

Living Donor Liver Transplantation for Hepatocellular Carcinoma within Milan Criteria in the Present Era

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Abstract. *Background:* The aim of the present study was to clarify the outcome of living donor liver transplantation (LDLT) in patients with hepatocellular carcinoma (HCC) within Milan criteria. *Patients and Methods:* The study comprised of 197 adult patients. One hundred twenty-nine patients were within Milan criteria. The overall and recurrence-free survival rates after the LDLT were calculated. *Results:* The 1-, 5- and 10-year overall survival rates were 94.5%, 89.9% and 88.6%, respectively. The 1-, 5- and 10-year recurrence-free survival rates were 100%, 97.0% and 94.0%, respectively. Four patients had HCC recurrence. The mean neutrophil to lymphocyte ratio (NLR) (6.75 vs. 2.75, $p=0.002$) or alpha-fetoprotein (AFP) (3,239 vs. 197, $p<0.001$) of these four recipients was significantly higher compared to that of 125 recipients without HCC recurrence. *Conclusion:* The outcome of LDLT for patients with HCC within Milan criteria was outstanding. Careful follow-up after LDLT is necessary for patients with high NLR or AFP.

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm worldwide and the third most common cause of cancer-related death. Its incidence is increasing because of the dissemination of hepatitis B and C virus infection. Liver transplantation (LT), which offers the theoretical advantage of removing both the tumor and the organ at risk of developing future malignancy, is an established therapy for HCC in patients with liver cirrhosis (1, 2). In Asian countries, religious, cultural and political ideologies have created significant obstacles to the transplantation of cadaver organs. Organ shortages have forced patients with HCC to endure long

waiting periods that are associated with tumor development. Thus, living donor LT (LDLT) is a choice for treating such patients after various treatments, such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE), with/without hepatic resection (3).

The Milan criteria (MC) have significantly improved the outcome of LT for HCC (4) and have become the gold standard for achieving favorable outcome after LT for HCC. We have reported expanded criteria used because the favorable outcomes have raised the question of whether selection criteria might be expanded (5, 6). Since Japanese national insurance started to cover LDLT for HCC within the MC in 2004, the number of LDLT patients within the MC is increasing. Poor recipient status, partial hepatic graft use, or uncontrollable infection due to immunosuppression in LDLT can cause patient death without HCC recurrence in contrast to other treatment modalities for HCC (7). Thus, it is important to investigate current outcomes of LDLT for patients within the MC.

The aim of the present study was to clarify the outcomes for HCC recurrence and mortality after LDLT in patients who met the MC.

Patients and Methods

Patients. One hundred and ninety-seven adult patients underwent LDLT for end-stage liver disease with HCC at the Kyushu University Hospital between April 1999 and March 2015. Pre-transplant imaging study revealed that 129 patients were within the MC and 68 were not. Among 129 patients within the MC, 19 recipients underwent LDLT for indications other than HCC but were included in the study as HCC was found on explant pathology. Among 197 patients, no patient was excluded from the study. One hundred and twenty-seven patients underwent pre-transplant treatment for HCC, such as RFA, TACE, microwave coagulation therapy, with/without hepatic resection depending on the patient's liver function and tumor status. Graft types included left lobe with caudate lobe graft (LL+C; $n=118$), right lobe graft without the middle hepatic vein ($n=72$), posterior segment graft ($n=6$), and dual graft ($n=1$). The etiology of liver cirrhosis was hepatitis C ($n=137$), hepatitis B ($n=34$), cryptogenic ($n=9$), alcohol abuse ($n=7$), autoimmune hepatitis ($n=4$), primary biliary cirrhosis ($n=4$), non-alcoholic steatohepatitis ($n=2$)

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Key Words: Living donor liver transplantation, hepatocellular carcinoma, Milan, criteria, NLR.

Table I. Characteristics of patients and donors (n=197) in this study.

