

# Liver transplantation for unresectable colorectal liver metastasis

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The rapid progression in the development of liver transplantation during the last decade is largely attributed by the standardization of operative techniques (1,2) and advances in the pharmacokinetics of immunosuppressive therapy (3). Such improvements in the perioperative management have rendered liver transplantation a safer operation and in turn translated into better long-term survival (4,5). As such, the indication for liver transplantation has been expanded to include malignant liver tumor other than liver cirrhosis. Since the proposal of Milan criteria by Professor Mazzaferro in the late 1990s, liver transplantation has been universally adopted as the curative treatment for early staged hepatocellular carcinoma (HCC) in patients with liver cirrhosis (6). As a result, the 5-year overall survival rate has reached up to 70% in various series (7,8). More importantly, the introduction of Milan criteria has since revolutionized the indications for transplantation and the allocation policy for cadaveric organs.

As success was witnessed in the surgical management of HCC with transplantation, the indication has been extended to include other form of solid liver malignancies such as neuroendocrine liver metastasis and cholangiocarcinoma in the hope that similar survival outcome could be attained.

Neuroendocrine tumor is a highly vascular tumor with variable aggressiveness. It embraces a wide spectrum of tumor that arises from the neuroendocrine cells in the gastrointestinal tract and pancreas. For untreated neuroendocrine liver metastasis, the 5-year survival is approximately 30-40%. With transplantation, the survival for patients with unresectable neuroendocrine liver metastasis has drastically improved to 80% at 5 years in recent study (9). On the other hand, transplantation in patients with cholangiocarcinoma had a longer history

of development that could be dated back to the early 1990s. At that time, the outcome was rather disappointing with a 5-year survival rate of merely 5-10% (10). With the advancement of chemoradiation in recent years, the survival outcome has been drastically improved. Using the Mayo protocol i.e., neoadjuvant radiotherapy, chemosensitization with 5-FU and oral capecitabine for patients with early cholangiocarcinoma <3 cm and concomitant primary sclerosing cholangitis, both the 3- and 5-year survival rates are reported to be approximately 80% respectively (11).

Despite the improved oncological outcome of liver transplantation to non-HCC liver tumor, the experience so far is limited to certain centers only. The lack of enthusiasm of transplant centers to embark on such a program is partly related to the scarcity of donor organ that prohibits a liberal allocation other than to those with end-stage liver diseases or early staged unresectable HCC. Second, the uncertain malignant potential of these tumors and the variable oncological outcomes after transplantation are major concerns for adoption of such treatment strategy. It is noteworthy to highlight that since this group of patients, by enlarge does not have liver failure or complications related to cirrhosis, the primary endpoint that defines the efficacy of transplantation in this setting should be the recurrence-free survival and overall survival. A high recurrence rate after transplantation could potentially pose another challenge to the clinicians. From our experience in HCC, recurrence after liver transplantation is often extrahepatic (12) and the lack of effective treatment options for extrahepatic recurrences is another important reason that limits the widespread application of transplantation to other types of liver malignancy.

As the incidence of colorectal cancer is on a rising trend in the developed world, it is conceivable to anticipate that the frequency of colorectal liver metastasis is bound to increase in the forthcoming era. Resection has been proven to be an efficacious treatment for colorectal liver metastasis with a 5-year survival rate of 40-50% (13,14). However, multiple bilobar liver metastases occur frequently that often preclude patients from potentially curative resection. In the May 2013 issue of *Annals of Surgery*, Hagness and co-workers proposed the use of transplantation for unresectable colorectal liver metastasis and reported their preliminary experience in twenty-one patients (15). The 5-year overall survival rate was 60% and eight patients remained eligible for further treatment when recurrences were developed. Although the findings of this study seemed to be rather promising, one has to be cautious on further analyzing their results. First, there were no standardized selection criteria for recruitment of patients for this treatment. Second, the follow up duration was merely 27 months with less than 50% of patients available for assessment at 3 years. More importantly, only 35% patients remained recurrence free at one year and no patient was recurrence free at two years. With regard to the post-transplant management, mTOR inhibitor was the preferred immunosuppressive agent for this cohort of patients. It remains questionable if mTOR inhibitor could inhibit the proliferation of metastatic cancer cells and in light of a 38% acute cellular rejection rate among their patients, the efficacy of adopting such immunosuppressive regimen is certainly subject to skepticism.

In my opinion, it is difficult to concur with the authors that liver transplantation is a feasible treatment for unresectable colorectal liver metastasis based on the survival figures that were provided by Hagness and co-workers (15). More clinical data needs to be accumulated by this center before we can truly 'say' this treatment strategy is feasible with oncological benefit. Until this time, liver transplantation for unresectable colorectal liver metastasis should not be undertaken as a routine procedure.

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