

# Living Donor Liver Transplantation for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis after Concurrent Chemoradiation Therapy

Dai Hoon Han<sup>1,2</sup>, Dong Jin Joo<sup>1,2,3</sup>, Myoung Soo Kim<sup>1,3</sup>, Gi Hong Choi<sup>1,2,3</sup>, Jin Sub Choi<sup>1,2,3</sup>, Young Nyun Park<sup>2,4</sup>, Jinsil Seong<sup>2,5</sup>, Kwang-Hyub Han<sup>2,6</sup>, and Soon Il Kim<sup>1,3</sup>

<sup>1</sup>Department of Surgery, <sup>2</sup>Liver Cancer Special Clinic, <sup>3</sup>Research Institute for Transplantation, Departments of <sup>4</sup>Pathology, <sup>5</sup>Radiological Oncology, and <sup>6</sup>Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.

Locally advanced hepatocellular carcinoma (HCC) with portal vein thrombosis carries a 1-year survival rate <10%. Localized concurrent chemoradiotherapy (CCRT), followed by hepatic arterial infusion chemotherapy (HAIC), was recently introduced in this setting. Here, we report our early experience with living donor liver transplantation (LDLT) in such patients after successful down-staging of HCC through CCRT and HAIC. Between December 2011 and September 2012, eight patients with locally advanced HCC at initial diagnosis were given CCRT, followed by HAIC, and underwent LDLT at the Severance Hospital, Seoul, Korea. CCRT [45 Gy over 5 weeks with 5-fluorouracil (5-FU) as HAIC] was followed by HAIC (5-FU/cisplatin combination every 4 weeks for 3–12 months), adjusted for tumor response. Down-staging succeeded in all eight patients, leaving no viable tumor thrombi in major vessels, although three patients first underwent hepatic resections. Due to deteriorating liver function, transplantation was the sole therapeutic option and offered a chance for cure. The 1-year disease-free survival rate was 87.5%. There were three instances of post-transplantation tumor recurrence during follow-up monitoring (median, 17 months; range, 10–22 months), but no deaths occurred. Median survival time from initial diagnosis was 33 months. Four postoperative complications recorded in three patients (anastomotic strictures: portal vein, 2; bile duct, 2) were resolved through radiologic interventions. Using an intensive tumor down-staging protocol of CCRT followed by HAIC, LDLT may be a therapeutic option for selected patients with locally advanced HCC and portal vein tumor thrombosis.

**Key Words:** Concurrent chemoradiation, hepatocellular carcinoma, living donor liver transplantation, thrombus, down-staging

The prognosis of locally advanced hepatocellular carcinoma (HCC) patients with portal vein tumor thrombosis (PVTT) re-

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**Co-corresponding authors:** Dr. Soon Il Kim, Department of Surgery, and Research Institute for Transplantation, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.

Tel: 82-2-2228-2118, Fax: 82-2-313-8289, E-mail: soonkim@yuhs.ac and Dr. Kwang-Hyub Han, Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.

Tel: 82-2-2228-1949, Fax: 82-2-393-6884, E-mail: gihankhys@yuhs.ac

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mains dismal. Median survival time without treatment is only 2.7 months.<sup>1</sup> Transarterial chemoembolization (TACE) and chemotherapy have been used as palliation,<sup>2-5</sup> and hepatic resection has been attempted as a curative measure, with less than satisfactory outcomes.<sup>5-8</sup> Under these circumstances, liver transplantation has been considered a contraindication.<sup>9-11</sup>

Chapman, et al.<sup>12</sup> have indicated that prolonged survival is achievable in this context through down-staging of HCC via neoadjuvant TACE and liver transplantation. Furthermore, Han, et al.<sup>13</sup> recently reported an objective response rate of 45% using other modes of adjuvant treatment, such as localized concurrent chemoradiotherapy (CCRT), followed by hepatic arterial infusion chemotherapy (HAIC). Moreover, Lee, et al.<sup>14</sup> recently reported surgical outcome of liver resection after down-staging of locally advanced HCC localized CCRT with 49.6% of 5-year overall survival rate. Herein, we report our early experi-

ence of living donor liver transplantation (LDLT) in eight patients with locally advanced HCC and PVTT after successful down-staging of tumor through CCRT followed by HAIC.