Variable	Within Milan criteria (n=129)	Not within Milan criteria (n=68)	p-Value
Recipient			
Gender: Male/female, n	60/69	51/17	<0.0001
Mean age, years	57.7	58.0	0.81
Etiology			
HCV	82	55	0.06
HBV	28	6	
Alcohol	4	3	
Cryptogenic	6	3	
AIH	4	0	
PBC	3	1	
NASH	2	0	
Mean MELD score	13.4	11.3	0.007
Diabetes mellitus: Yes/no, n	23/106	20/48	0.07
Splenectomy: Yes/no, n	99/30	33/35	<0.0001
CNI: TAC/CyA/none, n	73/52/4	27/39/2	0.08
MMF: Yes/no, n	120/9	57/11	0.03
Donor			
Gender: Male/female, n	94/35	45/22 [#]	0.24
Mean age, years	35.7	33.0	0.09
Graft: Left/right/posterior/dual, n	72/51/6/0	46/21/0/1	0.03
Mean GW-SLW ratio (%)	41.2	39.8	0.22
Tumor			
Mean Maximum size (cm)*	1.7	3.1	<0.0001
Median no. nodules*	1	5	<0.0001
Mean pre-transplant NLR	2.88	2.99	0.79
Mean pre-transplant AFP (ng/ml)	291	2011	0.005
Mean pre-transplant DCP (mAU/ml)	91	755	0.0002
Pre-transplant treatment: Yes/no, n	70/59	57/11	<0.0001
Mean no. of treatments	1	3	<0.0001
Mean maximum size on pathology (cm)	1.8	3.3	<0.0001
Median no. of nodules on pathology*	2	10	<0.0001
Microvascular invasion: Yes/no, n	19/109	40/28	<0.0001
Met Milan criteria by explant pathology, Yes/no, n	90/39	9/59	<0.0001
Pathological differentiation: Well/moderate/poor ^{\$} , n	15/95/16	2/35/31	<0.0001

HCV: Hepatitis C virus, HBV: hepatitis B virus, AIH: autoimmune hepatitis, PBC: primary biliary cirrhosis, NASH: non-alcoholic steatohepatitis, MMF: mycophenolate mofetil, MELD: model for end-stage liver disease, CNI: calcineurin inhibitor, TAC: tacrolimus, CyA: cyclosporine A, GW: graft weight, SLW: standard liver weight, NLR: neutrophil-to-lymphocyte ratio, AFP: α -fetoprotein, DCP: *des*- γ -carboxy prothrombin. One recipient received dual graft from male and female donors. *19 Cases for indications other than hepatocellular carcinoma (HCC), included as HCC was found on explant pathology. ^{\$}Results on pathological differentiation were lacking in two cases.

(Table I). Our selection criteria for performing LDLT for patients with HCC were as follows: (i) no modality except LDLT available for cure of HCC; (ii) no extrahepatic metastases; and (iii) no major vascular infiltration (5). There were no restrictions on tumor size, number of nodules, or pre-transplant treatment. Since we proposed our own criteria (5), we did not perform LDLT for patients with HCC with both tumor size exceeding 5 cm and *des*- γ -carboxy prothrombin (DCP) level exceeding 300 mAU/ml.

Pre-transplant imaging was used to estimate the maximum tumor size and number of nodules. Alpha-fetoprotein (AFP), DCP and the neutrophil to lymphocyte ratio (NLR) were measured just prior to LDLT. The histological grades obtained from the explanted livers were used for determining tumor differentiation and the presence of vascular invasion.

Donor and graft selection. Donors were selected from candidates who hoped to be living donors (6, 8). Donors were required to be up to/including a third degree blood relative of the recipients, or spouses, and to be between 20 and 65 years of age. For a any other donor, individual approval was obtained from the Ethics Committee of the Kyushu University Hospital. Good Samaritan donations were not used.

Eligible donors proceeded to the imaging studies, including chest and abdominal X-rays and 3-mm-slice computed tomography (CT) for graft volumetric analysis. Three-dimensional CT was introduced for volumetric analysis and delineation of vascular anatomy. The standard liver weight (SLW) of recipients was calculated according to the formula of Urata *et al.* (9). Graft weight (GW) was predicted by CT volumetric analysis. Our decision about graft type for recipients was based on the preoperatively predicted GW to SLW

