

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Expanding Liver Transplant Indications for Colorectal Liver Metastases and Cholangiocarcinoma



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G&H What is driving the expansion of liver transplant indications for malignancies such as colorectal liver metastases and cholangiocarcinoma?

VL Advancements such as normothermic regional perfusion, machine perfusion, and donation after cardiac death have increased access to more organ donors than historically. There has been a 70% increase in liver transplants since 2014, according to data from the Scientific Registry of Transplant Recipients. Approval of advanced perfusion technologies by the US Food and Drug Administration in 2021 as well as other technologies have improved donor organ viability and reduced ischemic injury, allowing for more livers to be transplanted. Having more donors available allows for the possibility of expanding indications for liver transplant.

Additionally, there has been a change in the perspective of the goal of transplant in patients with carcinoma, which traditionally has focused on disease-free survival and overall survival to a more comprehensive assessment that includes survival benefit, secondary treatment of recurrences, and quality of life. With improved understanding of tumor biology and microgenomics, it is now possible to better identify patients who would have a meaningful addition to their survival, even with cancer recurrence. We can better select patients who would have a positive outcome after transplant.

G&H What criteria are being used to select liver transplant candidates for colorectal liver metastases?

VL For liver transplant in a patient who has colorectal

liver metastases, it is most important to identify that the patient is not a candidate for resection. This requires a multidisciplinary team and assessment of the volume of disease in the liver. There are specific criteria for liver transplant for colorectal liver metastases. Institutions have refined the criteria with clinical trials to help identify which patients would have better overall and tumor-free survival. These criteria universally use laboratory values such as carcinoembryonic antigen, which is a serologic marker for colorectal cancer, and also examine imaging very closely. Patients are then assessed for the genetics of

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their tumor, as certain colorectal cancers have mutations that are very high risk for aggressive recurrence. Patients are also placed on a protocol that includes a minimum of 6 months of chemotherapy. During that time, we are able to assess whether a patient has a good response to the chemotherapy, if their disease is maintained within the liver only, and if the patient is someone who would have a beneficial outcome after liver transplant. Thus, only a very small subset of patients with colorectal cancer with liver metastases would qualify for a liver transplant because of these stringent criteria.

G&H How does long-term survival after liver transplant for this indication compare with other approaches such as resection or chemotherapy?

VL Colorectal cancer is one of the most prevalent malignancies worldwide. Blood from the colon is drained by the portal vein, and then the first site the blood goes through is the liver before going to the rest of the body. Therefore, approximately 50% of patients who have colorectal cancer develop liver metastases at some point during the course of their disease. Unfortunately, survival is incredibly low for patients who are diagnosed with colorectal cancer with liver metastases; less than 50% of patients will be alive in 5 years. Only 20% or 30% of patients are candidates for resection at the time they are diagnosed with liver metastases. Thus, many patients develop liver metastases, but very few qualify for resection.

Even if patients qualify for standard treatment options such as systemic chemotherapy and surgical resection, 5-year survival is only approximately 40% to 60%. Conversely, if a patient is selected for liver transplant, which again is a very specific, highly selected subset, 5-year survival can increase to 83%. Essentially, survival almost doubles if patients with colorectal liver metastases qualify for liver transplant.

G&H How common is recurrence following liver transplant for this indication, and what posttransplant surveillance is recommended?

VL Recurrence of colorectal cancer after liver transplant is very common. Again, we are looking at the goal of increased survival and quality of life, not just cancer-free survival. As I just mentioned, overall survival at 5 years was 83% in one study. However, at least 70% of those patients experienced recurrence of their cancer. Cancer recurs but does not impact survival, which is why our perspective has changed. We know there is a very high likelihood that the cancer will come back, most commonly in the lungs, but with chemotherapy and adjustment of posttransplant protocols, this recurrence does not mean that the patient will necessarily die from their disease. Because most of these recurrences are very slow-growing, very intense postoperative surveillance is used that requires frequent imaging and serologic testing. The posttransplant immunosuppression protocol is also adjusted because most cancers have a higher risk of recurrence on high amounts of immunosuppression. Thus, the type of immunosuppression is changed to a mammalian target of rapamycin inhibitor, which has a theoretical antineoplastic effect, in patients who receive a liver transplant to try to reduce the aggressiveness of recurrence. There are also many

biomarkers that may help with patient selection and early identification of recurrence in the future. The integration of personalized oncology will help improve outcomes in these posttransplant patients for the long haul.

