Notable Grand Rounds
of the
Michael & Marian Ilitch
Department of Surgery

Wayne State University
School of Medicine

Detroit, Michigan, USA

Shunji Nagai, MD, PhD, FACS

LIVER TRANSPLANTATION: PAST, PRESENT, AND FUTURE

August 14, 2024

About Notable Grand Rounds

These assembled papers are edited transcripts of didactic lectures given by mainly senior residents, but also some distinguished attending and guests, at the Grand Rounds of the Michael and Marian Ilitch Department of Surgery at the Wayne State University School of Medicine.

Every week, approximately 50 faculty attending surgeons and surgical residents meet to conduct postmortems on cases that did not go well. That “Mortality and Morbidity” conference is followed immediately by Grand Rounds.

This collection is not intended as a scholarly journal, but in a significant way it is a peer reviewed publication by virtue of the fact that every presentation is examined in great detail by those 50 or so surgeons.

It serves to honor the presenters for their effort, to potentially serve as first draft for an article for submission to a medical journal, to let residents and potential residents see the high standard achieved by their peers and expected of them, and by no means least, to contribute to better patient care.

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Liver Transplantation: Past, Present, and Future

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Edited transcript of a Grand Rounds Presentation

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Michael and Marian Ilitch Department of Surgery
Wayne State University School of Medicine

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Introduction

Today, I'm going to talk about liver transplantation. I have nothing to disclose. In today's talk, I'll cover the past and present of liver transplantation, with a focus on indications and outcomes. I also want to highlight a few key concepts, including transplant oncology—a term you might not have heard of before. Additionally, I'll showcase some innovations in liver transplantation, particularly in multivisceral transplantation.

Indications for Liver Transplantation

The main indication for liver transplantation is end-stage liver disease or acute liver failure, and sometimes metabolic diseases. However, the primary reason for liver transplants is cirrhosis. A decade ago, the most common indication for liver transplantation was hepatitis C. NASH (non-alcoholic steatohepatitis) was also on the rise, and alcohol-related liver disease was another major indication.

Hepatocellular carcinoma (HCC) often occurs in cirrhotic livers due to the damaged liver cells developing into liver cancer. Since 2013-2014, we've had very effective antiviral medications, known as direct-acting antivirals (DAAs), which have allowed us to eradicate hepatitis C. As a result, the number of hepatitis C-related liver transplants has dramatically decreased. Now, we see more patients with fatty liver disease and alcoholic liver disease. Recently, the hepatology field has changed the term "NASH" (non-alcoholic steatohepatitis) to "MASH" (metabolic dysfunction-associated steatohepatitis). MASH is now the preferred term, and it accounts for about 30% of liver transplants, with alcoholic liver disease being the most common indication today.

Trends in liver transplant indications have shifted. The number of patients with alcoholic liver disease (represented by the pink line in **Fig. 1**, next page) is increasing, while those with hepatitis C (green line) have decreased to less than 10%. Meanwhile, the incidence of MASH (blue triangles) is rising and now accounts for about 20% of liver transplants.

Liver Transplant Outcomes by Disease Etiology

We looked at liver transplant outcomes according to liver disease etiology, comparing NASH/MASH, hepatitis C, and alcohol-related liver disease. (**Fig. 2** below) We examined outcome trends year by year, era by era. Ten to fifteen years ago, outcomes for hepatitis C patients were the worst because of the high recurrence rate post-transplant, which was nearly 100%. This was a significant chal-

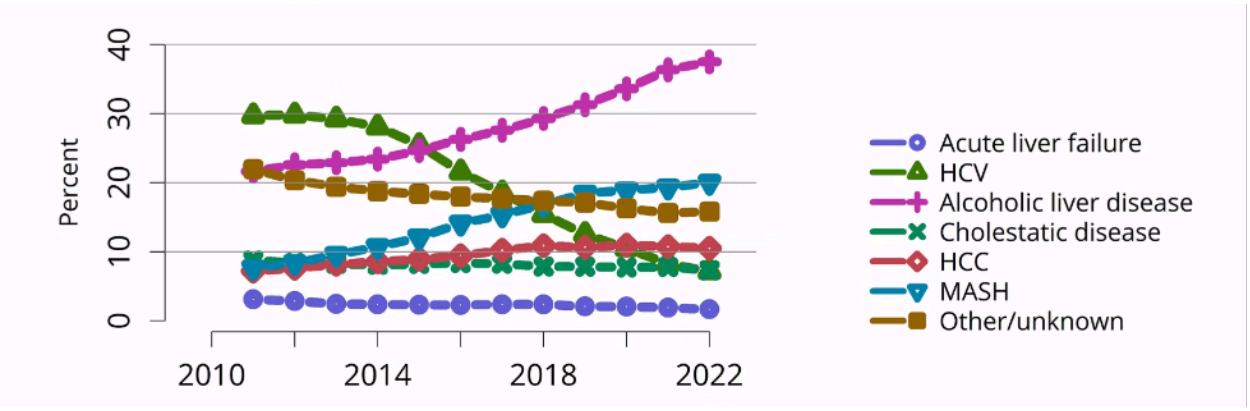

Fig. 1. **Distribution of adults waiting for liver transplant by diagnosis.** Candidates waiting for transplant at any time in the given year. Candidates listed at more than one center are counted once per listing. Active and inactive patients are included. *Source*: **Figure LI 6: in Kwang, AJ et al.** OPTN/SRTR 2022 Annual Data Report: Liver. https://srtr.transplant.hrsa.gov/annual_reports/2022/Liver.aspx