Diagnosis of HCC was based on either pathologic confirmation or radiologic findings. Patients with unresectable HCC and PVTT in the main trunk or first order branch were indicated for CCRT following HAIC. Resectability was decided through regular multidisciplinary approach meeting by hepatobiliary surgeons, transplantation surgeons, hepatologists, radiologists, and radiation oncologists, based on patient's liver function and radiologic image. To assess feasibility of LDLT, hepatobiliary surgeons and transplantation surgeons reviewed the degree and extent of portal vein thrombosis, checking for hepatic arterial stricture or stenosis, as well as viability of extra-hepatic bile duct and the need for vascular or biliary reconstruction. In patients with locally advanced HCC and PVTT, localized CCRT was administered according to the standard protocol established (1998) at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, followed by HAIC. This protocol has been described previously. Briefly, patients received a total radiation dose of 45 Gy in 25 fractions over a 5-week period, with concurrent HAIC of 5-fluorouracil (5-FU), 500 mg daily delivered via indwelling percutaneous hepatic arterial catheter during weeks 1 and 5 of radiotherapy. One month after localized CCRT, 5-FU (500 mg/m<sup>2</sup> over 5 hours on days 1–3) and cisplatin (60 mg/m<sup>2</sup> over 2 hours on day 2) were infused every 4 weeks for 3–12 months, adjusting for tumor response.<sup>13</sup> LDLTs were performed in eight consecutive patients who achieved successful down-staging of HCC by this means between December, 2011 and September, 2012. Upon approval of our Institutional Review Board, data of all consecutive patients were collected.

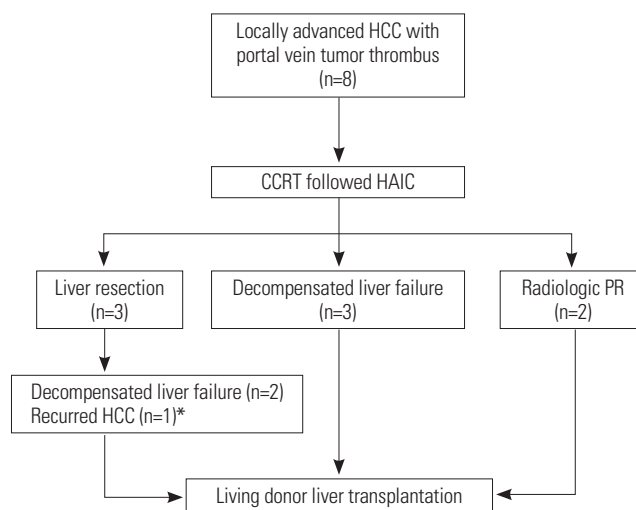
Histopathology of explanted liver was evaluated by a single pathologist with appropriate expertise (YNP). Trans-abdominal Doppler ultrasonography was performed on days 1, 2, and 4 post-transplantation to monitor the patency of hepatic and portal vascular anastomoses. Thereafter, dynamic multi-detector computed tomography (MDCT) was done on days 7, 14, and 21 post-transplantation, primarily to confirm patency of hepatic vessels and to monitor patients for potential postoperative complications. As surveillance for tumor recurrence, MDCT was performed every 6 months during the first year post-transplantation, then on a yearly basis. Tumor markers such as alpha-fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKA-II) were routinely checked each month. Disease-free survival rate was calculated by the Kaplan-Meier method with SPSS 20 for Windows (SPSS Inc., Chicago, IL, USA).

