This study has several limitations inherent to any observational cohort study, including a small sample size representing HL practice at a single center, potentiating the risk of a type 2 error. In this study, the heart was the primary organ for allocation in all HL recipients, which may not be representative of the national HL experience (*8*). The effects of bypassing candidates on the wait list are most likely pertinent at the first few match run positions, which we believe justifies our inclusion of only the first five candidates. Confirmation of the findings from this study awaits analysis of national data.

In summary, this analysis suggests that liver candidates bypassed by HL dual transplants do not incur a survival disadvantage. Our intention is to highlight the previously unstudied consequences of dual organ transplantation and spur further inquiries into the indications and allocation practices for dual organ transplantation. Guidelines for dual-organ transplantation will ultimately need to be established which provide equipoise to single as well as dual organ candidates.

MATERIALS AND METHODS

This is a single-center retrospective cohort study of candidates who were ranked in the first five positions in liver transplant match runs that generated HL transplants (n=16) performed between 2001 and 2011 at the Hospital of the University of Pennsylvania. A control cohort was identified by matching each HL match run to two match runs that resulted in LA transplants. Donor characteristics, including: year of transplant, donation after neurologic determination of death, ABO blood type, donor age (±5 years), sex, and race were used to identify control match runs. As with HL match runs, the control cohort included the first five liver waiting list candidates at the time of a liver match. Wait list survival was categorized into the following groups: active on list at time of study, survival to transplant, removal from waiting list because of death or illness, and removal from list for other reasons. National figures of HL transplantation were obtained from the United Network for Organ Sharing database (1987 through 2013).

Comparisons of baseline characteristics between cohorts were calculated by Student's *t* test for normally distributed continuous variables and chi-square for categorical data. All statistical analyses were performed with SPSS version 20 software.

Michael E. Sulewski[1]
Joshua H. Wolf[2]
Richard Hasz[3]
Sharon West[3]
David Goldberg[4]
Karen L. Krok[5]
Kim M. Olthoff[1]
Abraham Shaked[1]
Matthew H. Levine[1]
Peter L. Abt[1]

[1] Department of Surgery
University of Pennsylvania
Philadelphia, PA
[2] Department of Surgery
Johns Hopkins University
Baltimore, MD
[3] Gift of Life Institute
Philadelphia, PA
[4] Department of Medicine
University of Pennsylvania
Philadelphia, PA
[5] Department of Medicine
Penn State Milton S. Hershey Medical Center
Hershey, PA

