Perspective

Liver transplant for patients outside Milan criteria

Giovanni Battista Levi Sandri[1], Michel Rayar[2], Xingshun Qi[3], Pierleone Lucatelli[4]

[1]Department of Surgical Sciences, Sapienza University of Rome, Rome 00161, Italy; [2]Service de Chirurgie Hépatobiliaire et Digestive, CHU Rennes, Rennes, France; [3]Department of Gastroenterology, General Hospital of Shenyang Military Area, Shenyang 110000, China; [4]Department of Radiological Oncological and Anatomo-pathological Sciences, Vascular and Interventional Unit, Sapienza University of Rome, Rome, Italy

Correspondence to: Giovanni Battista Levi Sandri. Department of Surgical Sciences, Sapienza University of Rome, Rome 00161, Italy.
Email: gblevisandri@gmail.com.

Abstract: Hepatocellular carcinoma (HCC) is one of the most indication to Liver Transplantation (LT). Milan criteria are worldwide accepted as the gold standard for LT indication for HCC. Nevertheless, expanded criteria are often used to transplant patient outside Milan. We described the most important proposed criteria outside Milan criteria. From the University of California San Francisco, to the Toronto criteria. From East to Western, and for living donor liver transplantation. In order to achieve similar results the downstaging strategy is more frequently used and for patients with locally advanced HCC. Carefully selected patients beyond the traditional criteria for transplantation may achieve excellent LT outcomes through a planned, multidisciplinary approach to treatment.

Keywords: Liver transplantation; criteria; hepatocellular carcinoma (HCC); downstaging

Received: 07 September 2018; Accepted: 15 October 2018; Published: 26 October 2018.
doi: 10.21037/tgh.2018.10.03
View this article at: http://dx.doi.org/10.21037/tgh.2018.10.03

Introduction

Liver transplantation (LT) is a curative option for both hepatocellular carcinoma (HCC) and cirrhosis. Twenty years after first Milan criteria (MC) description, they are still identified as the benchmark for selection of patients and set the baseline of survival to achieve (1). When MC was first proposed in 1996, they rapidly became the keystone for the selection of patients with HCC waiting for LT (2). The use of the MC consented to very well selected patients at low risk for post-LT recurrence, consequently obtaining excellent survival rates (3). And yet, different extended criteria have been proposed in the last years all around the world. All of them have an intent to improve the ability to select patients for LT. MC competitors first used only macroscopic criteria and then associated with a biological parameter to find the best selection criteria.

Expanded criteria

Since the MC description, only morphological characteristics of HCC were used as the indication or not to LT. After a few years, other institutions revised these morphological characteristics in their enlarged criteria to cherry pick appropriate LT candidates.

Without doubts, the University of California San Francisco (UCSF) criteria described by Yao *et al.* in 2001 are one of the most important competitors of MC (4). UCSF reported a survival rate of 75% at five years with the following indications: a single nodule with a maximum diameter of 65 mm, or two or three tumors, each with a diameter with a maximum diameter of 45 mm, and a sum tumor diameter ≤80 mm. On the other hand, because a little number of patients outside MC but within the USCF criteria are candidates for LT, those criteria have not superseded MC in most centers (5).

As a reply to UCSF, Mazzaferro and the Metroticket Investigator Study Group also conducted a large sample retrospective study in 2007. The so-called up-to-seven criteria were described from a cohort of 283 patients with these morphological characteristics: the total of the size of the bigger tumor and the number of tumors no larger than 7. In the expanded criteria the overall survival rate achieved at 5-year was 71.2% (6).

The size and number of HCC in the waiting list for LT radiological images were used as well by other enlarged criteria. In the East, the Tokyo criteria named the "5-5 rule" was described for living donor liver transplantation (LDLT) (7). The University of Tokyo guidelines was up to five nodules with a maximum diameter of 5 cm, overall and recurrence-free survival rates at five years after transplantation were 75 and 90%, respectively.

"Asan criteria" from South Korea were proposed by Lee *et al.* for LDLT as the previous described Tokyo criteria (8). In this case indication for LT is six or fewer tumors with a diameter ≤50 mm. The overall survival rate for patients within the Asan criteria was 76.3% at five years, and the recurrence-free survival rate was 85%.

As previously but from the Catholic Medical Center, Choi *et al.* push over the limit with for patients with advanced HCC (9). Authors proposed to extend the suitable criteria for LDLT to up to seven tumors with the greatest diameter ≤70 mm. In their series, the overall survival at 5-year was 72%, and the recurrence-free survival was 87%.