Each patient initially presented with locally advanced HCC and intrahepatic PVTT as well as active hepatitis B viral infection; and each was subjected to a regimen of CCRT, followed by HAIC, for tumor down-staging. All but one were male (median age, 46 years; range, 38–52 years). Three patients first underwent hepatic resections (hemi-hepatectomies: left, 2; right,

1), but intrahepatic recurrences developed in all three. TACE procedures, performed for tumor down-staging, had resulted in peribiliary necrosis (n=2) and liver failure (n=3). Semi-elective LDLTs were performed as life-saving treatment in these five patients, whose hepatic functions were rapidly deteriorating (Fig. 1).

Biologic and morphologic status of HCC improved after CCRT and other treatments. In all patients, serum tumor markers were initially quite high [AFP: median, 4418.07 ng/mL (range, 4.06–69912.95 ng/mL); PIVKA-II: median, 2000 mAU/mL (range, 16–14044 mAU/mL)] but dropped dramatically prior to LDLT [AFP: median, 26.87 ng/mL (range, 1.70–251.34 ng/mL); PIVKA-II: median, 84.5 mAU/mL (range, 18–350 mAU/mL)]. Median tumor diameter (at maximum) was 10.8 cm initially (range, 6.4–15.4 cm) by radiologic assessment, falling to 3.8 cm (range, 1.3–9.0 cm) at post-transplantation pathologic examination (Fig. 2). No viable tumor was evident in the explanted livers of two patients, indicating complete resolution of HCC after CCRT followed by HAIC (Table 1, Fig. 3).

Median post-transplantation follow-up monitoring was 17 months (range, 10–22 months), and median survival time from initial diagnosis was 33 months (range, 22–48 months). No patient deaths occurred during the follow-up period, although three patients developed recurrent HCC at 4, 10, and 13 months post-transplantation as follows: multiple intrahepatic metastases (patient 6, day 119), supraclavicular node metastasis (patient 4, day 294), and solitary lung metastasis (patient 1, day 394) (Table 2). The lung and lymph node metastases were sur-

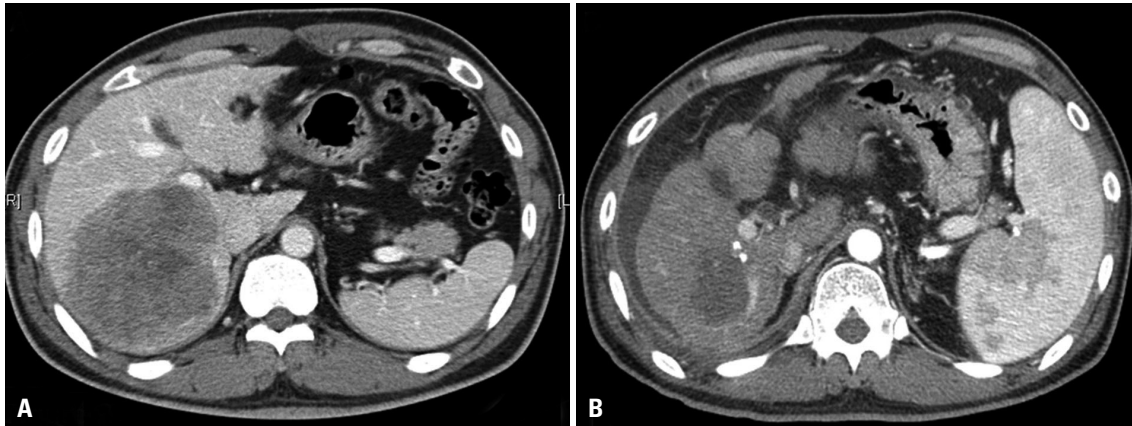


**Fig. 1.** Events leading to liver transplantation: overall, eight patients underwent living donor liver transplantation (LDLT) after concurrent chemoradiotherapy, followed by hepatic arterial infusion chemotherapy. Advanced status of tumor (with portal vein tumor thrombosis) was initially down-staged via pre-transplant regimen. In five patients, transplantations constituted rescue therapy for hepatic decompensation. \*The patient underwent LDLT after down-staging for recurrent HCC without decompensated liver failure. CCRT, concurrent chemoradiotherapy; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; PR, partial response.

gically resected with no further progression of disease. The patient with multiple intrahepatic metastases and portocaval lymph node metastasis underwent transcatheter arterial chemoinfusion (TACI), followed by oral sorafenib (Nexavar®; Bay-

er Pharma AG, Berlin, Germany).