G&H What criteria should be used to determine which patients are candidates for liver transplant for perihilar cholangiocarcinoma?

VL Liver transplant for perihilar cholangiocarcinoma has been performed in the United States for over a decade now. The initial criteria are known as the Mayo Clinic Protocol and are widely used across the United States. Patients who qualify for this protocol receive Model for End-Stage Liver Disease tumor exception points. Previously, these patients would not qualify to be transplant candidates. With this protocol, patients need to have a malignant-appearing stricture on either endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography, their cancer antigen 19-9 (CA 19-9) level should be greater than 100 U/mL, and either tissue brushings or a biopsy should be performed via endoscopy, not percutaneously. These findings help us understand whether a patient is potentially a transplant candidate for cholangiocarcinoma. Patients with metastatic disease or previous attempts at resection are not candidates because having a transplant would unfortunately not help their disease if it is already extrahepatic.

G&H Could you discuss liver transplant for early-stage or downstaged intrahepatic cholangiocarcinoma?

VL Intrahepatic cholangiocarcinoma is another indication for liver transplant. Most importantly, it does need to be early stage in order to justify utilization of the scarce resource of a liver donor for these patients. The tumor typically needs to be a solitary mass that is less than 3 cm in order to qualify for a liver transplant.

G&H What recurrence risk factors have emerged for cholangiocarcinoma patients posttransplant, and how do they inform surveillance or adjuvant therapy?

VL In my opinion, posttransplant recurrence of any type of carcinoma often has to do with pretransplant selection. Knowing the tumor biology and the extent of the disease prior to the transplant is the best way to prevent posttransplant recurrence. That is why we have highly scrutinized protocols involving neoadjuvant chemotherapy, tumor size, and surveillance. The most common risk

factors for recurrence are pretransplant variables such as the preoperative CA 19-9 level as well as nodal involvement or vascular invasion at the time of surgery, which can impact the risk of recurrence and increase recurrence within the first year of transplant. If a patient has a high probability of recurrence, their surveillance protocol is

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much more frequent as well as more aggressive. Their immunosuppression should also be adjusted. It is important to work in collaboration with medical oncologists for the early identification of patients who may benefit from posttransplant systemic therapy.

G&H Might expanding indications for liver transplant raise challenges regarding organ equity and scarcity?

VL It is very important that the transplant community does its best to continue equitable access to liver transplant. This requires responsible innovation and close monitoring of metrics for success. The transplant community has a responsibility to continue to collaboratively collect outcomes data, review the data regularly, and adjust protocols. Some strategies include utilizing living donor liver transplant, using liver grafts that may have previously been considered marginal, and utilizing different technologies to optimize a donor's liver that may have previously been discarded. Utilizing these avenues would not impact the donor pool for other etiologies since they are using donor livers that would otherwise not have been in the pool of donors for standard indications.

G&H Looking ahead, which other malignancies do you think are most likely to be incorporated into liver transplant indications next?

VL There has been some discussion of liver transplant for other types of carcinomas such as neuroendocrine tumors and liver sarcomas. There is already some evidence for liver transplant for metastatic neuroendocrine tumors. If these tumors are well-differentiated, patients have favorable outcomes after liver transplant, although these are not disease-free outcomes. The aforementioned shift in perspective of disease-free survival vs survival overall has opened up possibilities for probably most types of tumors that are isolated to the liver. The key, however, is the standard that most transplant centers use as an acceptable outcome—5-year patient survival above 50% to 60%.

G&H What has been learned in this area?

VL We have learned a lot through small clinical trials and fine-tuning selection criteria and then expanding protocols on a more international level. Much has also been learned from hepatocellular carcinoma—for example, that outcomes need to be continually analyzed and selection criteria adjusted in order to maintain the equity of outcomes among different indications.

Disclosures

Dr Loy has no relevant conflicts of interest to disclose.

Suggested Reading

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