts ($p<0.0001$).

A prospective study by Cascales-Campos (2018) assessed LT outcomes for those with donors aged 80 years and above (n=36) compared to those with donors under 65 years of age (n=283). They reported no significant differences in graft survival and overall survival.[82]

Paterno (2016) published a study that evaluated the outcome of LT from elderly donors.[83] Data from January 2007 to December 2011 was evaluated for patients who received a transplant from donors aged 70 years and older (n=540) or from patients younger than 60 years of age (n=10,473). The authors stated transplants from elderly donors in patients who meet criteria (i.e., no HCV and not on dialysis) had good outcomes and survival rates, but slightly lower graft survival.

A similar study by Dasari (2017) with 4,376 LT recipients compared outcomes for those receiving grafts from deceased donors over 70 years of age (n=880) and below 70 years of age (n=3,496).[84] In this study, graft and patient survival were similar between groups at one year, but there was better graft and patient survival at three and five years in the older donor group.

Elderly Recipients

Chen (2016) published a population-based cohort study that reported age-related LT mortality for patients in Taiwan.[85] Data were collected for patients receiving transplants from July 1, 1998 to December 31, 2012, and patients were followed until the end of the study or death. The authors stated the older a recipient, the higher risk of mortality, particularly for those with comorbidities.

Section Summary

Liver transplants for elderly recipients or from elderly donors can have positive health outcomes. More studies are needed to further identify survival rates and risks of mortality.

RETRANSPLANTATION

A registry analysis of pediatric retransplantation patients from Australia and New Zealand was published by Jeffrey (2020).[86] Between 1986 and 2017, 142 retransplantations in children were performed. Survival was higher in retransplantations performed between 2001 and 2017 compared with those performed between 1986 and 2001 ($p<0.001$), with 5-, 10-, and 15-year patient survival rates of 87%, 87%, and 71%, respectively, for the procedures between 2001 and 2017. There were no significant associations between survival and graft type, cause of graft failure, or number of transplants.

Agüero (2016) published an international cohort study that evaluated retransplantation for HIV patients who had HBV or HCV coinfection.[87] Thirty-seven patients with HBV or HCV coinfection underwent retransplant, with a survival rate of 80%. The authors concluded that patients coinfected with HBV or HCV, without HCV RNA had acceptable outcomes.

Abdelfattah (2015) reported on a retrospective cohort of 466 LT patients, 16 of whom underwent retransplantation.[88] The 16 retransplant patients were divided into those which had retransplantation within 30 days of the primary transplant, and those which had retransplantation more than 30 days after. Although the investigators stated that, overall patient and graft survival were lower after liver retransplant than primary liver transplant, and these outcomes were better in late than early liver retransplant; the study populations in the comparator groups was too small to draw meaningful conclusions. Studies of larger sample size are needed.

Bellido (2012) reported on a retrospective cohort study of 68 consecutive adult liver retransplantations using registry data.[89] Survival probability using Kaplan-Meier curves with log-rank tests to compare 21 urgent versus 47 elective retransplantations were calculated. Overall survival rates were significantly better in patients undergoing urgent procedures (87%), which were mostly due to vascular complications than elective procedures (76.5%) related to chronic rejection.

Remiszewski (2011) examined factors influencing survival outcomes in 43 liver retransplantation patients.[90] When compared to primary LT patients, retransplantation patients had significantly lower six-year survival rates (80% vs. 58%, respectively, $p=0.0001$). The authors also reported low negative correlations between survival time and time from original transplantation until retransplantation and between survival time and patient age. Survival time and cold ischemia time showed a low positive correlation.

Hong (2011) reported on a prospective study of 466 adults to identify risk factors for survival after liver retransplantation.[91] Eight risk factors were identified as predictive of graft failure, including age of recipient, MELD score greater than 27, more than one prior liver transplant, need for mechanical ventilation, serum albumin of less than 2.5 g/dL, donor age greater than 45 years, need for more than 30 units of packed red blood cells transfused intraoperatively, and time between prior transplantation and retransplantation between 15 and 180 days. The authors propose this risk-stratification model can be highly predictive of long-term outcomes after adult liver retransplantation and can be useful for patient selection.

Section Summary

Recent data regarding liver retransplantation suggest survival rates are not as good as with initial transplantation; however, overall survival rates appear to meet the benchmark of 50% five-year survival.

