Editorial

# Liver transplant oncology: is it time to revisit our ideas?

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Scarcity of cadaveric liver donors compared with the large number of patients with liver disease has been considered the main obstacle to use liver transplantation (LT) to treat hepatic malignancies and for the development of transplant oncology.

It is known that we are experiencing a true paradigm shift in the fundamental problem of transplantology, which is none other than the imbalance between donation and graft implants (1). Because the most common indication of LT in most countries [hepatitis C virus (HCV) cirrhosis] has started to decrease in the waiting lists (2,3). One might think that, for the first time in many years in Western countries, we could find a higher supply of organs than recipients for them.

In the last decade, great advances in the understanding of the genome and protein structure of the HCV have allowed the improvement of efficacy of its infection treatment. Multiple direct-acting antivirals (DAA) that target specific steps of the virus life cycle have been developed (4). Defined by their mechanism of action, four classes of DAA are described:

(I) Non-structural proteins 3/4 (NS3/4A) protease inhibitors (PIs) (suffix "previr");
(II) NS5B nucleoside polymerase inhibitors (NPIs) (suffix "buvir");
(III) NS5B non-nucleoside polymerase inhibitors (NNPIs);
(IV) NS5A inhibitor (suffix "asvir").

Most DAA are used as part of mixed-dose combinations for the treatment of chronic HCV disease. The treatment results in more than 90% sustained response of the hepatitis without undetectable HCV copies in the PCR blood examination. The use of second generation DAA agents since 2013 in the treatment of HCV infection has decreased the rate of LT waiting list for HCV complicated by decompensated cirrhosis by over 30% (3,4). Progressively diminished this end-stage liver disease as a leading indication for LT in most Western countries, such as the USA and Spain (5,6).

Scandinavia is a region where this has already happened. Primary sclerosing cholangitis, acute hepatic failure, alcoholic liver disease, primary biliary cirrhosis and hepatocellular carcinoma (HCC) have been historically the five most frequent primary indications, in this order, for LT in Scandinavian countries. Although over the recent years, there has been a steadily increasing number of patients referred for LT due to HCV cirrhosis, up to more than 10% of all indications of LT. HCV infection epidemic seems to have a time-shift as compared with the rest of the Western world. HCV and hepatitis B virus (HBV) prevalence has been low in the Nordic countries and cirrhosis due chronic C or B viral infection has accounted for only a small proportion of LT there (7). So, the lack of HCV cirrhotic patients to be transplanted, improved expanded oncologic criteria for LT, because the liver graft offer starts to exceed the demand.

Primary and secondary hepatic tumors have been considered formally a contraindication for LT. There are some accepted exceptions in very selected cases of small localized HCC following the Milan criteria (8), because survival after LT in patients with liver cirrhosis is similar to patients with small HCC (9). Other accepted indications for LT are hepatic metastases of well differentiated neuroendocrine tumors.

Hepatic metastases of colorectal carcinoma (CRC) are the most frequent secondary tumor of the liver. LT for hepatic metastases of CRC was performed at the beginning of LT with a 5-year overall survival (OS) of less than 20%. Due to the dismal results and the scarcity of cadaveric liver donor, LT was abandoned at that time.

However, during the last 30 years response to chemotherapy for CRC has dramatically improved. Results of LT are also better with a postoperative mortality lower than 10%. For these reasons LT has recently been proposed as an alternative treatment for unresectable colorectal liver metastases in selected patients with a 60% estimated OS at 5 years in a recent (SECAI) prospective Norwegian study (10). However, disease-free survival (DFS) in this preliminary study was poor with a 90% recurrence after LT.

A standard immunosuppressive protocol proposed by the University of Oslo team for unresectable CRC liver metastases consists of avoiding as early as possible calcineurin inhibitors and including antiproliferative immunosuppressors. Induction immunosuppression consists of Basiliximab (an anti-CD25 monoclonal antibody), tacrolimus (an anti-calcineurin inhibitor) for 4–6 weeks and then conversion to sirolimus (an M-TOR inhibitor). Glucocorticoids and mofetil mycophenolate (MMF) are also used during the induction immunosuppression for 3–6 months.