A third element

Latterly, different centers have added alternative parameters reflecting the biological comportment of tumors other than the traditional morphological parameters.

Alpha-fetoprotein (AFP) is the largely popular non-invasive biomarker jeopardy element for HCC recurrence after LT.

Using the Scientific Registry of Transplant Recipients database including up to 6,478 patients in the USA, Toso *et al.* suggest the total tumor volume as the latest predictor of potential HCC recurrence after LT. Authors work out a new composite of criteria associating the entire tumor volume of 115 cm^3 or less and a serum AFP level of 400 ng/mL or less (10). The reported in case of patients out of range the MC but inside the new criteria a reasonable recurrence rate (9%) and overall survival rate (75%) at four years after LT. Notwithstanding, the precise measurement of the total tumor volume deriving from tumor diameter is the most limitation of the criteria.

Like the ones described above, to expand the selection criteria, the Samsung Medical Center (SMC) used the serum AFP level too (11). Kim *et al.* advocated in case of HCC patients with no more than seven tumors ≤6 cm and with serum AFP levels ≤1,000 ng/ml that in those cases LDLT could realistically be performed. Authors obtained an 84% recurrence-free rate at 5-year.

In France, the Liver Transplantation French Study Group publish the "Duvoux Score" predicting the high risk of recurrence post LT according to AFP (12). The score includes a sum of variables: number of nodules (1–3=0 point; ≥4=2 points), largest diameter in cm (≤3=0 point; 3–6=1 point; >6=4 points) and AFP (ng/mL) (≤100=0 point; 100–1,000=2 points, >1,000=3 points). Patients with a score ≤2 points following down-staging treatment will be eligible for registration for liver transplantation.

In Japan, many centers use an alternative tumor marker, des-gamma-carboxy prothrombin (DCP), as well known as a protein induced by vitamin K absence or antagonist II. Waiting LT list serum DCP level was reported as a predictor of the risk of recurrence of HCC after LT as a possible indicator of microvascular invasion. Therefore, both Kyoto and Kyushu groups have at present updated their selection criteria to include pre-LT serum DCP level.

The Kyoto group advanced expanded criteria containing serum DCP level (13). These criteria are defined as the number of HCC nodules to ten in addition to the largest diameter ≤5 cm and serum DCP level ≤400 mAU/mL. The 5-year disease-free and overall survival rates were 93% and 82%, respectively.

Surprisingly, the Kyushu group eliminated the nodule number limitation in the proposed expanded criteria (14). Taketomi *et al.* included all HCCs with a diameter of ≤5 cm and DCP <300 mAU/mL. The 5-year recurrence-free rate was 80%. Authors advertise the Kyushu criteria as the most potent predictive criteria for post-LT HCC recurrence. However, this last two criteria deriving on Japanese studies were achieved in the setting of LDLT only and needs additional validation in the Western world both in the context of LDLT and post-mortem donor LT (15).

Both Hangzhou and Toronto groups included the HCC biopsy result in their selection criteria.

Hangzhou criteria were defined as total tumor diameter ≤8 cm or total tumor diameter >8 cm, with grade I or II at the histopathologic exam and preoperative AFP level ≤400 ng/mL, simultaneously (16). The 5-year survival rate was 72.3%.

Remarkably, Toronto proposed no limit of number or size of HCC provided that imaging studies excluded vascular invasion; no extra-hepatic disease was observed, and histopathologic exam the HCC was not poorly differentiated (17).

Even though, these two criteria need a pathological staging with a needle biopsy which is a risk factor for both tumor seeding and post-transplant recurrence as well as

possible high bleeding in patients with portal hypertension. The size and the number of nodules within the MC might reflect the outcome of biologically favorable tumors.

Down-staging

Tumor biology as differentiation, vascular invasion, and serum AFP has been demonstrated to predict post-transplant recurrence and survival better than the unique morphology parameters. A downstaging therapy selects thanks to the good tumor biology those patients outside standard criteria at presentation but with a high chance of acceptable outcome in case of LT.

Tumor downstaging is a process including enlarged criteria and the results of loco-regional treatment. It is defined as a reduction in the tumor burden using a loco-regional treatment specifically to meet acceptable criteria for LT. A growing number of experiences of the excellent result after downstaging therapy before LT in patients outside MC are now published.

Since a few years ago, portal vein tumoral thrombosis (PVTT) was judged to be an absolute contraindication for LT. Nonetheless, experience with successful LDLT after downstaging for patients with PVTT has been published by the Yonsei University Severance Hospital of Korea (18). Han *et al.* used a pre-waiting list LT treatment protocol consisting of localized concurrent chemoradiotherapy, followed by hepatic arterial infusion chemotherapy. If patients had a good response, they were transplanted.