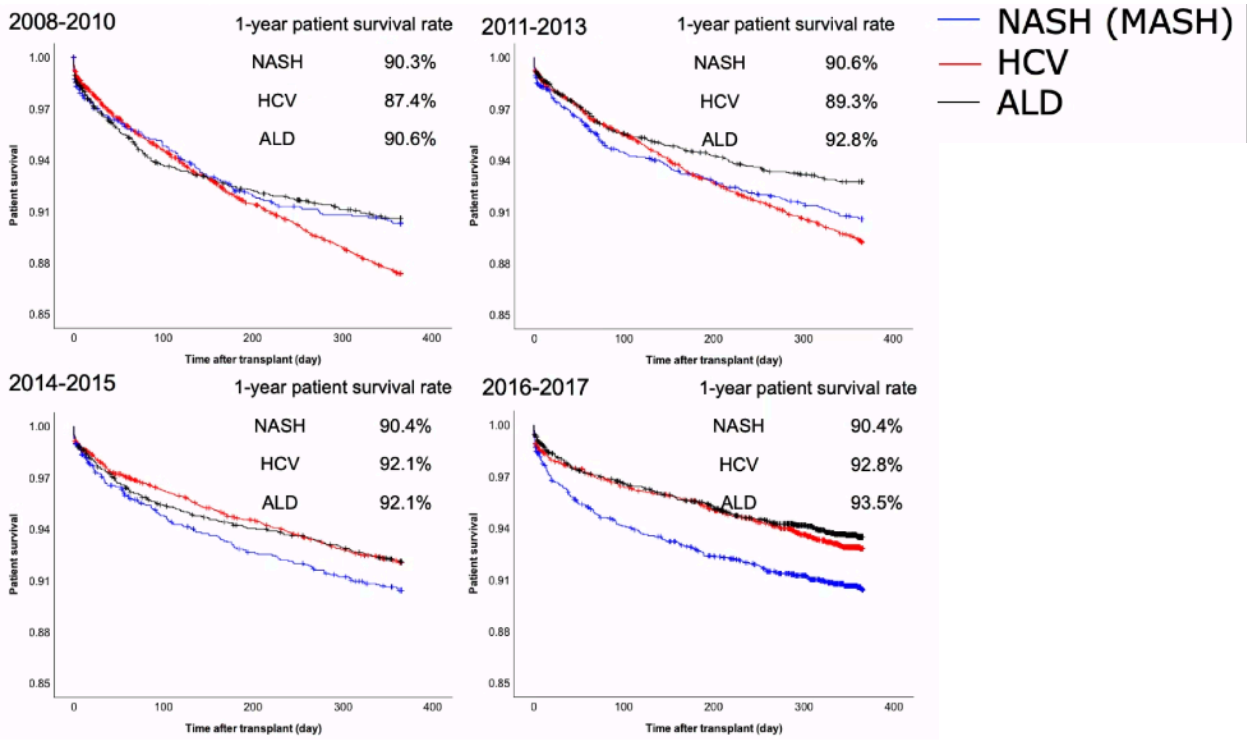

Fig. 2. **Outcome Trends**. *Source*: Nagai, Shunji et al. Increased Risk of Death in First Year After Liver Transplantation Among Patients With Nonalcoholic Steatohepatitis vs Liver Disease of Other Etiologies. *Clinical Gastroenterology and Hepatology*, Volume 17, Issue 13, 2759 - 2768.e5. https://www.cghjournal.org/article/S1542-3565(19)30423-9/fulltext

lenge, as some patients developed liver failure within just one or two months. However, outcomes improved dramatically after the introduction of DAAs between 2014 and 2017, with over 90% one-year survival rates.

Similarly, alcohol-related liver disease has consistently shown good outcomes post-transplant, with over 90% one-year survival rates, both 10-15 years ago and today. Interestingly, NASH/MASH outcomes (represented by the blue line) have remained stable over the past 15 years, with one-year survival rates at 90%. Despite advancements in surgical techniques and immunosuppressive medication management, patients with MASH still have poorer outcomes due to their older age and the presence of multiple comorbidities like diabetes and cardiovascular disease.

In summary, we are seeing more transplants in older patients with MASH, who have multiple comorbidities. The improvement in outcomes for these patients has not been as significant as for other liver disease etiologies. Additionally, we are observing an increase in alcoholic liver disease, which now accounts for 40% of liver transplants, with hepatitis C becoming less prevalent.

Alcoholic Hepatitis and Liver Transplantation

Alcoholic hepatitis is a somewhat different disease process. It often occurs suddenly, even in patients who have been drinking regularly but have no prior medical history of alcohol-related disease. These patients may present at the hospital, see a doctor, and be diagnosed with alcoholic hepatitis. This condition can manifest as acute hepatitis or as an acute-on-chronic condition, where liver damage has been ongoing, and the patient suddenly develops severe symptoms, including jaundice and hyperbilirubinemia. Alcoholic hepatitis is characterized by acute and progressive increases in bilirubin levels. It's important to note that 25% to 50% of these patients already have underlying cirrhosis, meaning the acute episode occurs on top of existing liver damage.

For these patients, the question arises: Can we perform a liver transplant? Traditionally, we required patients with alcoholic liver disease to abstain from drinking for at least six months before they could be considered for a transplant. This waiting period was intended to ensure that the patient could maintain sobriety post-transplant, as resuming drinking after the transplant would be detrimental. However, in cases of acute alcoholic hepatitis, patients are often critically ill, sometimes in the ICU, and cannot wait for six months. This has led to the concept of early transplantation for acute alcoholic hepatitis patients.

A national study[1] was conducted to evaluate liver transplantation for alcoholic hepatitis. The study included 432 patients. Out of these, 20 patients died, and 9 were removed from the transplant list due to improvement in their condition. Ultimately, 126 patients received a liver transplant, with a median MELD (Model for End-Stage Liver Disease) score of around 39, which is very high (the MELD score is capped at 40). Some patients were turned down for psychosocial or medical contraindications, but those who were approved for transplantation had excellent outcomes. The one-year survival rate for these transplanted patients was over 94%, and the three-year survival rate was still 84%, which is quite good.

A significant concern with liver transplantation in alcoholic hepatitis patients is the risk of sustained alcohol use post-transplant. The study found that the rate of alcohol relapse was 10% at one year and 17% at three years, which is comparable to relapse rates in patients who met the six-month abstinence criteria. The study concluded that early transplantation for alcoholic hepatitis patients can be justified, provided they meet certain criteria.

[1] Lee, Brian P et al. "Outcomes of Early Liver Transplantation for Patients With Severe Alcoholic Hepatitis." Gastroenterology vol. 155,2 (2018): 422-430.e1. doi:10.1053/j.gastro.2018.04.009

The Dallas criteria,[2] a consensus guideline that mainly focuses on the psychosocial background of the patient, ensure that the patient has a good support system and does not have significant psychiatric disorders. If a patient meets these criteria, they can be considered for liver transplantation even without a prolonged period of abstinence. We also use the Dallas criteria to evaluate liver transplant candidacy in patients with alcoholic hepatitis.

The criteria are:

- Lack of repeated unsuccessful attempts at addiction rehabilitation
- Lack of other current substance abuse or dependency
- Acceptance of ALD diagnosis with insight
- Commitment of patient to lifelong sobriety with support of sober caregivers to assist patient with abstinent goals
- Presence of close, supportive family members or caregivers
- Patient should be assessed while fully coherent (not intubated or floridly encephalopathic)

In summary, mortality in alcoholic hepatitis with medical therapy remains high, and there are no promising medical therapies on the horizon. Liver transplantation for alcoholic hepatitis can be performed with outcomes comparable to other indications. The traditional abstinence period is not always feasible for these patients, so as long as they meet certain psychosocial and medical criteria, we do not require them to stop drinking for six months before transplantation. However, alcohol relapse after liver transplantation remains a concern. Well-known risk factors for relapse include psychosocial factors, harmful drinking patterns such as binge drinking, the duration of abstinence before transplantation, other substance abuse, cigarette dependence, and family history.

