Review Article

# Living donor liver transplantation for hepatocellular cancer: an (almost) exclusive Eastern procedure?

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**Abstract:** Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and it is linked with chronic liver disease. Liver transplantation (LT) is the best curative treatment modality, since it can cure simultaneously the underlying liver disease and HCC. Milan criteria (MC) are the benchmark for selecting patients with HCC for LT, achieving up to 91% 1-year survival post transplantation. However, when considering intention-to-treat (ITT) rates are substantially lower, mainly due dropout. Additionally, Milan criteria (MC) are too restrictive and more inclusive criteria have been reported with good outcomes. Mainly, in Eastern countries, deceased donors are scarce, therefore Asian centers have developed living-donor liver transplantation (LDLT) to a state-of-art status. There are many eastern centers reporting huge numbers of LDLT with outstanding results. Regarding HCC patients, they have reported many criteria including more advanced tumors achieving reasonable outcomes. Western countries have well-established deceased-donor liver transplantation (DDLT) programs. However, organ shortage and restrictive criteria for listing patients with HCC endorses LDLT as a good option to offer curative treatment to more HCC patients. However, there are some controversial reports claiming higher rates of HCC recurrence after LDLT than DDLT. An extensive review included 30 studies with cohorts of HCC patients who underwent LDLT in both East and West countries. We reported also the results of our Institution, in Brazil, where it was performed the first LDLT. This review also addresses the eligibility criteria for transplanting patients with HCC developed in Western and Eastern countries.

**Keywords:** Liver transplantation (LT); hepatocellular carcinoma (HCC); living donors; Western World; Far East; Middle East

Received: 11 July 2017; Accepted: 21 July 2017; Published: 29 August 2017.
doi: 10.21037/tgh.2017.08.02
**View this article at:** http://dx.doi.org/10.21037/tgh.2017.08.02

## Introduction

Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and third most common cause of cancer-related mortality worldwide (1-3). In 70–90% of all cases, HCC develops in patients with chronic liver disease (4), being the leading cause of death among cirrhotic patients (5). Therefore, liver transplantation (LT) is the best curative treatment modality, since it can cure simultaneously the underlying liver disease and the HCC.

There are many important factors to determine the success of the procedure, but two of them are crucial: tumor's staging and timing to treatment. HCC stage is

directly correlated with the risk of recurrence. MC (one HCC of 5 cm or smaller, or up to three nodules of 3 cm or smaller, without vascular invasion or extrahepatic spread) (6) is the benchmark for patient selection for LT (7,8). In this context, LT confers optimal outcomes, achieving up to 91% 1-year survival in patients within MC. However, intention-to-treat (ITT) rates are substantially lower, mainly due dropout. Llovet *et al*. (9) identified 23% dropout rate of patients with HCC in the waiting list for a deceased donor LT (DDLT). An option to reduce drop out is to perform LT sooner, which is extremely more feasible in the living donor liver transplantation (LDLT) setting. Another advantage of LDLT is that it can be performed independently from tumor´s staging, enabling liver transplants to patients outside the restrict rules used to include patients with HCC in the DDLT waiting list.

The first LDLT was performed in 1988 at our Institution, in Brazil, a Western country (10). Since then, several surgical and radiologic innovations have established LDLT as a tool for overcoming the shortage of deceased donors. Historically, Western countries adopted LDLT mainly for pediatric patients and limited LDLT indications for adult's recipients. Interestingly, LDLT was exceptionally well accepted in Eastern countries where liver grafts from deceased donors are extremely scarce and up to 96% patients receive hepatic grafts from living donors (11).

This study aims to compare LDLT performed for HCC patients in Western and Eastern countries.

## Methods

### *Literature review*

For this review, a search was conducted with PubMed/MEDLINE database with a combination of the following entry terms: *living-donor living transplantation*, *LDLT*, *hepatocellular carcinoma* and *HCC*. Articles were restricted to the English language. We focused in studies reporting outcomes of LDLT for HCC. In case some of them contained updated data from previous series, only the most complete study was included in the analysis. Data from each center was encompassed to produce global results of Eastern and Western countries. Another search in the same database was performed with the entry terms: *hepatocellular carcinoma*, *HCC*, *selection criteria* and *liver transplantation* to recover articles reporting expanded selection criteria beyond Milan.