Intraoperative bleeding during LDLT was greater than expected, due to extensive adhesions and deteriorated states of perihepatic anatomy. Median intraoperative blood loss was 7550 cc

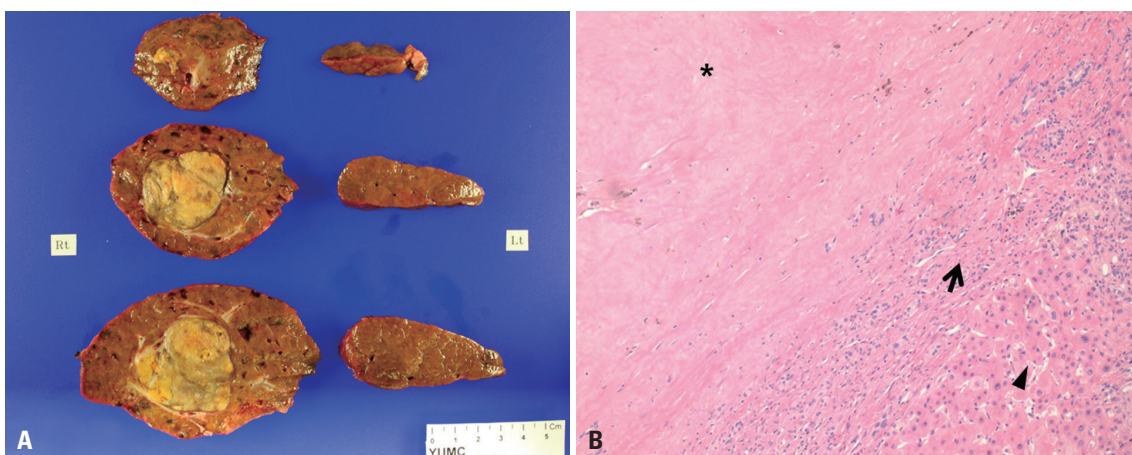


**Fig. 2.** Radiologic tumor response (to concurrent chemoradiotherapy, followed by hepatic arterial infusion chemotherapy): computed tomography demonstrates bulky 12 cm hepatocellular carcinoma of right lobe (A), decreasing to 6 cm size, seen without enhancement in arterial phase (B). Voluminous ascites and splenomegaly developed, due to severe parenchymal atrophy and progressive hepatic dysfunction (B).

**Table 1.** Biologic and Morphologic Responses before and after Liver Transplantation

Pt	Tumor marker response						Initial radiologic findings		Pathologic findings	
	Initial AFP	Pre-LT AFP	AFP at last F/U	Initial PIVKA-II	Pre-LT PIVKA-II	PIVKA-II at last F/U	Largest (cm)	Number	Largest (cm)	Viable tumor
1*	69912.95	42.88	11.65	2000	350	106	12.5	Multiple	2.8 (95% Nc)	3
2	356.21	4.06	2.96	16	58	14	9.6	4	1.3	1
3	3690.65	1.7	4.25	2000	166	15	15.4	2	6.5 (TNc)	0
4*	28754.5	40.52	1275.25	2000	46	888	12.0	2	4.8 (TNc)	0
5	5.3	13.21	4.39	468	21	731	7.0	1	1.5 (99% Nc)	1
6*	4.06	8.72	1.14	163	234	840	7.1	2	6.0 (TNc)	1
7	42166.28	202.27	287.02	2000	111	27	15.0	Multiple	9.0 (99% Nc)	4
8	5145.49	251.34	2.68	14044	18	23	6.4	1	1.4 (50% Nc)	2

AFP,  $\alpha$ -fetoprotein (ng/mL); LT, liver transplantation; Nc, necrosis; PIVKA-II, protein induced by vitamin K absence-II (mAU/mL); Pt, patient; TNc, total necrosis. \*Recurrence after liver transplantation.