Risk Factors for Alcohol Relapse Post-Transplant

Our group also examined the risk factors for alcohol relapse after liver transplantation, beyond the commonly recognized ones.[3] In our study of 190 patients, 26 experienced alcohol relapse post-transplant, and among them, three developed liver failure due to this relapse. This study underscores the risk of post-transplant complications. While other studies have primarily focused on patients' psychosocial backgrounds or pre-transplant drinking patterns, we concentrated on the post-transplant course. We hypothesized that if patients suffer from post-transplant complications, such as biliary strictures, multiple ERCPs, or frequent readmissions, it could significantly affect their mental health and potentially lead to a relapse in alcohol consumption.

We found that patients with significant post-transplant complications, defined as grade two or higher (with three or more complications), had a markedly increased risk of alcohol relapse after liver transplantation. Based on these findings, we developed a risk-scoring system where post-transplant complications are a key factor (**Fig. 3**, next page). This system guides our follow-up plans: patients identified as being at higher risk for alcohol relapse receive closer monitoring post-transplant, involving both psychologists and the medical team.

So far, I've discussed indications and outcomes, with a particular focus on diseases like alcoholic hepatitis. Now, I'd like to shift to the topic of transplant oncology. Some of you might not be familiar with this term. Transplant oncology refers to the use of liver transplantation as a treatment for cancer, particularly for hepatocellular carcinoma

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[2] Asrani, Sumeet K et al. "Meeting Report: The Dallas Consensus Conference on Liver Transplantation for Alcohol Associated Hepatitis." Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society vol. 26,1 (2020): 127-140. doi:10.1002/lt.25681

[3] Kitajima, Toshihiro et al. "Posttransplant Complications Predict Alcohol Relapse in Liver Transplant Recipients." Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society vol. 26,3 (2020): 379-389. doi:10.1002/lt.25712

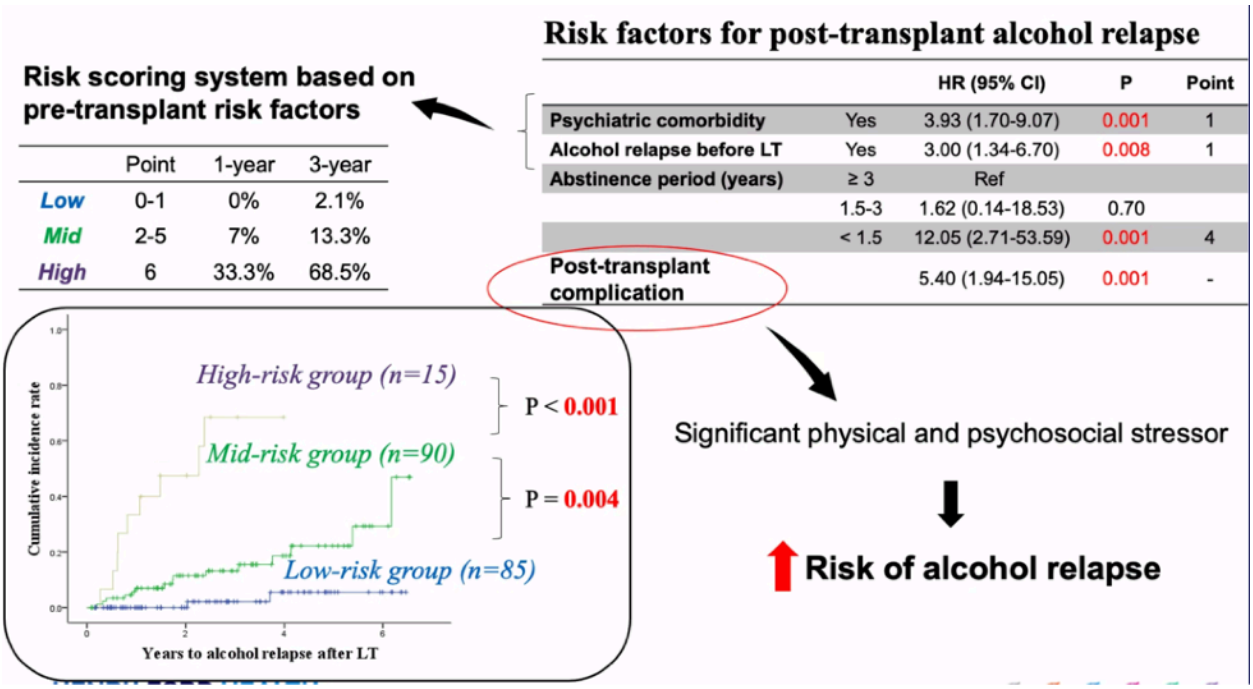


Fig. 3. **Risk factors for post-transplant alcohol relapse**. *Source*: footnote 3.

(HCC) and other liver cancers such as neuroendocrine tumors.[4]

Transplant Oncology and HCC

Liver transplants have traditionally been performed for patients with cirrhosis who develop HCC. In fact, liver transplantation can be considered a form of cancer treatment, specifically for HCC. About 15% to 20% of liver transplants in the United States are performed for HCC. Another indication is unresectable hilar cholangiocarcinoma, where the tumor is located at the bile duct hilum and cannot be surgically removed. In such cases, provided there are no metastases, liver transplantation is a viable option.

Additionally, neuroendocrine tumors with liver metastasis are another indication for liver transplantation, provided the primary tumor has been resected and the metastasis is confined to the liver. Colorectal cancer with liver metastasis, once considered a contraindication for liver transplantation 10 to 15 years ago, is now becoming an accepted indication as more data accumulates.

Another example of transplant oncology is the treatment of unresectable mesenteric tumors, where an intestinal transplant, including the removal of the entire mesentery and intestine, can be performed.

Let me discuss these concepts in more detail, starting with liver transplantation for HCC. In a study from 1963–1980, one- and three-year survival rates were below 50% (**Fig. 4**, next page) which was clearly unacceptable given the scarcity of donated livers. These early failures were likely due to multiple factors, including surgical techniques and immunosuppression challenges, but the primary issue was patient selection. If liver transplants are performed on patients with advanced cancer, the cancer is likely to recur, leading to patient death from cancer recurrence. Therefore, patient selection is critical for successful liver transplantation in cases of HCC.