### *Data collection from Sao Paulo University Medical School*

We also conducted a retrospective study of the data from our institution regarding LDLT cases for HCC from January 2003 to May 2017. Patients' characteristics and outcomes were extracted from medical charts. In our center, HCC cases are evaluated for LDLT on an individual basis, irrespective of tumor size or number of nodules. Biological variables such as serum AFP level, response to ablation therapy, patients' performance status, position in deceased-donors waitlist (when within MC) and donor's and recipient's opinion about the transplant scenario are all taken into account. The only absolute contra-indication is extra-hepatic disease. The results obtained in our series were added to the *Western countries* data.

## Results

A total of 30 articles (*Table 1*) were selected for reporting LDLT outcome data and divided according to the geographical location of the reporting center in Eastern or Western countries. Most articles were from Eastern centers and they also encompassed a larger amount of cases (3,854 *vs*. 457). The recurrence rates found in each region presented, however, a similar distribution. Interestingly, the proportion of cases outside MC was also similar between regions, being the largest one from our institution.

The most relevant selection criteria for LT in HCC found in literature are presented in *Table 2* (DDLT context) and *Table 3* (LDLT context). It is noteworthy that while most criteria for DDLT were conceived in the West (87.5%), all criteria for LDLT were created in the East.

## Discussion

In 2015, Brazil performed 1,805 LT. Even though LDLT represented only 8.5% of all transplants, it corresponded to 70% of cases in the pediatric population (51). This is probably the usual scenario in others Western countries as well, where LDLT is performed only as an auxiliary option to address graft shortage. This supporting hole of LDLT in Western countries could explain the impressive difference between the numbers of LDLT performed for HCC patients in West and East, as illustrated in *Table 1*. In the West, most countries already present a well-established program of brain-dead donors and some also allow the use of organs from DCD (donor after cardiac death). Therefore, LDLT is mainly used a complementary

 

**Table 1** Summary of papers reporting living donor liver transplantations for patients with hepatocellular cancer encompassed by cultural region

| Author | Center | Study period | Patients (n) | Recurrence rate (%) | Outside Milan (%) |
|---|---|---|---|---|---|
| Eastern countries | | | | | |
| Hwang [2005] (12) | Mulicentric, Korea | 1992–2002 | 237 | 15.5 | 27 |
| Karakayali [2006] (13) | Ankara, Turkey | 2004–2005 | 11 | 0 | – |
| Lo [2007] (14) | Hong Kong, China | 1995–2004 | 43 | 30 | 26 |
| Allam [2008] (15) | Menofeya, Egypt | 2001–2007 | 9 | 11.1 | – |
| Azzam [2011] (16) | Riyadh, Saudi Arabia | 2001–2010 | 19 | 10.5 | – |
| Shirabe [2011] (17) | Fukuoka, Japan | 1996–2008 | 109 | 18.3 | 49 |
| Isik [2012] (18) | Malatya, Turkey | 2006–2011 | 74 | 21.6 | – |
| Kaido [2013] (19) | Ehime, Japan | 1999–2011 | 198 | 15.6 | 40.4 |
| Park [2014] (20) | Seoul, Korea | 1999–2010 | 160 | 17.5 | – |
| Akamatsu [2014] (21) | Tokyo, Japan | 2000–2012 | 125 | 9 | 13 |
| Wan [2014] (22) | Shanghai, China | 2007–2010 | 40 | 25 | 40 |
| Xiao [2014] (23) | Chengdu, China | 1999–2012 | 84 | – | 69 |
| Kim [2014] (24) | Seoul, Korea | 2002–2008 | 180 | 15.5 | – |
| Ninomiya [2015] (25) | Fukuoka, Japan | 2002–2010 | 133 | 14 | 41 |
| Gunay [2015] (26) | Istanbul, Turkey | 2004–2012 | 109 | 14.7 | 47.7 |
| Chen [2015] (27) | Chengdu, China | 2005–2013 | 75 | – | 48 |
| Hu [2016] (28) | Multicentric, China | 1999–2009 | 389 | – | 6 |
| Togashi [2016] (29) | Tokyo, Japan | 1996–2015 | 139 | 11 | 14.3 |
| Hong [2016] (30) | Seoul, Korea | 2000–2015 | 532 | – | 31.6 |
| Kim [2016] (31) | Seoul, Korea | 2007–2013 | 461 | 16.7 | – |
| Umeshita [2016] (32) | Multicentric, Japan | 1989–2013 | 727[#] | – | – |
| Total | Eastern countries | 1989–2015 | 3,854 | – | – |
| Western countries | | | | | |
| Gondolesi [2004] (33) | Mount Sinai, New York, USA | 1988–2002 | 36 | 16.6 | 53 |
| Jonas [2007] (34) | Berlin, Germany | 1988–2005 | 21 | 15.7 | 62 |
| Sotiropoulos [2007] (35) | Essen, Germany | 1998–2006 | 45 | 10 | 49 |
| Di Sandro [2009] (36) | Milan, Italy | 2000–2007 | 25 | 4 | 20 |
| Vakili [2009] (37) | Burlington, USA | 1999–2007 | 28 | 28.6 | 25 |
| Bhangui [2011] (38) | Villejuif, France | 2000–2009 | 36 | 12.7 | 27 |
| Sandhu [2012] (39) | Toronto, Canada | 1996–2009 | 58 | 15.4 | 58 |
| Kulik [2012] (40) | Multicentric, USA | 1998–2010 | 100 | 38 | 56 |
| Azoulay [2016] (41) | Multicentric, France | 2000–2009 | 79 | 10.9 | 24.1 |
| Sao Paulo University | São Paulo, Brazil | 2008–2017 | 29 | 10.3 | 67.8 |
| Total | Western Countries | 1988–2017 | 457 | – | – |