**Fig. 3.** Gross and microscopic views of liver specimen: note expansile necrotic mass 4.8 cm in size, with diffuse macronodular parenchymal cirrhosis (A). At high magnification, complete necrosis of hepatocellular carcinoma (near asterisk), inflammatory change (near arrow), and normal hepatocytes (near arrowhead) are observed (B; hematoxylin and eosin stain,  $\times 100$ ).

**Table 2.** Survival Outcomes after Living Donor Liver Transplantation

Patients	Survival time (from initial diagnosis)	Follow-up duration (post-transplant)	Mortality	Recurrence	Time to recurrence after liver transplantation	Site of recurrence
1	28	22	-	+	13	Lung
2	48	21	-	-		
3	48	18	-	-		
4	34	17	-	+	10	Supraclavicular node
5	28	17	-	-		
6	44	14	-	+	4	Liver, portocaval lymph node
7	32	13	-	-		
8	22	10	-	-		
Median value	33	17				

Numerical values expressed in months.

**Table 3.** Perioperative Conditions of Patients

Pt	Sex/age	MELD	Pre-LT treatment			Transfusion of pRBC	Uncommon anastomosis			Postop Cx
			CCRT	TACE or TACI	Liver resection		PV	HA	BD	
1	M/46	12	+	+	-	5				BD stricture
2	F/48	22	+	+	+	15	iliac a. conduit	MCA inter.	RY	PV stricture
3	M/52	12	+	-	-	10		MHA		PV & BD stricture
4	M/45	7	+	+	-	7		RGEA trans.	RY	
5	M/44	7	+	+	-	0				
6	M/38	9	+	+	+	11				
7	M/51	8	+	+	-	5		LGA trans.	RY	
8	M/52	7	+	+	+	5		RGEA trans.		

BD, bile duct; CCRT, concurrent chemoradiotherapy; HA, hepatic artery; iliac a., iliac artery; inter., interposition; LGA, left gastric artery; LT, liver transplantation; MCA, middle colic artery; MELD, model for end-stage liver disease score; MHA, middle hepatic artery; Postop Cx, postoperative complication; pRBC, packed red blood cell (unit); PV, portal vein; RGEA, right gastroepiploic artery; RY, Roux-en Y hepaticojejunostomy; TACE, transarterial chemoembolization; trans., transposition.

(range, 2500–12200 cc). Patient 2 had suffered peribiliary necrosis prior to transplantation, resulting in significant hilar restructuring (i.e., portal vein anastomosis, using preserved iliac artery conduit; anastomosis of hepatic artery, with autologous middle colic artery interposition; and Roux-en Y hepaticojejunostomy for anastomosis of bile duct). Five of eight patients required unconventional hepatic artery anastomoses, using autologous arterial interposition or transposition graft. In three patients, Roux-en Y hepaticojejunostomy was done for bile duct reconstruction. Ultimately, four complications related to anastomoses were recorded in three patients (bile duct stricture, 2; portal vein stenosis, 2) (Table 3). All complications were successfully resolved through radiologic interventions.

Liver transplantation is considered one of the best treatment options for patients with early-stage HCC.<sup>15–17</sup> However, this accounts for only 10–20% of those with HCC overall. The majority of sufferers have more advanced disease.<sup>18</sup> Various down-staging procedures, including radiofrequency ablation, TACE, TACI, and transarterial radioembolization with Yttrium-90 microspheres (TARE-Y90), have been devised for advanced HCC.<sup>10,12,18–21</sup> However, recent use of liver transplantation after successful down-staging of tumors has yielded acceptable results compared with outcomes of liver transplantation in ear-

ly-stage HCC and in end-stage liver disease.<sup>22–24</sup>

TACE or TARE-Y90 are viewed as a relative contraindications in patients with advanced HCC and PVTT, because conventional down-staging protocols have had negligible success.<sup>25</sup> Using a regimen of localized CCRT followed by HAIC in precisely such patients, who were unresponsive to conventional therapy, Han, et al.<sup>13</sup> showed a substantial response rate (45%) and an acceptable median survival time (13.1 months). Localized radiotherapy (RT) of the liver has also emerged as an effective means of controlling the progression of HCC, compared with whole-liver RT.<sup>26</sup> Highly selective localized RT enables more intense targeting of masses in liver, with less hepatotoxicity.