Milan Criteria and Patient Selection for HCC

One of the most widely recognized and commonly used criteria for liver transplant

[4] Hibi, T and G Sapisochin. What is transplant oncology? *Surgery* 165:2, 281-285, February 2019. https://www.surgjournal.com/action/showPdf?pii=S0039-6060(18)30739-6

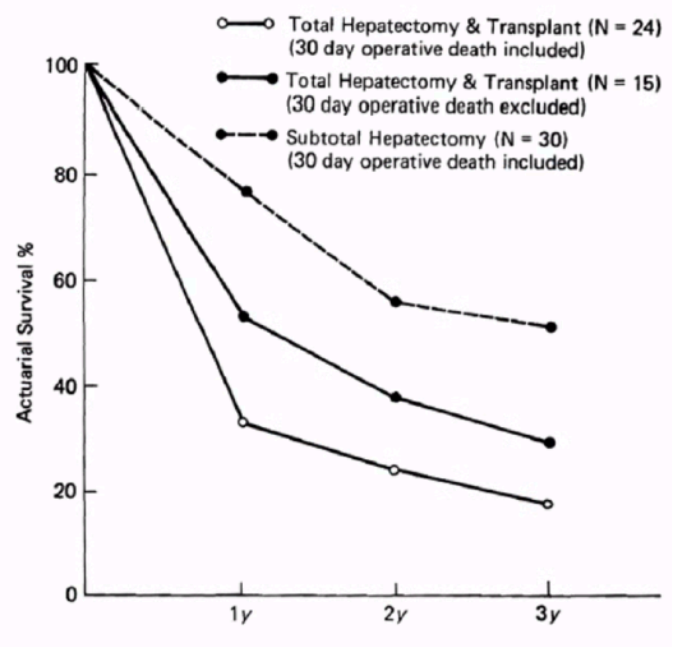


Fig. 4. **Too much recurrence!** *Source:* Fig. 1 in Iwatsuki S, Klintmalm GB, Starzl TE. Total hepatectomy and liver replacement (orthotopic liver transplantation) for primary hepatic malignancy. World J Surg. 1982 Jan;6(1):81-5. doi: 10.1007/BF01656377. PMID: 7046266; PMCID: PMC3002428.

eligibility, particularly for hepatocellular carcinoma (HCC), is the Milan Criteria. These criteria were established by a group from Milan about 20 years ago. According to the Milan Criteria, patients are eligible for a liver transplant if they have a single tumor not exceeding five centimeters, or up to three tumors, none of which exceed three centimeters (**Fig. 5**). This standard has remained the

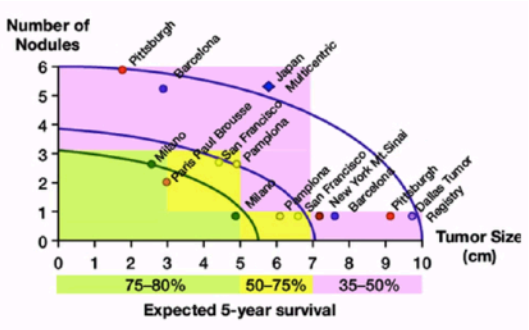


Fig. 5. **Why 3 nodules?**.*Source*: Fig. 4 in Mazzaferro, V. Results of Liver Transplantation: With or Without Milan Criteria? Liver Transplantation 3:S44-S47, 2007 supplement. https://aasldpubs.onlinelibrary.wiley.com/doi/pdf/10.1002/lt.21330

benchmark for patient selection in liver transplantation, although many other criteria have been proposed by different groups over the years.

When considering more aggressive approaches, there's always a trade-off. The more aggressive the criteria, the higher the risk of recurrence and lower five-year survival rates. Therefore, it's crucial to find a balance that justifies the use of a deceased donor graft. According to UNOS (United Network for Organ Sharing) guidelines, liver transplants can technically be performed on anyone, but to receive a MELD exception for HCC, patients must meet the Milan Criteria.

Hilar Cholangiocarcinoma and Liver Transplantation

Hilar cholangiocarcinoma is another complex and challenging disease. Liver resection is often the first-line treatment, but in cases where the tumor is invading the hilum or the second branch of the bile duct, resection may not be possible. In such cases, liver transplantation can be considered, provided there are no metastases (no lymph node involvement or intrahepatic metastasis) and the disease is localized to a single mass in the hilum, up to three centimeters in size.

Studies have compared outcomes between liver transplantation and resection for hilar cholangiocarcinoma, and the data shows that, when patients meet the appropriate criteria, liver transplantation provides much better survival outcomes compared to resection (**Fig. 6**, next page). For MELD exception in hilar cholangiocarcinoma, the criteria are strict: the diagnosis must be confirmed by biopsy or cytology, CA 19-9 levels must be below 100, the tumor must be less than three centimeters, and there must be no metastases. Additionally, patients must undergo pre-transplant neoadjuvant therapy, including chemo and radiation therapy, followed by operative staging to ensure no lymph node or metastasis involvement. Only then can they receive a MELD exception and proceed to liver transplantation.

The transplant procedure for hilar cholangiocarcinoma is not overly complex because the tumor is localized in the hilum. The procedure involves removing the entire liver along with the bile ducts and the vessels connect-