In Western countries, the San Camillo experience of downstaging strategy with trans-arterial radio-embolization achieved promising results for HCC with PVVT (19). The trans-arterial radio-embolization allows to downstage HCC and transplant patients with curative intents in the setting of LT (20,21).

External radiation therapy is an innovative choice for HCC. Therefore, as the HCC treatment paradigm continues to progress, ablative radiation therapy has moved onwards from a palliative treatment to both a bridge to LT and in some particular case to a definitive cure (22).

Conclusions

Many criteria have been published attempting to push the window open further than MC, and many demonstrate good and statistically similar results to MC. Expansion of MC recruits more LT candidates with HCC who cannot be treated by loco-regional therapy. To date though, none of them have found widespread acceptance in National allocation policies. Carefully selected patients beyond the traditional criteria for transplantation may achieve excellent LT outcomes through a planned, multidisciplinary approach to treatment.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Levi Sandri GB, Lai Q. Twenty years after: from Milan criteria to a "blended" approach. Transl Gastroenterol Hepatol 2017;2:62.
2. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-9.
3. Mazzaferro V, Bhoori S, Sposito C, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transpl 2011;17 Suppl 2:S44-57.
4. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394-403.
5. Patel SS, Arrington AK, McKenzie S, et al. Milan criteria and UCSF criteria: a preliminary comparative study of liver transplantation outcomes in the United States. Int J Hepatol 2012;2012:253517.
6. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35-43.
7. Sugawara Y, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. Dig Dis 2007;25:310-2.
8. Lee SG, Hwang S, Moon DB, et al. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. Liver Transpl 2008;14:935-45.

9. Choi HJ, Kim DG, Na GH, et al. Extended criteria for living donor liver transplantation in patients with advanced hepatocellular carcinoma. Transplant Proc 2012;44:399-402.
10. Toso C, Asthana S, Bigam DL, et al. Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the Scientific Registry of Transplant Recipients database. Hepatology 2009;49:832-8.
11. Kim JM, Kwon CH, Joh JW, et al. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma. Transplant Proc 2014;46:726–9.
12. Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:986-94.e3; quiz e14-5.
13. Kaido T, Ogawa K, Mori A, et al. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. Surgery 2013;154:1053-60.
14. Taketomi A, Sanefuji K, Soejima Y, et al. Impact of des-gamma-carboxy prothrombin and tumor size on the recurrence of hepatocellular carcinoma after living donor liver transplantation. Transplantation 2009;87:531-7
15. Lai Q, Iesari S, Levi Sandri GB, et al. Des-gamma-carboxy prothrombin in hepatocellular cancer patients waiting for liver transplant: a systematic review and meta-analysis. Int J Biol Markers 2017;32:e370-4.
16. Zheng SS, Xu X, Wu J, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation 2008;85:1726-32.
17. DuBay D, Sandroussi C, Sandhu L, et al. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. Ann Surg 2011;253:166-72.
18. Han DH, Joo DJ, Kim MS, et al. Living donor liver transplantation for advanced hepatocellular carcinoma with portal vein tumor thrombosis after concurrent chemoradiation therapy. Yonsei Med J 2016;57:1276-81.
19. Levi Sandri GB, Ettorre GM, Colasanti M, et al. Hepatocellular carcinoma with macrovascular invasion treated with yttrium-90 radioembolization prior to transplantation. Hepatobiliary Surg Nutr 2017;6:44-8.
20. Levi Sandri GB, Ettorre GM, Giannelli V, et al. Trans-arterial radio-embolization: a new chance for patients with hepatocellular cancer to access liver transplantation, a world review. Transl Gastroenterol Hepatol 2017;2:98.
21. Ettorre GM, Levi Sandri GB, Laurenzi A, et al. Yttrium-90 Radioembolization for Hepatocellular Carcinoma Prior to Liver Transplantation. World J Surg 2017;41:241-9.
22. Chino F, Stephens SJ, Choi SS, et al. The role of external beam radiotherapy in the treatment of hepatocellular cancer. Cancer 2018. [Epub ahead of print].

doi: 10.21037/tgh.2018.10.03
Cite this article as: Levi Sandri GB, Rayar M, Qi X, Lucatelli P. Liver transplant for patients outside Milan criteria. Transl Gastroenterol Hepatol 2018;3:81.