Conventional systemic chemotherapy has proven ineffective in HCC, and toxicity is an issue. However, HAIC allows local delivery of chemotherapeutic agents in greater concentrations, alleviating systemic toxicity.<sup>2,27–29</sup> With concurrent use of hepatic RT and HAIC, response rates in patients with locally advanced HCC stand to improve, although roughly a 30% rate of hepatic decompensation has been reported with the use of CCRT followed by HAIC in this setting.<sup>13</sup>

Generally, patients with locally advanced HCC and PVTT have been ineligible for liver transplantation, even with down-staging, due to high rates of tumor recurrence.<sup>9–11</sup> Earlier, we per-

formed LDLTs as life-saving interventions in five patients, who suffered from rapid hepatic functional deterioration after CCRT and HAIC. Given satisfactory short-term outcomes in these initial five attempts, we then performed LDLTs in another three patients, who achieved down-staging of HCC. No mortalities occurred during the follow-up periods, and the 1-year disease-free survival rate was 75.0%.

There are two critical factors in this group of patients, in terms of eligibility for LDLT. The first issue is operative feasibility, which is often hampered by significant anatomic deterioration after various down-staging procedures, including RT, HAIC, and other treatments (e.g., TACE or liver resection). Radiation alone is known to damage the microvasculature and induce hepatic fibrosis.<sup>30</sup> Moreover, HAIC and TACE create significant hepatic hilar inflammation and intimal arterial injury, and their inflict may result in vascular thrombosis, adding to radiation effect.<sup>18,31</sup> In this particular group of patients, LDLTs are demanding procedures, subject to elaborate preoperative preparation.

Only three of our eight patients were suited for conventional anastomoses of hilar structures. Modifications were otherwise required for reconstruction of hepatic vessels and biliary drainage. In patient 2, cryopreserved iliac artery was used as a conduit for portal vein anastomosis (due to thrombosis); hepatic artery anastomosis required autologous middle colic artery interposition graft (due to stenosis); and Roux-en-Y hepaticojejunostomy was performed for bile duct reconstruction. These types of complex and technically demanding anastomoses in damaged areas resulted in some postoperative complications: in three patients, a total of two portal vein and two bile duct strictures developed at anastomotic sites, but all complications were resolved through radiologic interventions. Nevertheless, reconstruction of vascular and biliary system was feasible, and all complications were resolved through radiologic interventions. Thus, LDLTs are not off-limits in these patients.

The second critical issue is the achieved degree of tumor down-staging. For survival of both patient and graft, successful down-staging of HCC is a prerequisite, as determined by radiologic and biologic response to treatment. Tumor necrosis and change in tumor size on imaging studies are the indices of radiologic response. Biologic response is evaluated by declining levels of serum tumor factors, such as AFP and PIVKA-II. In most published studies, an acceptable serum AFP level is <400 ng/mL, which all of our patients displayed. Median pre-transplantation serum AFP level was 26.87 ng/mL (range, 1.7–251.34) (Table 1).

There were three instances of tumor recurrence during post-transplantation follow-up periods (Table 2). Two patients (solitary pulmonary nodule and supraclavicular node metastasis, respectively) were treated by surgical resection, with no further disease progression. The remaining patient, showing multiple intrahepatic metastases, underwent TACI, followed by adjuvant sorafenib. Unfortunately, portocaval lymph node metas-

tasis then presented. In patients with locally advanced HCC, chances of systemic recurrence after liver transplantation are actually quite high.<sup>15,32,33</sup> Thus, early detection of tumor recurrence and active treatment might be important for survival in these patients. Although one study has addressed the utility of adjuvant treatment for HCC after liver transplantation, controversy persists.<sup>34</sup> The recurrence pattern and prognosis will be further analyzed in future with agents of choice for adjuvant use.