PRACTICE GUIDELINE SUMMARY

In December 2010, 10 international liver diseases or transplantation societies held an international consensus conference on liver transplantation for HCC.[92] Consensus criteria for selecting candidates for LT were developed at the conference. Milan criteria were recommended for use as the benchmark for patient selection and as the basis for comparison with other suggested criteria for selecting non-HCC patients. The Milan criteria set limits on the size and quantity of tumors and have been shown to be an independent prognostic factor for outcomes after LT.[92, 93] Panel members did refer to several studies which indicated that in some circumstances, the Milan criteria may be modestly expanded for patients who do not have HCC. It was warned, however, that expanding Milan criteria could result in a variety of outcomes and that patients, "…would need to achieve 5-year survival of 60% or higher to prevent a substantial decrement to the life-years available to the entire population of candidates for liver transplantation."[92] In addition, candidates for LT should also have a predicted survival of five years or more. The consensus criteria indicate alpha-fetoprotein concentrations may be used with imaging to assist in determining patient prognosis.

With respect to liver retransplantation, the consensus criteria issued a weak recommendation indicating retransplantation after graft failure of a living donor transplant for HCC is acceptable in patients meeting regional criteria for a deceased donor liver transplant. A strong recommendation was issued indicating liver retransplantation with a deceased donor for graft failure for patients exceeding regional criteria is not recommended. And the consensus criteria issued a strong recommendation that liver retransplantation for recurrent HCC is not appropriate. However, a de-novo HCC may be treated as a new tumor and retransplantation may be considered even though data to support this are limited.

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES (AASLD)

Evaluation for Liver Transplantation

The AASLD issued separate updated, evidence-based guidelines for evaluating pediatric[94] and adult[95] patients for LT. These guidelines update the 2005 guidelines[96] which addressed all ages. While the disease categories are similar for adult and pediatric (below 18 years of age) patients, separate guidelines were considered warranted because of differences between these age groups in specific etiologies and outcomes. Furthermore, the AASLD guidelines indicate patients should be assessed by a transplantation center to determine whether LT is appropriate. While the AASLD guidelines indicate LT may be appropriate in patients with CCA and metastatic NETs, these recommendations and many of the recommendations in the AASLD guidelines are based on opinion.

- In 2014 the AASLD in conjunction with the American Society of Transplantation (AST) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition issued evidence-based guidelines for the evaluation of pediatric patients for liver transplantation.[94] Each of the 93 recommendations was classified for strength of recommendation and quality of evidence. Strength of recommendation 1 and 2 is defined as a strong or weak recommendation, respectively. Quality of evidence A, B, or C is

defined as high, moderate, or low quality, respectively. Contact of or referral to a liver transplant center was recommended for any of the following indications:

  - Acute liver failure or acute decompensation of an established liver disease (*Strength of recommendation 1; quality of evidence A [1-A])*
  - Liver-based metabolic crises refractory to medical and/or surgical therapy *(1-B)*
  - Unresectable hepatoblastoma or hepatocellular carcinoma *(1-B)*
  - Biliary atresia patients with total bilirubin > 6 mg/dL beyond 3 months post-hepatoportoenterostomy (*1-B*); liver transplant evaluation should be considered in these patients if total bilirubin remains between 2-6 mg/dL. *(1-B)*
  - Anticipate referral for evaluation for children with chronic liver disease and evidence of deteriorating liver function (i.e., poor weight gain, growth failure, variceal hemorrhage, intractable ascites, recurrent cholangitis, or episodes of spontaneous bacterial peritonitis, pruritus, advancing encephalopathy, and/or uncorrectable coagulopathy *(1-B)*

- The 2013 AASLD/ATS guideline for evaluation of adults for LT state that LT is indicated for acute or chronic liver failure when the limits of medical therapy have been reached.[95] The following are some of the included recommendations:

  - Consideration for liver transplantation is recommended for acute liver failure complications of cirrhosis, liver-based metabolic conditions with systemic manifestations, and systemic complications of chronic liver disease (i.e., hepatopulmonary syndrome; portopulmonary hypertension)
  - Liver transplant in combination with neoadjuvant chemoradiation for early-stage unresectable peri-hilar cholangiocarcinoma *(1-B)*.
  - Intrahepatic cholangiocarcinoma is a listed contraindication to liver transplant
  - Extrahepatic malignancy is a contraindication to liver transplant
  - Live donor transplant should be considered only when a deceased donor is unlikely to become available within a reasonable time frame for the recipient's liver disease

Long-term Management after Liver Transplant

The AASLD has also issued joint evidence-based guidelines with the AST for management of pediatric[97] and adult[98] patients following successful LT. Numerous recommendations are included and each is graded for strength of recommendation and quality of the supporting evidence. The stated intent of the guidelines is to provide flexible, preferred approaches to the diagnostic, therapeutic, and preventive aspects of care.

The 2013 guideline for pediatric (age 0 to 18 years) post-LT patients includes 54 recommendations.[97] "Pediatric liver transplant has dramatically changed the prognosis for many infants and children with liver failure and metabolic disease. As survival increases, long-term maintenance resources exceed perioperative care requirements. The most common indication for LT in children is biliary atresia which accounts for 50% of all children requiring transplant in the U.S. and 74% in Europe."