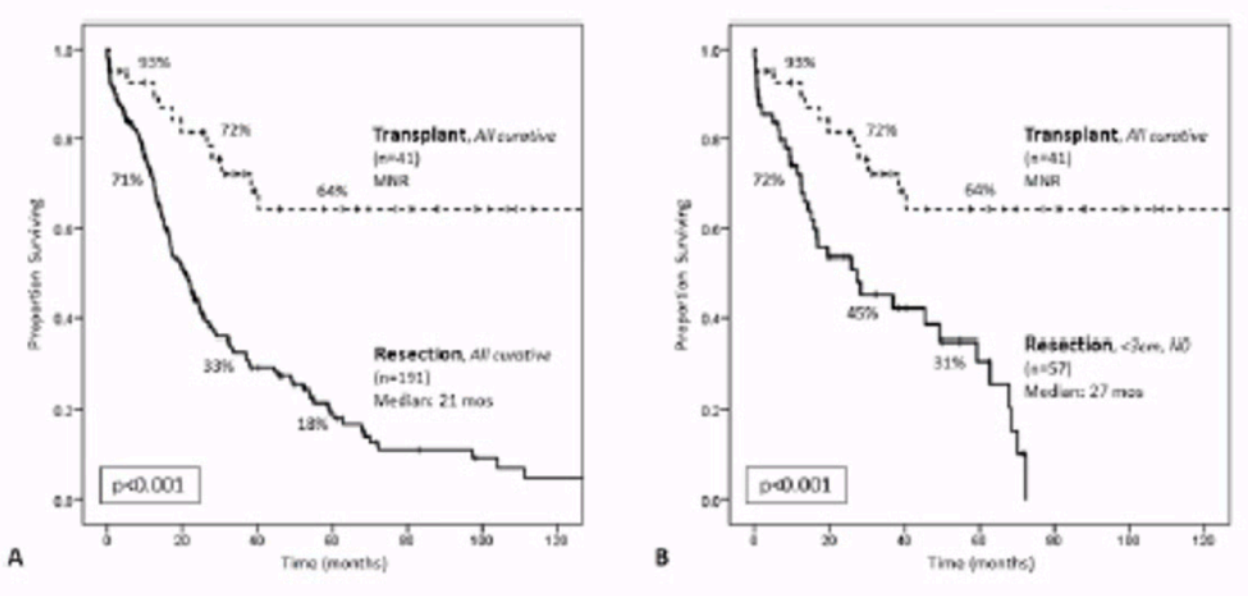


Fig. 6. **234 resections vs 70 LTs (<3cm, RO or R1 resection)**. *Source*: Ethun et al. Ann Surg 2018;267:797-805.

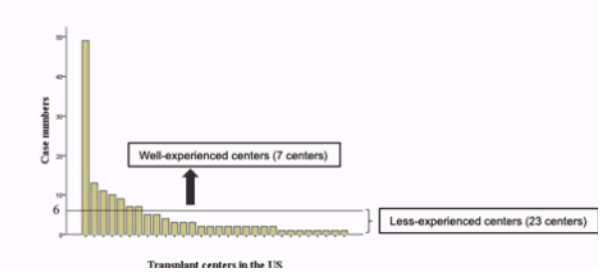


Fig. 7. **Case numbers in each center between 2010 and 2017**. *Source*: Kitajima, Toshihiro et al. "Center Experience Affects Liver Transplant Outcomes in Patients with Hilar Cholangiocarcinoma." *Annals of surgical oncology* vol. 27,13 (2020): 5209-5221. doi:10.1245/s10434-020-08682-5

ed to the hilum. Our review of national data on liver transplants for hilar cholangiocarcinoma shows that centers with greater experience in performing these transplants have significantly better survival outcomes (**Figs. 7 and 8** above). This suggests that the patient selection process, neoadjuvant therapy, and operative staging require experience to optimize post-transplant outcomes, which explains the differences in outcomes between more and less experienced centers.

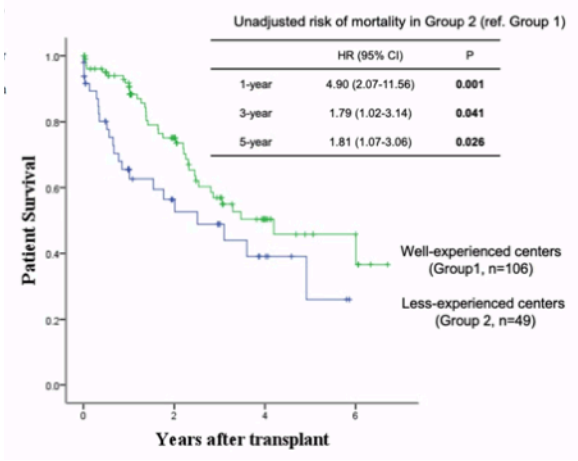
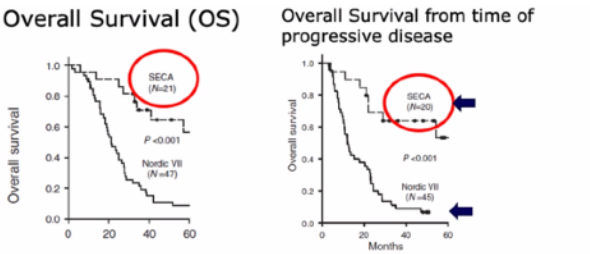


Fig. 8. **Post-transplant patient survival**. *Source*: Kitajima, Toshihiro et al. "Center Experience Affects Liver Transplant Outcomes in Patients with Hilar Cholangiocarcinoma." *Annals of surgical oncology* vol. 27,13 (2020): 5209-5221. doi:10.1245/s10434-020-08682-5

Colorectal Cancer Liver Metastasis and Transplantation

Colorectal cancer with liver metastasis was almost considered a contraindication for liver transplantation about 20 years ago. However, things have changed significantly since then. Advances in chemotherapy and oncol-



	5 year OS
LT	56%
Chemo	9%

	5 year OS after relapse
LT	53%
Chemo	-

Fig. 9. **Survival rates for colorectal liver metastases**. *Source*: Dueland S, et al. Ann Surg, 2015.

ogy management have led some groups to explore the potential of liver transplantation for colorectal metastasis.

One major center leading this research is in Oslo, Norway. They compared survival outcomes between patients receiving liver transplants and those receiving chemotherapy alone. With proper patient selection, liver transplantation has shown significantly better survival outcomes compared to chemotherapy alone (**Fig. 9** above). They further analyzed the risk factors and compared survival between colorectal cancer metastasis and HCC. The identified high-risk factors include a CEA level over 80, the largest tumor being over 5.5 centimeters, a duration of less than two years between primary surgery and liver transplantation, and disease progression at the time of transplant. If patients have these risk factors, outcomes may not be satisfactory. However, if patients do not have these risk factors, the survival outcomes for colorectal cancer with liver metastasis can be similar to, or even better than, those for HCC.

This emerging data justifies considering liver transplantation for carefully selected patients with colorectal cancer metastasis, offering them a significant survival benefit. Additionally, new promising data on this topic was presented at ASCO (American Society of Clinical Oncology) just two months ago. This study is currently under review and should be published soon.[5]

European Study on Colorectal Liver Metastasis

A recent controlled study from Europe provides more evidence on this topic. The study looked at a total of 94 patients, with 47 in the chemotherapy alone group and 47 in the liver transplant plus chemotherapy group. The results are striking: five-year survival was 93% in the liver transplant plus chemotherapy group, compared to only 9% in the chemotherapy-alone group. This suggests that combining liver transplantation with chemotherapy significantly improves survival in patients with unresectable colorectal liver metastasis compared to chemotherapy alone, which is highly promising data. I'm eagerly awaiting the publication of this paper, which should be available soon.