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Address correspondence to: Peter L. Abt, M.D., Division of Transplant, Department of Surgery, Hospital of the University of Pennsylvania, 3400 Spruce St. 1 Founders, Philadelphia, PA 19104.
E-mail: peter.l.abt@uphs.upenn.edu
M.E.S., JH.W., and P.L.A. participated in research design, writing of the article, performance of the research, and data analysis. R.H. and S.W. participated in the performance of the research. D.G., K.L.K., K.M.O., A.S., and M.H.L. participated in research design, writing of the article.
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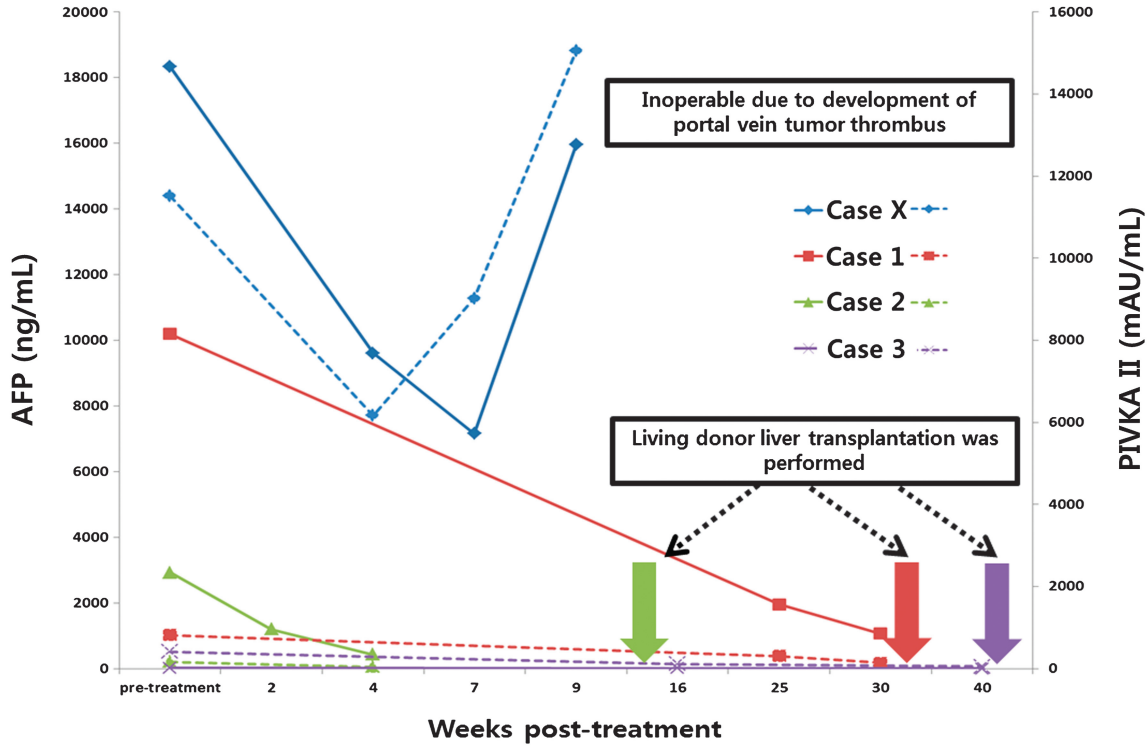
Usefulness of Radioembolization in Identifying Patients With Favorable Tumor Biology Before Living Donor Liver Transplantation

Transplantation societies continuously make collective efforts to identify patients with hepatocellular carcinoma (HCC) who have favorable tumor biology. Defining tumor biology before liver transplantation for HCC is of tremendous clinical significance and is critical to ensure optimal treatment outcome. So far, it has been largely dependent on tumor size and number, which have shown both usefulness and limitation (*1,2*). In a previous publication, Ettorre et al.(*3*) reported on the short-term outcomes of a patient with portal vein tumor thrombosis who underwent transarterial radioembolization with yttrium-90 (^{90}Y) microspheres before liver transplantation, and suggested a potential benefit on using ^{90}Y microspheres for downstaging or as bridge treatment for liver transplantation. In our experience of living donor liver transplantations (LDLT) as well, we found a potential benefit of radioembolization in identifying patients with advanced HCC who have favorable tumor biology.

Initially, four patients underwent radioembolization with ^{90}Y (SIR-Spheres; Sirtex Medical Ltd., Sydney, Australia) with the intention of both palliative treatment and tumor biology evaluation for potential LDLT. All patients had hepatitis B virus–related liver cirrhosis



Case X	AFP	18331.5		9615	7164	15960			
	PIVKAII	11515		6164	9029	15047			
Case 1	AFP	10195					1957	1069	
	PIVKAII	823					313	143	
Case 2	AFP	2928.2	1203	435.6					
	PIVKAII	208		62					
Case 3	AFP	17.9				15.2			4.6
	PIVKAII	523				147			73

FIGURE 1. AFP (*solid lines*) and PIVKA II (*dashed lines*) levels of four patients before and after treatment with radioembolization. The points in time at which living donor liver transplantation was performed (cases 1–3) (*colored arrows*). One patient (case X) was deemed inoperable because of the development of portal vein tumor thrombus. AFP, alpha-fetoprotein; PIVKA II, protein-induced by vitamin K absence or antagonist II.