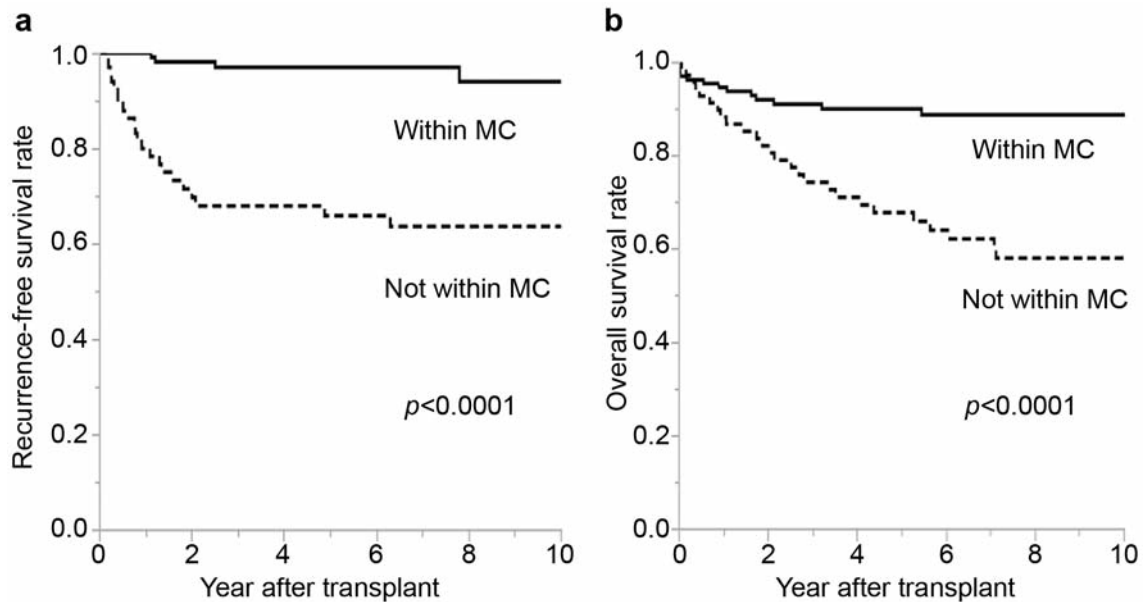


Figure 1. Recurrence-free survival and overall survival after LDLT: living donor liver transplantation for hepatocellular carcinoma. Recurrence-free (a) and overall (b) survival of transplant recipients divided according to whether they were within or not within Milan criteria (MC).

ratio. LL+C graft was used when the preoperatively predicted GW to SLW ratio was $\geq 35\%$. When the GW to SLW ratio with LL+C graft was $<35\%$ and remnant donor liver volume after right lobectomy was $\geq 35\%$, right lobe graft was used. Posterior segment graft was considered when the donor's vascular anatomy was suitable for taking a posterior segment (10).

Postoperative management. The graft retrieval technique, recipient surgery and perioperative management of the recipients, including immunosuppression regimens have been described previously (11). Immunosuppression was initiated using a protocol based on either tacrolimus (Prograf; Astellas Pharma Inc., Tokyo, Japan) or cyclosporine A (Neoral; Novartis Pharma K.K., Tokyo, Japan) with steroid with/without mycophenolate mofetil (MMF; Chugai Pharmaceutical Co. Ltd., Tokyo, Japan). Tacrolimus was used for 100 recipients, and cyclosporine for 91 recipients. Six recipients did not receive calcineurin inhibitor due to poor postoperative course. A target trough level of tacrolimus was set at 10 ng/ml for 3 months after LDLT, followed by 5-10 ng/ml thereafter. A target trough level of cyclosporine A was set at 250 ng/ml for 3 months after LDLT, followed by 150-200 ng/ml thereafter. Methylprednisolone was initiated on the day of LDLT, tapered and converted to prednisolone 7 days after LDLT. Prednisolone treatment was tapered and discontinued 6 months after LDLT. MMF was used for 177 recipients and was started at 1-2 g/day on the day after LDLT, tapered and discontinued until 6 months after LDLT. A trough level was not measured for MMF.

All patients had monthly follow-ups, and the median follow-up period was 2,231 days, with 782 days and 3448 days as the 25th and 75th percentiles, respectively.

Post-LDLT tumor recurrence. HCC recurrence after LDLT was set as the primary end-point. Tumor recurrence was defined when any

imaging studies, such as chest or abdominal CT scan, or bone scintigraphy revealed recurrence of HCC. Recurrence-free survival was defined as the time period between LDLT and tumor recurrence. Recipient mortality after the LDLT was set as the secondary end-point. Overall survival was defined as the time period between LDLT and recipient death.