[#], this is a Japanese national registry study. Therefore we excluded patients already enrolled in Japanese series in this table.

 

**Table 2** Selection criteria for liver transplantation for HCC in DDLT

| Criteria | Study group | Year | Center | Eligibility criteria | Casuistics | Outcome |
|---|---|---|---|---|---|---|
| Milan | Mazzaferro *et al*. (6) | 1996 | University of Milan, Italy | 1 tumor ≤5 cm; up to 3 tumors ≤3 cm | 35 patients | 4-y OS: 92%; 4-y DFS: 85% |
| UCSF | Yao *et al*. (42) | 2007 | University of California, San Francisco, USA | 1 tumor ≤6.5 cm or 2–3 tumors ≤4.5 cm and total tumor diameter ≤8 cm | 168 patients | 5-y DFS: 81% |
| Clinica Universitaria de Navarra (CUN) | Herrero *et al*. (43) | 2008 | Navarra University, Spain | 1 tumor ≤6 cm or 2–3 tumors ≤5 cm | 85 patients | Beyond Milan criteria (n=26) 5-y DFS: 78% |
| Valencia | Silva *et al*. (44) | 2008 | Valencia, Spain | Up to 3 tumors with maximum diameter ≤5 cm and total tumor diameter ≤10 cm | 257 patients | Beyond Milan criteria (n=26) 5-y DFS: 69% |
| Hanzhou | Zheng *et al*. (45) | 2008 | Zhejiang University School of Medicine, China | Total tumor diameter ≤8 cm or total tumor diameter >8 cm with grade I or II on biopsy and AFP ≤400 ng/mL | 195 patients | Beyond Milan criteria (n=99) 5-y DFS: 72% |
| Alberta | Toso *et al*. (46) | 2008 | University of Alberta, Canada | Total volume ≤115 $cm^3$ | 288 patients | Beyond Milan criteria (n=251) 5-y DFS: 80% |
| Up-to-seven | Mazzaferro *et al*. (47) | 2009 | Milan and international multicenter | Sum of the number of tumors and diameter of largest tumor ≤7 cm | 1,556 patients | Beyond Milan criteria and without microvascular invasion (n=283) 5-y DFS: 71%; beyond Milan criteria and with microvascular invasion (n=116) 5-y DFS: 47% |
| Toronto | Dubay *et al*. (48) | 2011 | University of Toronto and Toronto General Hospital, Canada | Unrestricted tumor size and number, but not poorly-differentiated histology on biopsy if beyond Milan Criteria | 294 patients | Beyond Milan (n=105) 5-y DFS: 70% |

HCC, hepatocellular carcinoma; DDLT, deceased-donor liver transplantation; OS, overall survival; DFS, disease-free survival.

tool to overcome organ shortage. On the other side, in many Eastern countries, deceased-donors are extremely scarce due to cultural issues.