combined with HCC and were beyond the University of California San Francisco criteria on initial imaging. They underwent a single session of radioembolization (the average dose, 1.20 Gbq) without complications. After treatment, the target lesions of all patients showed partial response according to the modified Response Evaluation Criteria in Solid Tumors on follow-up imaging. Three patients showed a marked decrease in alpha-fetoprotein levels after radioembolization (Fig. 1) and subsequently underwent LDLT. The time interval from radioembolization to LDLT was 13, 32, and 40 weeks, respectively. All these three patients received a right lobe graft during liver transplantation, and the mean graft-to-recipient weight ratio was 0.97. No immediate complications were noted after liver trans plantation. All patients are currently alive without recurrence at 22, 25, and 26 months after surgery. The remaining one patient showed a rebound increase in alpha-fetoprotein levels 7 weeks after radioembolization. Further evaluation revealed the development of portal vein tumor thrombus, and the patient was deemed inoperable (Fig. 1).

One of the biggest concern regarding the use of LDLT for HCC is the potential risk of early tumor recurrence leading to poor outcomes because the tumor burden is frequently larger than conventional criteria at the time of transplantation and because of the short time interval between HCC diagnosis and transplantation, which disables the natural filter effect by the waiting list for orthotopic liver transplantation (*4*). Therefore, the evaluation of tumor biology becomes much more important in this clinical setting.

Lewandowski et al. reported a promising result of radioembolization as a downstaging modality compared to transarterial chemoembolization (*5*). Otto et al. (*6*) suggested that a sustained

response to transarterial chemoembolization was a better selection criterion than the initial assessment of tumor size or number in cases of deceased donor liver transplantation, emphasizing the clinical significance of candidate selection using a biologic selection tool. From that perspective, radioembolization may provide additional benefit as a biologic selection tool because of its inherent characteristics, such as increased potency, longer duration of treatment effect, fewer treatment sessions, and low likelihood of confusion in image interpretation because lipiodol is not used, and treatment repetition is not necessary (Table 1).

In our case series, the interval between radioembolization and LDLT ranged from 3 to 8 months. During this time, tumor marker levels decreased dramatically without progression of target lesions on imaging studies (Fig. 1). We believe that radioembolization provided a sustained therapeutic effect after only a single treatment session and provided practical insights into tumor biology, in addition to reducing the tumor burden. Because the typical tumor response by Response Evaluation Criteria in Solid Tumors or World Health Organization criteria is expressed maximally between 10 and 14 weeks, and at least a 3-month period is required before retreatment with radioembolization becomes possible (*7*), from our experience, we recommend a waiting period of at least 3 months before decision to proceed with transplantation.

In the setting of LDLT, the importance of adequate candidate selection among HCC patients with out-of-conventional tumor burden becomes more critical to avoid futile transplantation, considering the risk to the living donor. Candidate selection criteria for LDLT for HCC can be different depending on institutional policy, and it is difficult to be set solely based on imaging results; therefore, evaluation of tumor biology using response to noncurative treatment with an adequate time interval may provide more meaningful information on individual patients. However, further investigation in a larger scale is warranted to elucidate the optimal usage of this treatment modality in such clinical settings.

In conclusion, although long-term follow-up is required, radioembolization using ^{90}Y microspheres showed promising

TABLE 1. Clinical demographics and tumor characteristics of the three patients who received living donor liver transplantation after radioembolization

Case	Sex/ age	Prior treatment	Maximum size, cm	Tumor characteristics before TARE			Tumor characteristics before LT			Response assessment		Explant pathology				
				Number	Vascular invasion	Maximum size, cm	Number	Target lesions	Overall	Time to LT after TARE	Total number of HCC	Number of viable HCC	Maximum size of viable HCC, cm	Grade	Vascular invasion
1	M/48	TACE	7.3	3	no	4.8	Multiple[a]	PR	PD	32 weeks	20[b]	15	3.0	IV+III	no
2	F/63	none	6.2	4	no	3.5	3	PR	PR	13 weeks	2	1	0.9	III	no
3	M/58	none	6.9	4	no	4.3	Multiple[a]	PR	PD	40 weeks	13[b]	12	4.0	IV+III	no

[a] Although no local tumor progression in previously treated lesions, multiple small (<2 cm) HCCs developed in both lobes.