This is the first-ever report of successful consecutive LDLTs in patients with locally advanced HCC and PVTT, after down-staging by using CCRT and HAIC. Nevertheless, appropriate patient selection, proper timing of transplants, and effective post-transplantation adjuvant therapy should be further investigated on a larger scale in a randomized controlled study. In the present study, median patient and graft survival of 33 months (range, 22–48 months) was achieved after initial diagnosis of HCC, compared with an expected 1-year survival of <10%.<sup>1,35,36</sup>

In conclusion, acceptable oncologic outcomes and short-term survival times are achievable in patients with locally advanced HCC and PVTT, using a down-staging regimen of CCRT followed by HAIC. However, long-term outcomes have yet to be determined.

## REFERENCES

- Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999;29:62-7.
- Ando E, Yamashita F, Tanaka M, Tanikawa K. A novel chemotherapy for advanced hepatocellular carcinoma with tumor thrombosis of the main trunk of the portal vein. *Cancer* 1997;79:1890-6.
- Liang LJ, Hu WJ, Yin XY, Zhou Q, Peng BG, Li DM, et al. Adjuvant intraportal venous chemotherapy for patients with hepatocellular carcinoma and portal vein tumor thrombi following hepatectomy plus portal thrombectomy. *World J Surg* 2008;32:627-31.
- Peng BG, He Q, Li JP, Zhou F. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. *Am J Surg* 2009;198:313-8.
- Peng ZW, Guo RP, Zhang YJ, Lin XJ, Chen MS, Lau WY. Hepatic resection versus transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma with portal vein tumor thrombus. *Cancer* 2012;118:4725-36.
- Lin DX, Zhang QY, Li X, Ye QW, Lin F, Li LL. An aggressive approach leads to improved survival in hepatocellular carcinoma patients with portal vein tumor thrombus. *J Cancer Res Clin Oncol* 2011;137:139-49.
- Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, et al. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. *Ann Surg Oncol* 2010;17:2073-80.
- Zhou Q, Wang Y, Zhou X, Peng B, Yang J, Liang L, et al. Prognostic analysis for treatment modalities in hepatocellular carcinomas with portal vein tumor thrombi. *Asian Pac J Cancer Prev* 2011;12:2847-50.
- Choi HJ, Kim DG, Na GH, Hong TH, You YK. Extended criteria for living donor liver transplantation in patients with advanced hepatocellular carcinoma. *Transplant Proc* 2012;44:399-402.