To summarize the future perspective for liver transplantation in colorectal metastasis, highly selected patients could benefit from liver transplants. However, they must meet specific criteria: CEA levels below 80, the largest lesion not exceeding 5.5 centimeters (though there's still some debate about this size, with UNOS allowing for tumors up to 10 centimeters), a duration of over two years between primary surgery and liver transplantation, and no progression of the disease at the time of transplant. This emerging field, transplant oncology, is expanding the possibilities of liver transplantation for cancer patients.

The major indication for liver transplantation remains HCC, but colorectal metastasis is increasingly being considered. Additionally, other indications include hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, neuroendocrine tumors, and mesenteric desmoid tumors, all of which fall under the umbrella of transplant oncology.

[5] Rene Adam et al., Chemotherapy and liver transplantation versus chemotherapy alone in patients with definitively unresectable colorectal liver metastases: A prospective multicentric randomized trial (TRANSMET). JCO 42, 3500-3500 (2024). DOI:10.1200/JCO.2024.42.16_suppl.3500

Organ Procurement and Normothermic Machine Perfusion

Donor organs are, of course, a limited resource. There were about 24,000 patients on the liver transplant waitlist in 2022, and by the end of the year, over 10,000 patients were still waiting.[6] However, the actual number of available donors is far fewer than the number of patients on the waitlist, highlighting the scarcity of this resource. To address this, we have two main strategies: increasing the number of donations and decreasing the rate of discarded organs. Although many donor organs are available, various factors prevent their utilization.

For example, in donation after circulatory death (DCD), the traditional limit for liver transplantation has been 30 minutes—if the donor doesn't expire within this window, the liver typically isn't used. However, recent advancements in technology, specifically normothermic machine perfusion (NMP) (**Fig. 10**), are changing this. This technology allows the liver to be placed on a machine where human blood is circulated through it, maintaining function and producing bile while being monitored for blood flow and pressure. This innovation has significantly expanded the donor pool. With NMP, we can now consider livers even if the donor expires within 60 minutes, not just 30. The liver can recover on the pump, minimizing ischemic damage, and then be transported to the recipient hospital, where it is immediately implanted. This process reduces ischemic damage, making it possible to expand the liver donor pool, especially for DCD donations.

NMP also allows us to consider using older donors, such as those over 75 or even 80 years old, and previously unsuitable fatty livers. In the past, if a liver had more than 30% macrosteatosis, it was often considered unusable due to the poor function and the high risk of ischemic damage. However, with NMP, the combination of fatty liver and ischemic damage becomes less problematic, enabling us to utilize these organs as well.

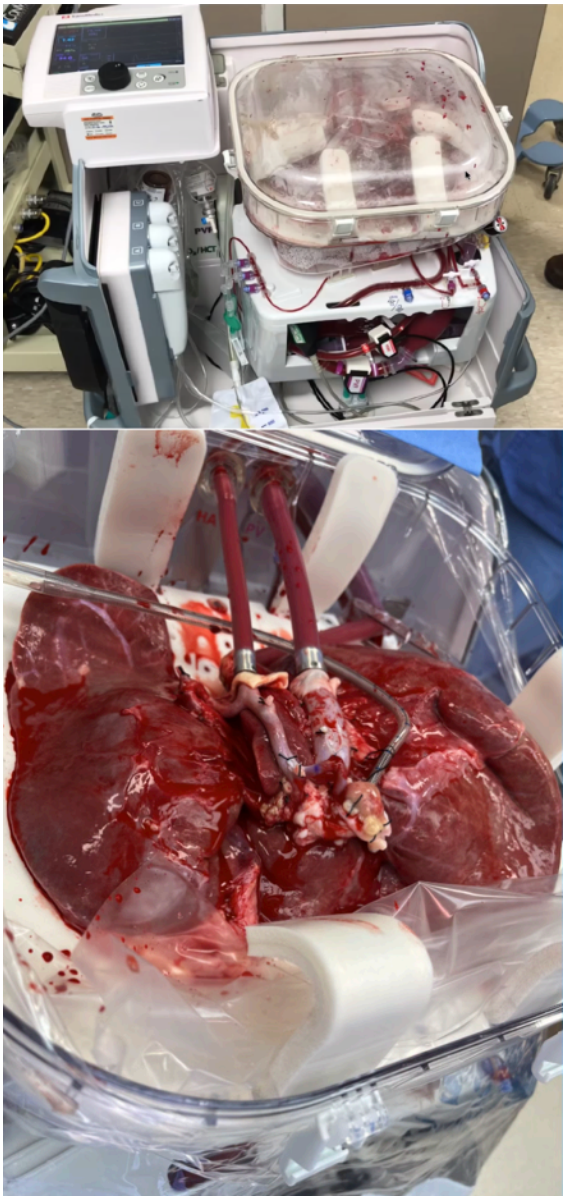


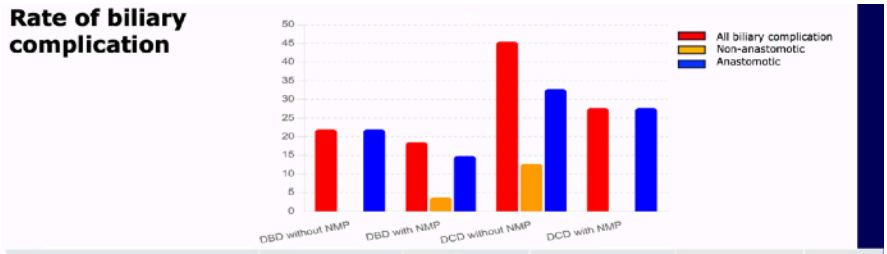
Fig. 10. **Normothermic Perfusion Machine**

Interestingly, this technology is not limited to liver transplants. For instance, heart transplants can now be performed using DCD donors. Even after the heart has stopped, it can be placed on a similar pump, where it begins to beat again, and then it can be transplanted. This has the potential to ex-

[6] Kwong, Allison J et al. “OPTN/SRTR 2022 Annual Data Report: Liver.” American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons vol. 24,2S1 (2024): S176-S265. doi:10.1016/j.ajt.2024.01.014

pand the donor pool for heart transplants significantly.

At Henry Ford, we've been using normothermic machine perfusion for liver transplants for almost eight or nine years, participating in national clinical trials from the beginning. Our experience has shown promising results. For example, ischemic cholangiopathy—a condition where the liver's bile ducts suffer from diffuse strictures and damage, potentially leading to graft loss and patient death—occurred in about 12% of DCD liver transplants without NMP. However, with NMP, this complication rate dropped to zero, which has a significant impact on patient outcomes (**Fig. 11)**.