The 2012 AASLD/AST practice guideline for adults after LT includes 93 recommendations.[98] "LT is the treatment of choice for patients with decompensated cirrhosis, acute liver failure, small hepatocellular carcinomas (HCCs), or acute liver failure…long-term survivors are at risk of early death and increased morbidity. The purpose of this guideline is to assist in the management of adult recipients of LT, identify the barriers to maintaining their health, and

make recommendations on the ways to best prevent or ameliorate these barriers. This guideline focuses on management beyond the first 90 days after transplantation."

Alcohol-Associated Liver Disease

The AASLD (2019) guideline on alcohol-associated liver disease provides recommendations on the timing of referral and selection of candidates for liver transplant.[99] The guidance notes that the patient's history of addiction to alcohol is a primary driver in selecting appropriate candidates for liver transplantation. Clinical characteristics that should trigger an evaluation and consideration for liver transplant include decompensated alcohol-associated cirrhosis, Child-Pugh-Turcotte class C cirrhosis, or a MELD-Na score ≥21. Additionally, the guideline notes that candidate selection "should not be based solely on a fixed interval of abstinence" and instead a formal psychological evaluation can help stratify patients into higher- or lesser-risk strata for relapse.

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

The NCCN guidelines on hepatobiliary cancers (v1.2022) recommend referral to a liver transplant center or bridge therapy for patients with HCC meeting United Network of Organ Sharing criteria of a single tumor measuring 2 to 5 cm, or two to three tumors 3 cm or less with no macrovascular involvement or extrahepatic disease.[36] Patients should be referred to the transplant center. Patients should be referred to the transplant center before the biopsy. In patients who are ineligible for transplant and in select patients with Child-Pugh class A or B liver function with tumors that are resectable, the NCCN indicates resection is the preferred treatment option; locoregional therapy may also be considered. Patients with unresectable HCC should be evaluated for liver transplantation; if the patient is a transplant candidate, then referral to a transplant center should be given or bridge therapy should be considered. These are level 2A recommendations based on lower-level evidence and uniform consensus.

The NCCN guidelines on neuroendocrine and adrenal tumors (v1.2022) indicate that liver transplantation for neuroendocrine tumor metastases in the liver is considered investigational despite "encouraging" five-year survival rate.[100]

SUMMARY

There is enough research to show that liver transplantation can improve survival for patients with irreversible, end-stage liver failure due to certain conditions. Clinical guidelines based on research recommend liver transplantation for some people with irreversible, end-stage liver failure. Therefore, liver transplantation may be considered medically necessary in patients who meet the policy criteria.

There is enough research to show that liver transplantation does not improve health outcomes for patients with hepatocellular carcinoma that has extended beyond the liver, or for patients with active alcohol and/or substance abuse. Therefore, liver transplantation is considered not medically necessary for these patients.

There is not enough research to show that liver transplantation improves survival for patients with intrahepatic cholangiocarcinoma, extrahepatic malignancy other than those noted in the policy criteria, or neuroendocrine tumors metastatic to the liver. Therefore, liver

transplantation is investigational for these populations when the policy criteria are not met.

RETRANSPLANTATION

There is enough research to show that liver retransplantation improves survival for pediatric and adult patients for primary graft nonfunction, hepatic artery thrombosis, chronic rejection, ischemic type biliary lesions after donation after cardiac death, or recurrent non-neoplastic disease-causing late graft failure. Therefore, liver retransplantation may be considered medically necessary in patients with one of these diagnoses who meet the policy criteria. There is not enough research to show that liver retransplantation improves survival in patients for other conditions. Therefore, liver retransplantation is investigational when the policy criteria are not met.

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CODES

Codes	Number	Description
CPT	47133	Donor hepatectomy (including cold preservation) from cadaver donor
	47135	Liver allotransplantation; orthotopic; partial or whole, from cadaver or living donor, any age
	47140	Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
	47141	Donor hepatectomy (including cold preservation), from living donor; total left lobectomy (segments II, III and IV)
	47142	Donor hepatectomy (including cold preservation), from living donor; total right lobectomy (segments V, VI, VII and VIII)
	47143	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; without trisegment or lobe split
	47144	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with trisegment split of whole liver graft into two partial liver grafts (i.e., left lateral segment (segments II and III) and right trisegment (segments I and IV through VIII))
	47145	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein,

Codes	Number	Description
		hepatic artery, and common bile duct for implantation; with lobe split of whole liver graft into two partial liver grafts (i.e., left lobe (segment II, III, and IV) and right lobe (segments I and V through VIII)
	47146	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
	47147	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each
	47399	Unlisted procedure, liver
HCPCS	None	

Date of Origin: *January 1996*