[b] Most lesions were smaller than 2 cm.

TARE, transarterial radioembolization; LT, liver transplantation; PR, partial response; PD, progressive disease; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; M, male; F, female.

results in selecting patients with advanced HCC who have favorable tumor biology.

Young-Dong Yu[1]
Dong-Sik Kim[1]
Sung-Won Jung[1]
Yunhwan Kim[2]
Sung-Ock Suh[1]

[1] Division of HBP Surgery and Liver Transplantation, Department of Surgery
Korea University Medical Center
Korea University Medical College
Seoul, Korea
[2] Department of Radiology
Korea University Medical Center
Korea University Medical College
Seoul, Korea

The authors declare no funding or conflicts of interest.

Address correspondence to: Dong-Sik Kim, M.D., Ph.D., Division of HBP Surgery and Liver Transplantation, Department of Surgery, Korea University College of Medicine, Seoul, Korea.
E-mail: kimds1@korea.ac.kr

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Novel Valganciclovir Desensitization Protocol

Successful desensitization to acyclovir has been reported in the past but not to valganciclovir. This is the first successful desensitization to valganciclovir in a liver transplant recipient.

Valganciclovir—a nucleoside analogue antiviral drug—is the drug of choice for treatment of cytomegalovirus (CMV) disease and prophylaxis in high-risk liver transplant recipients (*1*). Nucleoside analogues including acyclovir, famciclovir, and ganciclovir are known to cause immediate hypersensitivity cutaneous reactions. In case of allergic reactions to nucleoside analogues or acyclovir-resistant herpes infections, sodium—a DNA chain inhibitor of phosphorylation—may be used as an alternative, although it may cause nephrotoxicity. We report a successful desensitization to valganciclovir in a liver transplant recipient with CMV infection.

A 64-year-old patient with a history of liver transplant caused by hepatocellular carcinoma presented with fatigue and anorexia 1 month after his transplant. Both, recipient and donor were CMV positive. The patient was diagnosed with CMV viremia by polymerase chain reaction and was started on valganciclovir. He developed a generalized pruritic urticaria on his trunk and upper extremities without other symptoms on the fourth day of therapy. There was a concern for drug reaction with eosinophilia and systemic symptoms syndrome because of increased peripheral eosinophil with an eosinophil count of 8.1% (range, 0%–3%). Skin biopsy was not performed. The patient's rash improved after use of antihistamines and discontinuation of valganciclovir. The use of sodium as an alternative failed because of acute renal toxicity with a serum creatinine of 2.2 mg/dL (baseline, 1.3; range, 0.7–1.3).

Allergy and immunology was consulted for desensitization to valgan ciclovir. Skin testing was not performed because of concomitant use of antihistamines for severe pruritus and urticaria. We designed a novel 12-step desensitization protocol (Table 1) adapted from previous recommended guidelines (*2, 3*). In an intensive care unit setting and use of prior medications (diphenhydramine 25 mg intravenous and famotidine 20 mg intravenous), oral desensitization with valganciclovir was performed. He completed the desensitization protocol without adverse reactions. Within days, the patient's serum creatinine and eosinophil count normalized to 1.3 mg/dL and 0.2%, respectively. The patient completed a 2-week induction therapy with valganciclovir 450 mg twice per day without further reactions and is currently on lifetime valganciclovir 450 mg once daily.

There are three previous reports of successful desensitization to acyclovir (*4–6*). We report the first successful desensitization to valganciclovir.

TABLE 1. Valganciclovir desensitization protocol

Step	Time, min	Dose, mg	Total dose, mg
1	0	0.1	0.1
2	15	0.2	0.3
3	30	0.4	0.7
4	45	0.8	1.5
5	60	1.6	3.1
6	75	3.5	6.6
7	90	7	13.6
8	105	14	27.6
9	120	28	55.6
10	135	58	113.6
11	150	115	228.6
12	165	225	453.6

Next dose 8–12 hr after step 12 is 450 mg tablet PO then 450 mg PO twice per day. PO, oral route