10. De Luna W, Sze DY, Ahmed A, Ha BY, Ayoub W, Keeffe EB, et al. Transarterial chemoinfusion for hepatocellular carcinoma as downstaging therapy and a bridge toward liver transplantation. *Am J Transplant* 2009;9:1158-68.
11. Hwang S, Moon DB, Lee SG. Liver transplantation and conventional surgery for advanced hepatocellular carcinoma. *Transpl Int* 2010;23:723-7.
12. Chapman WC, Majella Doyle MB, Stuart JE, Vachharajani N, Crippin JS, Anderson CD, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. *Ann Surg* 2008;248:617-25.
13. Han KH, Seong J, Kim JK, Ahn SH, Lee DY, Chon CY. Pilot clinical trial of localized concurrent chemoradiation therapy for locally advanced hepatocellular carcinoma with portal vein thrombosis. *Cancer* 2008;113:995-1003.
14. Lee HS, Choi GH, Choi JS, Kim KS, Han KH, Seong J, et al. Surgical resection after down-staging of locally advanced hepatocellular carcinoma by localized concurrent chemoradiotherapy. *Ann Surg Oncol* 2014;21:3646-53.
15. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693-9.
16. Yao FY. Liver transplantation for hepatocellular carcinoma: beyond the Milan criteria. *Am J Transplant* 2008;8:1982-9.
17. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;33:1394-403.
18. Toso C, Mentha G, Kneteman NM, Majno P. The place of downstaging for hepatocellular carcinoma. *J Hepatol* 2010;52:930-6.
19. Barakat O, Wood RP, Ozaki CF, Ankoma-Sey V, Galati J, Skolkin M, et al. Morphological features of advanced hepatocellular carcinoma as a predictor of downstaging and liver transplantation: an intention-to-treat analysis. *Liver Transpl* 2010;16:289-99.
20. Graziadei IW, Sandmueller H, Waldenberger P, Koenigsrainer A, Nachbaur K, Jaschke W, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. *Liver Transpl* 2003;9:557-63.
21. Ravaioli M, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. *Am J Transplant* 2008;8:2547-57.
22. Di Sandro S, Giacomoni A, Slim A, Lauterio A, Mangoni I, Mihaylov P, et al. Living donor liver transplantation for hepatocellular carcinoma: the impact of neo-adjuvant treatments on the long term results. *Hepatology* 2012;59:505-10.
23. Gordon-Weeks AN, Snaith A, Petrinic T, Friend PJ, Burls A, Silva MA. Systematic review of outcome of downstaging hepatocellular cancer before liver transplantation in patients outside the Milan criteria. *Br J Surg* 2011;98:1201-8.
24. Lei J, Wang W, Yan L. Downstaging advanced hepatocellular carcinoma to the Milan criteria may provide a comparable outcome to conventional Milan criteria. *J Gastrointest Surg* 2013;17:1440-6.
25. Lau WY, Lai EC. Salvage surgery following downstaging of unresectable hepatocellular carcinoma--a strategy to increase resectability. *Ann Surg Oncol* 2007;14:3301-9.
26. Robertson JM, Lawrence TS, Dworzancin LM, Andrews JC, Walker S, Kessler ML, et al. Treatment of primary hepatobiliary cancers with conformal radiation therapy and regional chemotherapy. *J Clin Oncol* 1993;11:1286-93.
27. Park JY, Ahn SH, Yoon YJ, Kim JK, Lee HW, Lee DY, et al. Repetitive short-course hepatic arterial infusion chemotherapy with high-dose 5-fluorouracil and cisplatin in patients with advanced hepatocellular carcinoma. *Cancer* 2007;110:129-37.
28. Park MS, Kim SU, Park JY, Kim do Y, Ahn SH, Han KH, et al. Combination treatment of localized concurrent chemoradiation therapy and transarterial chemoembolization in locally advanced hepatocellular carcinoma with intrahepatic metastasis. *Cancer Chemother Pharmacol* 2013;71:165-73.
29. Ueshima K, Kudo M, Takita M, Nagai T, Tatsumi C, Ueda T, et al. Hepatic arterial infusion chemotherapy using low-dose 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma. *Oncology* 2010;78 Suppl 1:148-53.
30. Mueller CK, Schultze-Mosgau S. Radiation-induced microenvironments--the molecular basis for free flap complications in the pre-irradiated field? *Radiother Oncol* 2009;93:581-5.
31. Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB, et al. Liver transplantation for unresectable perihilar cholangiocarcinoma. *Semin Liver Dis* 2004;24:201-7.
32. Iwatsuki S, Starzl TE, Sheahan DG, Yokoyama I, Demetris AJ, Todo S, et al. Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991;214:221-8.
33. Ringe B, Pichlmayr R, Wittekind C, Tusch G. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. *World J Surg* 1991;15:270-85.
34. Fujiki M, Aucejo F, Kim R. Adjuvant treatment of hepatocellular carcinoma after orthotopic liver transplantation: do we really need this? *Clin Transplant* 2013;27:169-77.
35. Pawarode A, Voravud N, Sriuranpong V, Kullavanijaya P, Patt YZ. Natural history of untreated primary hepatocellular carcinoma: a retrospective study of 157 patients. *Am J Clin Oncol* 1998;21:386-91.
36. Yeung YP, Lo CM, Liu CL, Wong BC, Fan ST, Wong J. Natural history of untreated nonsurgical hepatocellular carcinoma. *Am J Gastroenterol* 2005;100:1995-2004.