Statistical analysis. Recurrence-free and overall survival rates were calculated by the Kaplan-Meier product-limited method. Data are expressed as means. All statistical analyses were performed using JMP 9.0 software (SAS, Inc., Cary, NC, USA). A *p*-value of <0.05 was considered significant.

Results

The characteristics of the present patients and donors are shown in Table I. More female patients were included within the MC. Patients within the MC had higher model for end-stage liver disease (MELD) score. Simultaneous splenectomy was performed more frequently in patients within the MC. Right lobe or posterior graft was used more frequently in recipients within the MC. The pre-transplant AFP or DCP level was lower in patients within the MC, whereas the pre-transplant NLR was not different between the two groups. Pre-transplant treatment for HCC was more frequently performed in patients not within MC. Microvascular invasion on explant pathology was more frequently revealed in patients not within MC as was poor pathological tumor differentiation. Pathological examination revealed 39 livers (30.2%) were not within MC in patients defined as within

Table II. Characteristics of four patients within Milan criteria who had hepatocellular carcinoma recurrence after living donor liver transplantation (LDLT).

Variable	Case no.			
	1	2	3	4
Recipient				
Gender	Female	Female	Female	Female
Age at LDLT, years	59	58	47	60
Etiology	HCV	HCV	HBV	HCV
MELD score	3	11	18	17
Diabetes mellitus	No	No	Yes	No
Splenectomy	No	No	Yes	Yes
CNI	CyA	CyA	TAC	TAC
MMF	Yes	No	Yes	Yes
Donor				
Gender	Male	Male	Male	Male
Age at LDLT, years	28	36	38	63
Graft	Left	Left	Left	Posterior
GW-SLW ratio (%)	56.2	38.9	35.6	44.6
Tumor				
Maximum size (cm)	3	1	3	3.5
Number of nodules	3	1	3	1
Pre-transplant NLR	1.28	6.38	16.3	3.05
Pre-transplant AFP (ng/ml)	93.1	10.1	2.6	12,852
Pre-transplant DCP (mAU/ml)	102	7	37	636
Pre-transplant treatment	Yes	Yes	Yes	Yes
Times of Treatment	1	4	2	3
Treatment	TACE/RFA	MCT/TACE	TACE	MCT/TACE/radiation
Maximum size on pathology (cm)	3.2	3.2	3	3
Number of nodules on pathology	1	5	4	1
Microvascular invasion	No	No	No	No
Pathological differentiation	Moderate	Well	Moderate	Poor
Recurrence				
Recurrence site	Liver	Lymph node	Adrenal gland, liver, bone	Bilateral lung
Recurrence-free survival, years	7.81	1.13	2.52	1.22
Overall survival, years	11.0	11.0	7.1	1.7
Status at 2015/10/31	Alive	Alive	Alive	Dead

MELD: Model for end-stage liver disease, CNI: calcineurin inhibitor, MMF: mycophenolate mofeti, NLR: neutrophil-to-lymphocyte ratio, TAC: tacrolimus, CyA: cyclosporine A, GW: graft weight, SLW: standard liver weight, AFP: α -fetoprotein, DCP: *des*- γ -carboxy prothrombin, LDLT: living donor liver transplantation; TACE: transarterial chemoembolization; MCT: microwave coagulation therapy; RFA: radiofrequency ablation.

the MC by pre-transplant imaging, while in contrast, nine livers (13.2%) were within the MC in patients not within MC pre-transplant.

The 1-, 5-, and 10-year recurrence-free survival rates for patients within MC were 100%, 97.0% and 94.0%, respectively. In contrast, those in patients not within MC were 79.9%, 65.8% and 63.5%, respectively ($p < 0.0001$, Figure 1a).