Factor	DBD without NMP	DBD with NMP	DCD without NMP	DCD with NMP	P value
All Biliary complication <180 days post-LT (%)	64 (21.9)	5 (18.5)	25 (45.5)	13 (27.7)	<.01
Ischemic cholangiopathy <180 days post-LT (%) (non-anastomotic)	0 (0.0)	0(0)	7 (12.7)	0 (0.0)	<.01
Anastomotic biliary complication (Stricture or leak) <180 days post-LT (%)	64 (21.9)	4 (14.8)	18 (32.7)	13(27.7)	.21

Fig. 11. **Rate of Biliary Complication**. *Source:* Kirby, E. et al. Normothermic Machine Perfusion in Donation After Circulatory Death for Liver Transplants May Not Reduce Risks of all Biliary Complications. Rapid Fire Oral Abstract at ATC2024 on June 2, 2024.

We initially expected that using NMP would reduce biliary complications like strictures or leaks from anastomoses, but we didn't observe a significant change in these rates. We investigated why and found that one patient who received a brain-dead donor liver with NMP had a long segmental anastomotic stricture, which is unusual. Typically, strictures are focal, occurring in small segments. In this case, the stricture extended about two centimeters, leading us to believe that the edge of the bile duct wasn't perfused well enough by the machine. In the future, we may need to trim the bile duct more extensively to prevent such complications.

NMP is now a commercialized technology available to any transplant center, and we use it in about 30% to 40% of liver transplants, contributing to better outcomes. Another technique that expands the donor pool is normothermic regional perfusion (NRP), which is specifically designed for DCD donors.

Normothermic Regional Perfusion (NRP)

To simplify the explanation of NRP, let's look at how it works with a DCD donor. After the donor's heart stops, we wait for a mandatory "no-touch" period, typically around five minutes. Instead of immediately starting the organ procurement surgery, we can initiate ECMO (Extracorporeal Membrane Oxygenation) to restart circulation in the donor's body. This allows blood to flow through the organs again, stabilizing their condition over a couple of hours before we begin the procurement surgery. This process makes the procedure more like brain-dead donor procurement, where everything can be done calmly and carefully.

NRP essentially restores circulation in the donor's body using ECMO. There are two main types of NRP: abdominal NRP, which circulates blood through the abdominal organs, and thoracoabdominal NRP, which circulates blood through the heart, lungs, and all organs. At places like the University of Michigan, thoracoabdominal NRP is used for almost every DCD case. Other centers, like ours, are starting to implement abdominal NRP programs. For out-of-state donors, we might send a team to perform abdominal NRP, allowing us to make better use of DCD organs.

Recent data published in JAMA Surgery showed that using NRP significantly decreases the rate of biliary complications, such as ischemic strictures, compared to static cold storage. In fact, ischemic cholangiopathy was reduced to zero in NRP cases.

This technology is making a substantial contribution to improving liver transplant outcomes in DCD cases. (**Fig. 12**, next page)

Living Donor Liver Transplantation

Next, let's shift gears to discuss living donor liver transplantation. Deceased donors account for nearly 90% of liver transplants, with living donors making up just 3-5%. In living donor liver transplantation, we must carefully decide which portion of the liver to use—either the left or right lobe.

The right lobe comprises about 60-70% of the liver and is usually used for larger recipients, while the left lobe is smaller and may be used for recipients with smaller body sizes, such as females or lean individuals. However, the size of the donor's body also plays a role in this decision. The most crucial factor in living donor liver transplantation is donor safety. Since donors are healthy individuals undergoing major surgery voluntarily, we must minimize the risk of post-operative complications.

Comparing outcomes, data shows that donors who undergo left lobe resection have a significantly lower risk of post-operative complications, such as bile leaks, abscesses, or ascites, compared to those who donate the right lobe. Therefore, from a safety perspective, using the left lobe is often preferable.[7,8]

However, the size of the graft must be carefully matched to the recipient's body weight. The graft-to-recipient weight ratio (GRWR) is a key metric: if the graft weight is less than 0.8% of the recipient's body weight, there is a higher risk of complications. For example, in a 100-kilogram recipient, a liver graft weighing 800 grams would have a GRWR of 0.8%. While techniques and outcomes have improved significantly since this threshold was first established, the size of the graft still matters. A graft that is too small can lead to

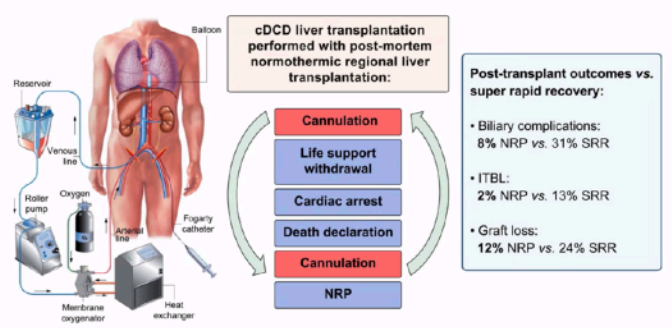


Fig. 12. **Normothermic Regional Perfusion (NRP)**. *Source*: Hessheimer, AJ, et al. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *Journal of Hepatology* 70:4, 658-665. 2019. https://doi.org/10.1016/j.jhep.2018.12.013.

complications such as small-for-size syndrome, which includes issues like biliary complications, ascites, bleeding, infection, and renal dysfunction. These complications are difficult to manage once they occur, so accurate size assessment is crucial in living donor liver transplantation.

Overcoming Small-for-Size Syndrome

To overcome small-for-size syndrome (SFSS) in living donor liver transplantation, several strategies can be employed, focusing primarily on the modulation of portal flow. It's been established that high portal flow and pressure can cause injury to the liver graft, which in turn increases the risk of SFSS. By controlling and reducing portal flow and pressure, we can mitigate this risk.

Here are the main approaches to manage portal flow:

- *Splenic Artery Ligation*: This involves ligating the splenic artery at its bifurcation from the celiac artery. By doing so, the blood flow to the spleen is reduced, which in turn decreases the outflow from the spleen and ultimately lowers portal flow to the liver graft.[9]

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[7] Brubaker, Aleah L et al. "US Liver Transplant Outcomes After Normothermic Regional Perfusion vs Standard Super Rapid Recovery." *JAMA surgery* vol. 159,6 (2024): 677-685. doi:10.1001/jamasurg.2024.0520

[8] Kiuchi, T et al. "Impact of graft size mismatching on graft prognosis in liver transplantation from living donors." *Transplantation* vol. 67,2 (1999): 321-7. doi:10.1097/00007890-199901270-00024

[9] Troisi R, et al. Modulation of portal graft inflow: a necessity in adult living-donor liver transplantation? Ann Surg. 2003 Mar;237(3):429-36. doi: 10.1097/01.SLA.0000055277.78876.B7. PMID: 12616129; PMCID: PMC1514313.