In recent years, however, the number of LDLT is growing in Western countries, especially for HCC patients. The main reason is that LDLT offers a valuable opportunity of drastically reducing the waiting time for transplantation. Thereby, it diminishes not only waitlist mortality but also dropout rates due to tumor progression beyond established criteria for DDLT, which usually are very restrictive. The most common worldwide is the MC (6). Patients within MC present a 5-year overall survival (OS) of 65% to 78%. These numbers are particularly encouraging when compared to 5-year survival rates of non-HCC transplanted patients, which range from 68 to 87 (52).

Unfortunately, MC is also over-restrictive and many patients when diagnosed with HCC are already outside it. Even employing annual surveillance in cirrhotics by means of liver ultrasound combined with serum levels of alfa-fetoprotein measurement, HCC can be discovered beyond

 

**Table 3** Selection criteria for liver transplantation for HCC in LDLT

| Criteria | Study group | Year | Center | Eligibility criteria | Casuistics | Outcome |
|---|---|---|---|---|---|---|
| Tokyo (5-5 rule) | Sugawara *et al*. (49) | 2007 | University of Tokyo, Japan | Number of tumors ≤5 cm and size ≤5 cm | 78 patients | 5-y OS: 75%<br>5-y DFS: 90% |
| Kyoto | Kaido *et al*. (19) | 2013 | Kyoto University, Japan | Number of tumors ≤10, size ≤5 cm or DCP level ≤400 mAU/mL | 198 patients | Beyond Milan criteria (n=189)<br>5-y OS: 82%<br>5-y DFS:96%% |
| Asan | Lee *et al*. (50) | 2008 | Asan Medical Center, South Korea | Number of tumors ≤6 and size ≤5 cm | 229 patients | Beyond Milan criteria (n=189)<br>5-y OS: 76%<br>5-y DFS:85% |
| Kyushu | Shirabe *et al*. (17) | 2011 | Kyushu University, Japan | Any number of tumors, size <5 cm or DCP <300 mAU/mL | 54 patients | Beyond Milan criteria (n=48)<br>5-y DFS: 80% |
| Samsung | Kim *et al*. (24) | 2014 | Sungkyunkwan University School of Medicine, South Korea | Number of tumors ≤7, size of tumors ≤6 cm and AFP level ≤1,000 ng/mL | 180 patients | 5-y DFS: 84% |

HCC, hepatocellular carcinoma; LDLT, living-donor liver transplantation; OS, overall survival; DFS, disease-free survival; AFP, alpha-fetoprotein; DCP, des-y-carboxy prothrombin.

MC in 20% of the patients (53). That is the reason why expanded criteria have been proposed throughout the last decade. The most relevant of them are mentioned in *Table 2*. Despite increasing the number of patients suitable for LT, these criteria present outcomes comparable to patients within MC.

Most expanded criteria modify the number and size of nodules originally determined in MC. Nonetheless, apart from and gross pathologic tumor features (size, number and location of nodules—bilobar distribution and multicentric nodules are also related to more aggressive tumor), many others factors have been related to recurrence, especially serum tumors biomarkers, histopathological features (microvascular invasion and poorly-differentiated tumors) and markers of inflammatory response (neutrophil-to-lymphocyte ratio and C-reactive protein (54). The latter has not achieved clinical use so far though and the routine use of nodule biopsy for patient selection is still a matter of debate, albeit being advocated by some centers (48). The main novel approach in the last years therefore has been the inclusion of serum biologic markers in selection criteria, since they can act as predictor of dropout or recurrence in patients with HCC. The most used ones are alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) (55). The initial serum levels and its variation during locoregional treatment are independent predictors of prognosis (56,57). They can be combined with traditional variables of tumors recurrence to select patients with more advanced HCC but favorable biological behavior, resulting in comparable outcomes to patients within MC.

Another recent identified independent prognostic factor is preoperative $^{18}$F-FDG PET uptake. Lee *et al*. (58) evaluated retrospectively 59 HCC patients who underwent LDLT according to PET positivity (defined as $T_{SUVmax}/L_{SUVmax}$ of 1.15 or more). The 2-year recurrence-free survival rate was 97% for patients PET-negative and 42% for patients PET-positive (P<0.001). The same institution reported 22 patients with far advanced HCC (including 11 cases with macrovascular invasion) who underwent LDLT, the 2-year disease free survival rate was 23.9%. Nonetheless, the selected patients with low AFP (<200 ng/mL), and PET-negative, exhibited an outstanding 2-year recurrence-free survival of 66.7% (59).