Four out of the 129 patients within MC had HCC recurrence after LDLT. Detail id data of these four patients are shown in Table II. Patient 1 had HCC recurrence 7.8 years after LDLT due to uncontrollable hepatitis C virus (HCV) recurrence. Therefore, this recurrence was believed to be *de novo* HCC. Patients 2 and 3 had high pre-transplant

NLR. Furthermore, patient 4 had high pre-transplant AFP and DCP levels. The mean NLR of these four patients was significantly higher compared to that of 125 patients without HCC recurrence (6.75 *vs.* 2.75, $p = 0.002$). Additionally, the mean AFP level of these four patients was higher compared to that of 125 patients without HCC recurrence (3,239 *vs.* 197 ng/ml, $p < 0.001$). Other variables, including DCP, were not statistically different between the group with HCC recurrence and that with no recurrence.

The 1-, 5-, and 10-year overall survival rates for the patients within MC were 94.5%, 89.9% and 88.6%, respectively. In contrast, those for the patients not within MC were 88.1%, 67.6% and 57.8%, respectively ($p < 0.0001$, Figure 1b).

Table III. Characteristics of 13 recipients within Milan criteria who died after living donor liver transplantation (LDLT).

Variable	Case no.												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Recipient gender	Female	Male	Female	Female	Male	Male	Female	Female	Female	Female	Male	Male	Female
Recipient age at LDLT, years	43	62	21	60	59	47	69	53	62	60	63	65	61
Etiology	HCV	HCV	HCV	HCV	HCV	HBV	HCV	HCV	HCV	HCV	HBV	HCV	HCV
MELD score	3	17	7	8	8	4	24	10	16	17	13	15	15
Diabetes Mellitus	No	No	No	No	No	No	Yes	No	No	No	No	Yes	No
Splenectomy	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CNI	CyA	CyA	CyA	CyA	TAC	None	CyA	None	TAC	TAC	None	CyA	CyA
MMF	Yes	Yes	Yes	Yes	Yes	None	Yes	Yes	Yes	Yes	None	Yes	Yes
Donor gender	Male	Male	Male	Female	Male	Male	Male	Male	Male	Male	Female	Female	Male
Donor age at LDLT, years	22	33	49	31	28	48	34	52	61	63	62	28	31
Graft	Left	Left	Left	Left	Left	Left	Left	Posterior	Left	Posterior	Right	Left	Left
GW-SLW ratio (%)	34.6	44.4	44.2	30.1	42.2	34.9	31.7	26.7	35.4	44.6	34.1	29.0	52.3
Maximum tumor size (cm)	3	3	0	2.5	1	4	2	1	0	3.5	2.5	0	2.6
Number of nodules	2	2	0	1	1	1	1	1	0	1	2	0	1
NLR	3.60	1.64	3.43	1.15	0.40	4.02	3.32	0.72	7.08	3.05	0.94	0.85	8.09
AFP (ng/ml)	30.5	12.0	90.6	83.5	21.9	2.0	2.0	11.8	3.70	12,852	23.7	9.9	816.7
DCP (mAU/ml)	13	258	3	22	13	48	276	10	89	636	50	29	75
Maximum size on pathology (cm)	3	2.8	0.6	2.5	1.2	3.5	2	0.8	0.6	3	3.8	1.6	1.8
Number of nodules on pathology	5	3	1	1	2	1	1	3	1	1	3	2	7
Microvascular invasion	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No
Pathological differentiation	Poor	Mod	Well	Mod	Well	Mod	Mod	Mod	Well	Poor	Mod	Mod	Mod
Survival, years	5.46	3.22	0.18	1.63	2.14	0	0.91	0.04	0.04	1.74	0.02	1.08	0.56
Cause of death	Accident	HCV	Sepsis	HCV	HCV	Blood loss	Accident	Graft failure	Cerebral hemorrhage	HCC	Graft failure	Sudden death	Cerebral hemorrhage

HBV/HCV: Hepatitis B virus/hepatitis C virus, CNI: calcineurin inhibitor, MMF: mycophenolate mofetil, MELD: Model for end-stage liver disease, NLR: neutrophil-to-lymphocyte ratio, TAC: tacrolimus, CyA: tacrolimus A, GW: graft weight, SLW: standard liver weight, AFP: α -fetoprotein, DCP: *des*- γ -carboxy prothrombin, mod: moderate.

Thirteen out of the 129 patients within MC died within 10 years after LDLT. Causes of death were HCV recurrence (n=3), cerebral hemorrhage (n=2), hepatic graft failure (n=2), accident (n=2), HCC recurrence (n=1), sepsis (n=1), blood loss during LDLT (n=1), and sudden death of unknown origin (n=1) (Table III).