- *Splenectomy*: A more aggressive approach is to remove the spleen entirely. This significantly reduces the return flow from the spleen, thereby decreasing portal pressure.[10]
- *Splenic Artery Embolization*: This procedure can be performed after transplantation if signs of SFSS develop. Interventional radiology (IR) can embolize the splenic artery, reducing portal flow and helping to alleviate SFSS.

Summary of Graft Types in Living Donor Liver Transplantation:

Right Lobe Grafts: These are larger, providing a better match for the recipient in terms of liver function but carry a higher risk of complications for the donor. The larger size of the graft makes it less likely to cause SFSS, but donor safety must be carefully managed.

Left Lobe Grafts: These are smaller and pose a lower risk to the donor, but they come with a higher risk of SFSS in the recipient, especially if the graft size is not sufficient. Careful assessment is crucial to avoid complications.[11]

Experience and Outcomes

Since 2000, we have performed over 200 living donor liver transplants. Good candidates for living donor transplants typically have a low MELD score but significant symptoms, such as refractory ascites or hepatic encephalopathy. These patients are unlikely to receive a deceased donor liver in a timely manner but can achieve excellent outcomes with a living donor transplant. Our one-year survival rate for these patients is about 95%, which is significantly better than national averages. The complication rate for donors is approximately 24%, with severe complications (grade IIIA or above) occurring in about 10% of cases. We have not encountered any cases with complications exceeding grade III.

Our surgical technique for living donor liver transplants involves a mini-incision approach.[12] We utilize a laparoscopic camera from the outset to mobilize the liver, which allows us to perform the entire right lobe resection through a 10-centimeter incision. Over the last 15 years, we have consistently completed these procedures without needing to extend the incision.

Multi-Visceral Transplantation

Multi-visceral transplantation involves transplanting all abdominal organs together, including the stomach, pancreas, intestines, colon, and liver. The classic indication for this procedure is short gut syndrome with liver failure, although it is relatively rare. More commonly, we see patients with diffuse portal and mesenteric thrombosis, with or without liver cirrhosis. In these cases, a good inflow for the liver is essential, but if the mesenteric blood vessels are thrombosed, a multi-visceral transplant becomes necessary. This procedure is also indicated for patients with unresectable neuroendocrine tumors with liver metastasis, where a comprehensive transplant of multiple organs can offer the best chance for survival.

Transplant Oncology and Neuroendocrine Tumors

This is another innovative concept in transplant oncology. Neuroendocrine tumors can originate in the pancreas, mesentery, or other parts of the gastrointestinal system and may metastasize to the liver, making them unresectable. If the primary tumor is still present, one potential approach is to remove all af-

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[10] Ogura, Yasuhiro et al. "Portal pressure <15 mm Hg is a key for successful adult living donor liver transplantation utilizing smaller grafts than before." Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society vol. 16,6 (2010): 718-28. doi:10.1002/lt.22059

[11] Iida, Taku et al. "Surgery-related morbidity in living donors for liver transplantation." *Transplantation* vol. 89,10 (2010): 1276-82. doi:10.1097/TP.0b013e3181d66c55

[12] Nagai, Shunji et al. "Mini-incision right hepatic lobectomy with or without laparoscopic assistance for living donor hepatectomy." Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society vol. 18,10 (2012): 1188-97. doi:10.1002/lt.23488

fected organs and achieve a "cancer zero" state by performing a multi-visceral transplant. Although rare, this procedure can be done with careful patient selection.

The procedure is particularly suited for patients with a complex surgical history, such as those with protein-losing enteropathy, enteric fistulas, or uncontrollable fistulas requiring decompression tubes, where the abdomen has become a "surgical catastrophe." In these cases, a multi-visceral transplant, where the liver, pancreas, stomach, and intestines are transplanted en bloc, can be lifesaving.

The surgical technique is conceptually straightforward but technically challenging. There are only two main inflows to consider: the superior mesenteric artery (SMA) and the celiac artery. During the procedure, the donor's aorta, including patches from the SMA and celiac artery, is connected to the recipient's aorta in a single arterial anastomosis. The outflow from all these organs is managed through the hepatic vein, which is connected to the inferior vena cava (IVC), similar to a standard liver transplant. After the connections are made, the upper gastrointestinal tract is connected to the lower gastrointestinal tract. Although the concept is simple, the procedure typically takes over 12 hours.

For example, a fellow and I performed this type of surgery nearly 10-15 years ago. We connected the donor's thoracic aorta to an aortic patch that included the SMA and celiac arteries for the inflow. After retrieving the organs, nothing remained in the abdomen, so we placed the entire block of organs—intestines, liver, pancreas, and stomach—into the recipient's abdomen. We then connected the IVC, clamping and unclamping it like in a standard liver transplant. The entire process of reconnecting the bowel, achieving hemostasis, and ensuring proper organ perfusion took several additional hours.

Here are two specific examples:

- *A Patient with a Sclerosed SMA*: This patient was critically ill, with a massively dilated gastrointestinal tract requiring decompression and nearly all the bowel resected. We performed a multi-visceral transplant, removing all affected organs and replacing them with new ones.
- *A Neuroendocrine Tumor Patient*: This patient had multiple liver metastases and a primary tumor still present in the mesentery and pancreas. We achieved a "cancer zero" state by resecting all affected tissues and performing a multi-visceral transplant.

Xenotransplantation: The Future of Organ Transplantation?

In addition to multi-visceral transplantation, there's emerging interest in xenotransplantation—transplanting organs from animals to humans. Although not yet a common practice, this could represent the future of organ transplantation. Recently, a team at Massachusetts General Hospital performed a xenotransplant using a pig kidney in a human. The patient survived for about two months, with the kidney functioning well, although the patient eventually died from a cardiac event. While xenotransplantation is still in its early stages, it holds promise for addressing the shortage of human donor organs.

Conclusion

In summary, liver transplantation continues to evolve, expanding its role in treating not only liver diseases but also cancers through transplant oncology. We've seen numerous innovations, such as NRP and NMP, and have taken on challenging surgeries like living donor and multi-visceral transplants. The field is dynamic, with many exciting developments on the horizon, including the potential for xenotransplantation.

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