On the other hand, some concern has been raised

 

regarding the LDLT for HCC, when some series reported higher tumor recurrence in LDLT patients when compared to DDLT. In 2007, Fisher *et al*. (60) reported the initial results of the Adult-to-adult Living Donor transplantation Cohort Study (A2ALL), encompassing nine American centers. Fifty-eight LDLT were performed and the 3-years recurrence rate in LDLT and DDLT recipients was 29% and 0%, respectively (P=0.002). In 2012, Kulik *et al*. (40) published the updated results of A2ALL cohort, with 100 LDLT and 97 DDLT. The 5-year recurrence rate remained higher in LDL group (38% *vs*. 11%, P=0.01). In both reports, nevertheless, patients were more likely to have higher AFP serum levels, microvascular invasion, larger tumors or tumors beyond Milan and UCSF criteria. They also were less likely to receive pretransplant ablation therapy (59% *vs*. 79%, P=0.03), which reflected in a shorter transplant waiting time. Thereby, the authors concluded that the differences in outcome between LTLD and DDLT were more probably the result of patient selection rather than the type of graft per se. Despite the mentioned selection-bias, several hypothesis were made to explain these findings, including faster tumor progression due cytokine and growth factors released during liver regeneration, which is accentuated in LDLT (61,62). Another theory linked small-for-size grafts with higher endothelial growth-factor expression and consequently angiogenesis (63). More recent studies, however, have questioned these hypotheses (64).

The waitlist for transplantation seems to jeopardize recipients with potential curable HCCs, due the constant risk of cancer progression beyond accepted staging criteria. A recent meta-analysis reported dropout rates ranging from 9.2% to 31% (65). As the procedure is virtually done without any delay, LDLT minimizes this risk. Bhangui *et al*. (66) reported the waiting time for LDLT patients (2.8±2.4 months) significantly shorter than DDLT (7.9±9 months; P<0.001) in the same institution. Waiting time can be even shorter in others centers where LDLT is performed within a median of 44 days (25). Therefore, LDLT for patients with HCC is a more inclusive option, minimizing (or almost excluding) the risk of dropout.

Conversely, time can be tricky in LT for patients with HCC, since longer waiting time between being listed to transplant may offer better long-term outcomes. Patients with HCC waiting more than 120 days for DDLT have 1-year posttransplant recurrence rate significantly lower than patients waiting less than 120 days (2.2% *vs*. 3.9%, P=0.002) (67). Halazun *et al*. (68) evaluated the United Network for Organ Sharing (UNOS) data regarding DDLT recipients with HCC who had longer waiting time (median 7.6 months) with shorter waiting time (1.6 months). Longer waiting time was identified as a risk factor for death on the list (8.4% *vs*. 1.6%, P<0.001), while both intent-to-treat and post-transplant survivals were better in this group. A short waiting time was an independent predictor of poor patient survival on multivariate analysis. These paradoxical findings highlight time as important selection criteria. Waiting longer for LT could reveal the biological behavior of the tumor and then patients with aggressive HCC patterns would dropout before transplantation. Lai *et al*. (69) compared HCC recurrence after LDLT (n=116) or LT (n=157), interestingly in two different centers in Asia and Europe, respectively. They identified waiting time higher than 3 months before transplantation as a better outcome factor regardless the type of transplantation. Moreover, excluding salvage transplantations, recurrence rates were similar. Additionally, during longer waiting periods patients are usually treated with sequential locoregional therapy, such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE). Allard *et al*. (70) demonstrated that complete or nearly complete pathologic response after TACE improves long-term survival after LT independently of other pathological factors. Five-year overall and disease free survival after LT were higher in patients with complete pathological response compared to those without, 84% *vs*. 65% (P=0.09) and 94% *vs*. 73% (P=0.007), respectively. Finally, the "fast-track" effect commonly adopted in LDLT could lead to inferior long term outcomes (40).