Discussion

LT is an effective treatment for HCC when disease is defined by the widely accepted MC (12). Transplantation for patients within MC generally leads to a 5-year overall survival rate of 70 to 80% and a recurrence rate of around 10% (13). In other words, 10% of patients even within MC have HCC recurrence and 20% of patients would die within 5 years after LT. It is important to consider the ethical aspects of transplanting using living donors. Donor safety is the paramount concern in any donor surgery in LDLT. The risk to the donor must balance the benefit to the donor in terms of survival of the recipient (14). The final goal of LDLT is to achieve patient survival as long as possible.

It is of great interest that only one patient among 129 patients within MC died due to HCC recurrence after LDLT in the present study. This patient underwent microwave coagulation therapy, TACE and radiation for HCC and had high AFP and DCP levels before LDLT. Multiple lung metastases were revealed 1.2 years after LDLT. This means that the patient had micrometastases in the lung before LDLT. When patients within MC have extremely high levels of tumor markers, distant micrometastasis rather than poor tumor behavior of the original liver tumor might be suspected. The other three patients with recurrence are alive after successful surgical resection for liver, bone or lymph node metastasis. Similarly to a previous report, surgical resection is useful for recurrent HCC in order to improve the outcome, when resection is feasible (15).

It is well-known that systemic inflammation is strongly associated with patient prognosis. The NLR has recently emerged as a useful prognostic factor for recurrence of several gastroenterological malignancies. It has been demonstrated that a preoperatively elevated NLR is an adverse predictor of recurrence-free survival for patients

undergoing hepatic resection for HCC (16). Furthermore, an elevated NLR significantly increases the risk of HCC recurrence after LT (6, 17). Pre-transplant NLR in two patients was elevated and the mean NLR of four patients who had HCC recurrence was significantly higher than that of 125 recipients without HCC recurrence. There are several possible mechanisms to explain the predictive role of preoperatively elevated NLR (18). Infiltration of proinflammatory macrophages, cytokines, and chemokines in the tumor microenvironment can boost tumor growth, invasion, and metastasis (19, 20). Furthermore, high expression of granulocyte colony-stimulating factor in tumor tissue and macrophage colony-stimulating factor in peritumoral tissue are associated with an increase in circulating neutrophils and poor prognosis (21). Halazun *et al.* showed that an elevated NLR is correlated with microvascular invasion and poorly differentiated tumor (22). The results of the present study were inconsistent with previous findings due to the small number of patients with recurrence. An elevated NLR in patients within MC could be a marker of distant metastasis, similarly to AFP and DCP. Several studies have suggested the benefit of adjuvant chemotherapy after LT for advanced HCC (23-25). Patients within MC with elevated NLR, AFP or DCP would be candidates for adjuvant chemotherapy after LT. Further study is needed because agents for chemotherapy for treating HCC are not well established.

HCV infection is the leading indication for LT worldwide. One patient in the present study had *de novo* HCC 7 years after LDLT and three patients died due to interferon treatment failure for HCV. After LT, HCV recurrence is universal among patients with viremia before LT (26) and is the leading cause of death in LT recipients. The standard care for the treatment of recurrent HCV after LT was peg-interferon with ribavirin, although with response rates of only 13 to 43% (27). In addition, interferon-based therapies can induce alloimmune graft injury, reducing patient survival (28). Recent advances of an interferon-free, direct-acting anti-viral (DAA) regimen seems to be able to change the fate of such patients. Such a multi-targeted DAA regimen resulted in a 97% sustained virological response rate for patients with HCV recurrence after LT (27).

In conclusion, the outcome of LDLT for patients with HCC within MC was outstanding. Careful follow-up after LDLT is necessary for patients with a high NLR or AFP level. An increase in NLR or AFP suggests distant micrometastasis before LDLT which might need adjuvant systemic chemotherapy.

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Conflicts of Interest

The Authors declare no conflicts of interest.