In a more recent study from the same group (SECAII), 15 patients were treated by LT for liver-only metastases of CRC (11). The patients had more than one year from diagnosis of CRC liver metastases and time of listing for LT. Extrahepatic disease was discarded using positron emission tomography and computed tomography (PET-CT) and at least 10% response to chemotherapy was required. Tumors were smaller than 5 cm after chemotherapy and carcinoembryonic antigen (CEA) lower than 30 µg/mL. OS at 1, 3 and 5 years were 100%, 83% and 83%. The 1-, 3- and 5-year DFS were 100%, 73% and 73%. In the SECAI study all patients that have been observed for more than 11 months after LT presented a recurrence. While in the SECAII study 4 patients had no relapse with a follow-up of 31 to 49 months.

These results should be considered excellent and suggest that liver metastases of CRC may be considered a good indication for LT in very selected patients with liver-only CRC metastases.

However, several authors showed their disagreement with various aspects of the study (12). Criteria for unresectability varies greatly among surgeons in different centers and studies. Techniques of liver resection for CRC liver metastases has also improved with the introduction of portal vein embolization (PVE), two stage liver resection, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure and other surgical techniques have greatly extended our ability to safety resect many lesions from the liver and should be considered an alternative to LT (12).

A novel concept published in 2015 was a hybrid of the auxiliary LT and the ALPPS procedure (13). The resection and partial liver segments 2–3 LT with delayed total hepatectomy (RAPID) propose a two stage hepatectomy. The first step consists of segment 1–3 resection and transplantation of a left lateral segment (2 and 3) graft. After the donor graft reaches the 0.8% body weight, or 35–45% standard liver volume, a standardized portion of the native liver is resected.

In the March issue of JAMA Surgery, the Oslo group presents original investigation data that see LT for CRC in a new light (14). Fifty patients with unresectable liver metastases of CRC, previously enrolled in LT studies between 2006–2019, were compared with a retrospective cohort of well-matched 53 patients with similar selection criteria who underwent PVE and liver resection. In an intention to treat analysis, fifteen (28%) of the PVE group did not undergo liver resection due to tumor progression or insufficient liver regeneration. All patients enrolled in the transplant list underwent LT.

For each patient the tumor burden score (TBS) was calculated. TBS is the Cartesian result using the Pythagorean theorem of the maximal tumor diameter and number of LM. Patients were divided in 3 groups, according to the TBS model. Zone 1 (TBS <3), zone 2 (TBS 3 to <9) and zone 3 (TBS >9) (15). There were no differences among 3 groups regarding the TBS.

In the PVE group, there was a significant difference in 5-year OS between patients who underwent only PVE 0% and PVE with liver resection 40%. There was also a significant difference in 5 years of OS in patients of the PVE with low 50% and high TBS 8%.

Among the patients in the LT group there was a significant difference in 5-year OS, when the primary tumor had a high TBS. In the ascending sided primary tumor 5-year OS was 20% while in the sigmoid and left sided primary tumor was 60% in the high TBS groups. This study demonstrates that LT has a definitive role in the treatment of liver-only CRC metastases and is superior to other surgical techniques like PVE.

However, considering the scarcity of cadaveric donors,

 

it is important to select the best candidates with the highest possibilities of survival. In patients with high TBS, a right-sided primary has a low survival. LT should be indicated with caution in this group of patients.

There is, however, an ongoing multicenter liver transplant trial (Transmet). Patients with liver-only metastases of CRC are randomized comparing patients receiving neoadjuvant chemotherapy and LT, versus chemotherapy alone. The endpoint is the 5-year OS. Results will show the real role of chemotherapy with or without LT (16).

We dare to conclude that what for a long time was considered a practically absolute contraindication for LT nowadays is beginning to be thought of as a growing indication with a solid future. So, without any doubts, the era of transplant oncology has already started (17).

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