An important ITT study was published by Azoulay *et al*. (41) in 2016 with five centers in France performing 79 LTLD and 782 DDLT. A total of 162 patients were removed from the list while waiting for DDLT, resulting in a drop-out rate of 20.7%. The major cause for removal was tumor progression (91.3%). The only contraindication for transplantation was extrahepatic disease or vascular invasion on radiological exams, irrespective of the level of involvement (from the main trunk to the segmental level). Interestingly, patients in LDLT group exhibited higher MELD and Child scores (14.7 *vs*. 12.7, P<0.01 and 35.9% of Child C *vs*. 23.4%, P=0.05), had larger tumors (2.97 *vs*. 2.67 cm, P=0.02) and had higher AFP serum levels (305 *vs*. 105 ng/mL, P=0.01). The proportion of patients undergoing TACE/RFA as bridge-therapy was similar in both groups (68.4% *vs*. 64.4%, P=0.2). Retransplantation and postoperative mortality were also similar (5.1% *vs*. 5.3%, P=0.92 and 7.6%

 

*vs.* 7.7%, P=0.96, respectively). The ITT 5-year OS trended in favor of LDLT (73.2% *vs.* 66.7%, P=0.062). Multivariate analysis however identified LDLT and the time-of- listing MELD lower than 25 as predictors of better survival. It is noteworthy that this difference in survival no longer exists when comparing only transplanted patients (5-year OS: 73.2% *vs.* 73%, P=0.4). Regarding recurrence, the rates were similar between LDLT and DDLT (10.9% *vs.* 11.2%, P=0.8), nonetheless time to recurrence was longer in LDLT group (67.5 *vs.* 50.6 months, P<0.01). Multivariate analysis identified macrovascular invasion, tumors outside MC and AFP model score higher than 2 as independent predictors of recurrence. Even though multicentric, the strength of this series is that all patients were selected according to the same criteria and under the same allocation rules and transplanted by similar centers offering both modalities, during a limited span of time. Authors concluded that LDLT shortens waiting time and improves ITT OS, not representing a risk factor for recurrence. Thereby, it should be encouraged when available.

Liver grafts from living donors are typically of good quality, with minimal fat and reduced ischemic time. On the other side, LDLT is more complex than DDLT due surgical technical aspects and ethical issues that do not exist in DDLT arise: is it correct to risk the donor's integrity, a healthy and active person, in favor of a cirrhotic patient with limited life expectative? Firstly, the donor safety must be the main priority. The donor procedure indeed presents 10% morbidity in high volume centers (71), but its incidence might be higher in low volume ones. Secondly, there is the ethical concern regarding exposing the donor to this risk when the recipient has advanced HCC with expected higher recurrence rate (72). For this reason, the institution should take a clear position and the transplantation team must provide full disclosure to donor and recipients. Finally, LDLT for patients with HCC beyond accepted criteria for deceased donation are usually forbidden to get access to re-transplantation in case of graft failure. Re-transplantation because of graft failure after LDLT is a rare event, although when needed, outcomes after LDLT are not different from DDLT (73). However, these patients would not have qualified for DDLT in the first place, then re-transplantation using a deceased donor is not recommended in this context (8).

In summary, Eastern countries have proved that LDLT has an outstanding potential for HCC patients. It allows the inclusion of patients with more advanced tumors without jeopardizing outcome, through a careful selection of patients with predictors of better prognosis, such as low values/favorable slopes of serological markers; PET negativity; response to locoregional therapies; and excluding patients with poor differentiation tumors. Timing to transplantation is also important, it might be managed to avoid too long or too short periods. Ideally, it should avoid excessive dropout, but must be long enough to identify tumors with aggressive biology. Western countries have a limited, but encouraging experience using LDLT for HCC patients. These countries should expand the indication of LDLT to patients with prolonged time in the waiting list in order to reduce dropout; and for patients presenting more advanced tumors, with predictors of favorable biological behavior.

## Acknowledgements

None.

## Footnote

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

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doi: 10.21037/tgh.2017.08.02
**Cite this article as:** Pinheiro RS, Waisberg DR, Nacif LS, Rocha-Santos V, Arantes RM, Ducatti L, Martino RB, Lai Q, Andraus W, D'Albuquerque LA. Living donor liver transplantation for hepatocellular cancer: an (almost) exclusive Eastern procedure? Transl Gastroenterol Hepatol 2017;2:68.

 