References

- Vitale A, Morales RR, Zanusi G, Farinati F, Burra P, Angeli P, Frigo AC, Del Poggio P, Rapaccini G, Di Nolfo MA, Benvegna L, Zoli M, Borzio F, Giannini EG, Caturelli E, Chiaramonte M, Trevisani F and Cillo U: Barcelona clinic liver cancer staging and transplant survival benefit for patients with hepatocellular carcinoma: A multicentre, cohort study. *Lancet Oncol* 12(7): 654-662, 2011.
- Llovet JM, Burroughs A and Bruix J: Hepatocellular carcinoma. *Lancet* 362(9399): 1907-1917, 2003.
- Yoshizumi T, Ikegami T, Yoshiya S, Motomura T, Mano Y, Muto J, Ikeda T, Soejima Y, Shirabe K and Maehara Y: Impact of tumor size, number of tumors and neutrophil-to-lymphocyte ratio in liver transplantation for recurrent hepatocellular carcinoma. *Hepatol Res* 43(7): 709-716, 2013.
- Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A and Gennari L: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 334(11): 693-699, 1996.
- Taketomi A, Sanefuji K, Soejima Y, Yoshizumi T, Uchiyama H, Ikegami T, Harada N, Yamashita Y, Sugimachi K, Kayashima H, Iguchi T and Maehara Y: Impact of des-gamma-carboxy prothrombin and tumor size on the recurrence of hepatocellular carcinoma after living donor liver transplantation. *Transplantation* 87(4): 531-537, 2009.
- Yoshizumi T, Ikegami T, Toshima T, Harimoto N, Uchiyama H, Soejima Y, Yamashita Y, Shirabe K and Maehara Y: Two-step selection criteria for living donor liver transplantation in patients with hepatocellular carcinoma. *Transplant Proc* 45(9): 3310-3313, 2013.
- Yoshizumi T, Ikegami T, Bekki Y, Ninomiya M, Uchiyama H, Iguchi T, Yamashita Y, Kawanaka H, Shirabe K and Maehara Y: Re-evaluation of the predictive score for 6-month graft survival in living donor liver transplantation in the modern era. *Liver Transpl* 20(3): 323-332, 2014.
- Yoshizumi T, Shirabe K, Taketomi A, Uchiyama H, Harada N, Ijichi H, Yoshimatsu M, Ikegami T, Soejima Y and Maehara Y: Risk factors that increase mortality after living donor liver transplantation. *Transplantation* 93(1): 93-98, 2012.
- Urata K, Kawasaki S, Matsunami H, Hashikura Y, Ikegami T, Ishizone S, Momose Y, Komiyama A and Makuuchi M: Calculation of child and adult standard liver volume for liver transplantation. *Hepatology* 21(5): 1317-1321, 1995.
- Yoshizumi T, Ikegami T, Kimura K, Uchiyama H, Ikeda T, Shirabe K and Maehara Y: Selection of a right posterior sector graft for living donor liver transplantation. *Liver Transpl* 20(9): 1089-1096, 2014.
- Yoshizumi T, Shirabe K, Ikegami T, Kayashima H, Yamashita N, Morita K, Masuda T, Hashimoto N, Taketomi A, Soejima Y and Maehara Y: Impact of human t cell leukemia virus type 1 in living donor liver transplantation. *Am J Transplant* 12(6): 1479-1485, 2012.
- Miltiados O, Sia D, Hoshida Y, Fiel MI, Harrington AN, Thung SN, Tan PS, Dong H, Reville K, Chang CY, Roayaie S, Byrne TJ, Mazzaferro V, Rakela J, Florman S, Schwartz M and Llovet JM:

- Progenitor cell markers predict outcome of patients with hepatocellular carcinoma beyond milan criteria undergoing liver transplantation. *J Hepatol* 63(6): 1368-1377, 2015.
- 13 Easl-eortc clinical practice guidelines: Management of hepatocellular carcinoma. *J Hepatol* 56(4): 908-943, 2012.
 - 14 Yoshizumi T, Shirabe K, Soejima Y, Taketomi A, Yamashita N, Ikegami T, Uchiyama H, Kayashima H, Ninomiya M and Maehara Y: Living donor liver transplantation in patients older than 60 years. *Transplantation* 90(4): 433-437, 2010.
 - 15 Taketomi A, Fukuhara T, Morita K, Kayashima H, Ninomiya M, Yamashita Y, Ikegami T, Uchiyama H, Yoshizumi T, Soejima Y, Shirabe K and Maehara Y: Improved results of a surgical resection for the recurrence of hepatocellular carcinoma after living donor liver transplantation. *Ann Surg Oncol* 17(9): 2283-2289, 2010.
 - 16 Gomez D, Farid S, Malik HZ, Young AL, Toogood GJ, Lodge JP and Prasad KR: Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma. *World J Surg* 32(8): 1757-1762, 2008.
 - 17 Motomura T, Shirabe K, Mano Y, Muto J, Toshima T, Umemoto Y, Fukuhara T, Uchiyama H, Ikegami T, Yoshizumi T, Soejima Y and Maehara Y: Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. *J Hepatol* 58(1): 58-64, 2013.
 - 18 Wang GY, Yang Y, Li H, Zhang J, Jiang N, Li MR, Zhu HB, Zhang Q and Chen GH: A scoring model based on neutrophil to lymphocyte ratio predicts recurrence of hbv-associated hepatocellular carcinoma after liver transplantation. *PLoS One* 6(9): e25295, 2011.
 - 19 Mantovani A, Allavena P, Sica A and Balkwill F: Cancer-related inflammation. *Nature* 454(7203): 436-444, 2008.
 - 20 Shirabe K, Mano Y, Muto J, Matono R, Motomura T, Toshima T, Takeishi K, Uchiyama H, Yoshizumi T, Taketomi A, Morita M, Tsujitani S, Sakaguchi Y and Maehara Y: Role of tumor-associated macrophages in the progression of hepatocellular carcinoma. *Surg Today* 42(1): 1-7, 2012.
 - 21 Zhu XD, Zhang JB, Zhuang PY, Zhu HG, Zhang W, Xiong YQ, Wu WZ, Wang L, Tang ZY and Sun HC: High expression of macrophage colony-stimulating factor in peritumoral liver tissue is associated with poor survival after curative resection of hepatocellular carcinoma. *J Clin Oncol* 26(16): 2707-2716, 2008.
 - 22 Halazun KJ, Hardy MA, Rana AA, Woodland DCt, Luyten EJ, Mahadev S, Witkowski P, Siegel AB, Brown RS Jr. and Emond JC: Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. *Ann Surg* 250(1): 141-151, 2009.
 - 23 Lin HS, Wan RH, Gao LH, Li JF, Shan RF and Shi J: Adjuvant chemotherapy after liver transplantation for hepatocellular carcinoma: A systematic review and a meta-analysis. *Hepatobiliary Pancreat Dis Int* 14(3): 236-245, 2015.
 - 24 Xu J, Shen ZY, Chen XG, Zhang Q, Bian HJ, Zhu P, Xu HY, Song F, Yang XM, Mi L, Zhao QC, Tian R, Feng Q, Zhang SH, Li Y, Jiang JL, Li L, Yu XL, Zhang Z and Chen ZN: A randomized controlled trial of licartin for preventing hepatoma recurrence after liver transplantation. *Hepatology* 45(2): 269-276, 2007.
 - 25 Schlitt HJ and Schnitzbauer AA: Hepatocellular carcinoma: Agents and concepts for preventing recurrence after curative treatment. *Liver Transpl* 17(Suppl 3): S10-12, 2011.
 - 26 Berenguer M, Prieto M, Rayon JM, Mora J, Pastor M, Ortiz V, Carrasco D, San Juan F, Burgueno MD, Mir J and Berenguer J: Natural history of clinically compensated hepatitis c virus-related graft cirrhosis after liver transplantation. *Hepatology* 32(4 Pt 1): 852-858, 2000.
 - 27 Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R, Jr., Gordon F, Levitsky J, Terrault NA, Burton JR Jr., Xie W, Setze C, Badri P, Pilot-Matias T, Vilchez RA and Forns X: An interferon-free antiviral regimen for hcv after liver transplantation. *N Engl J Med* 371(25): 2375-2382, 2014.
 - 28 Levitsky J, Fiel MI, Norvell JP, Wang E, Watt KD, Curry MP, Tewani S, McCashland TM, Hoteit MA, Shaked A, Saab S, Chi AC, Tien A and Schiano TD: Risk for immune-mediated graft dysfunction in liver transplant recipients with recurrent hcv infection treated with pegylated interferon. *Gastroenterology* 142(5): 1132-1139 e1131, 2012.

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