













Table 2

## Regression Models for Risk Factors Associated with LTP

Patient and Vessel Characteristics	OR	95% CI	P Value
<b>Patient characteristics</b>			
Age at enrollment (y)	0.950	0.865, 1.044	.291
MELD score at treatment	0.811	0.596, 1.105	.186
Index tumor diameter (mm)	0.965	0.866, 1.075	.517
No. of lesions	2.351	0.913, 6.050	.076
Ablation diameter (mm)	1.034	0.965, 1.108	.337
Total power (W)	1.005	0.984, 1.017	.955
Follow-up period (mo)	0.960	0.909, 1.014	.146
<b>Vessel characteristics</b>			
No. of patent hepatic arteries	5.858	1.338, 25.641	.024
No. of patent hepatic veins	1.278	0.112, 14.598	.570
No. of patent portal veins	3.667	0.818, 16.447	.137

Note.—For patient characteristics, *P* values were calculated with multivariate logistic regression model, and for vessel characteristics, *P* values were calculated with Fisher exact test.

portal branch. Likewise, hepatic artery occlusion did not lead to lobar infarctions but was found to significantly correlate with a decreased risk for LTP.

The mechanism behind the increased rate of occlusion in portal veins compared with hepatic arteries and hepatic veins is likely related to differences in flow pattern, flow velocity, and the total amount of blood flow. Portal veins have slower blood flow because of drainage into high-resistance hepatic sinuses. This relatively sluggish flow is exacerbated in patients with cirrhosis and portal hypertension, who have even higher sinus pressures and slower antegrade portal vein flow (23). Slow flow is less effective at dissipating heat, resulting in vessel occlusion (18). Conversely, the drainage pathway of hepatic veins is into the lower resistance inferior vena cava. Caval blood flow is also subject to transmitted backpressure from the heart throughout the cardiac cycle, resulting in a substantially faster and more pulsatile flow pattern compared with that in the portal veins. In addition, hepatic veins carry more blood flow per vessel because all of the blood flow exiting the liver traverses the hepatic veins, whereas hepatic inflow is divided between the hepatic arteries and portal veins. Subsequently, hepatic veins dissipate heat more quickly,

leading to fewer occlusions (19). Hepatic arteries, which were as resistant to occlusion as hepatic veins, are also characterized by high-flow velocity and pulsatility (24). The presence of patent hepatic arteries was significantly correlated with increased rates of LTP, a finding likely due to the heat-sink effect, which preserves microvascular tumor invasion (25).

Our data are consistent with those from prior studies that characterized rates of vessel occlusion within thermal ablation zones, with notable exceptions. Previous animal studies showed that vessels smaller than 3 mm in diameter were more likely to be occluded during microwave or RF ablation (16,17). Our study showed the 3-mm vessel size cutoff to be accurate in humans, but only for portal veins. Hepatic veins were found to be more resistant to occlusion, with vessels larger than 1.5 mm in diameter being relatively protected from occlusion. The increased rate of portal vein occlusion compared with hepatic vein occlusion within the ablation zone (39.7% vs 15.0%, respectively), with equivalent size distributions, is also similar to the results of previous in-vivo studies (19).

After RF ablation, LTP has been linked to the presence of nearby vessels (11). A previous study demonstrated that increased arterial enhancement of HCC at preablation contrast-enhanced CT is

a prognostic factor for LTP (26). The authors hypothesized that the increased hepatic arterial supply to a tumor corresponds to a less differentiated, more aggressive HCC that is more likely to recur, even after ablation (27). Another possible explanation is that increased arterial enhancement results from the presence of larger hepatic arteries, which have a greater heat-sink effect and are more difficult to thrombose and, thus, preserve nests of tumor. Regardless of the mechanism, physicians should consider a more aggressive treatment approach to tumors with robust hepatic arterial supply. Microwave ablation, which has a higher tissue heating rate than RF ablation, may effectively occlude more of these vessels. Other possible ablation strategies include increasing ablation time and the number of antennas to deliver a higher thermal dose to the tumor tissue and combining ablation with intraarterial therapies, such as transarterial chemoembolization.

The primary limitation of our study is that it was performed with a unique microwave ablation system that is able to use multiple synchronized antennas. Thus, our results are difficult to generalize to clinical trials that use single-antenna systems and deliver less energy to target tissues (28,29). There are methods to quantify thermal dose response in ex-vivo tissue to account for different energy delivery approaches, but data on the relationship with blood vessels are limited (30). The retrospective nature of our study also precludes the collection of additional data that may be relevant to vessel occlusion, namely blood flow velocity. A prospective vessel occlusion study may benefit from obtaining Doppler US measurements or performing quantitative MR imaging to assess blood flow velocity between vessel groups before an ablation procedure. Lastly, our study did not look at the long-term data involving vessel patency. Aside from the previously mentioned main portal vein thrombosis, it is unknown whether the acutely occluded vessels remained occluded or if they eventually recannulized.

In conclusion, our study shows that, during microwave tumor ablation of HCC, hepatic veins and arteries are

more resistant to occlusion than are portal veins, but only hepatic arterial patency within an ablation zone is related to LTP. Portal veins occluded at twice the rate of hepatic veins within an ablation zone. Despite being substantially smaller, hepatic arteries occluded at the same rate as did hepatic veins, likely because of their faster velocity and more pulsatile blood flow. Additional studies that incorporate blood flow data and thermal dose models will be necessary to fully characterize the effect of blood vessels within an ablation zone and their relationship to LTP.

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## References

- Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53(3):1020-1022.
- European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; 56(4):908-943.
- Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int* 2010;4(2):439-474.
- Ahmed M, Brace CL, Lee FT Jr, Goldberg SN. Principles of and advances in percutaneous ablation. *Radiology* 2011;258(2):351-369.
- Bhardwaj N, Strickland AD, Ahmad F, Atanesyan L, West K, Lloyd DM. A comparative histological evaluation of the ablations produced by microwave, cryotherapy and radiofrequency in the liver. *Pathology* 2009;41(2): 168-172.
- Huang J, Yan L, Cheng Z, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg* 2010; 252(6):903-912.
- Andreano A, Huang Y, Meloni MF, Lee FT Jr, Brace C. Microwaves create larger ablations than radiofrequency when controlled for power in ex vivo tissue. *Med Phys* 2010; 37(6):2967-2973.
- Lubner MG, Brace CL, Hinshaw JL, Lee FT Jr. Microwave tumor ablation: mechanism of action, clinical results, and devices. *J Vasc Interv Radiol* 2010;21(8 Suppl):S192-S203.
- Dodd GD 3rd, Dodd NA, Lanctot AC, Glueck DA. Effect of variation of portal venous blood flow on radiofrequency and microwave ablations in a blood-perfused bovine liver model. *Radiology* 2013;267(1):129-136.
- Kosari K, Gomes M, Hunter D, Hess DJ, Greeno E, Sielaff TD. Local, intrahepatic, and systemic recurrence patterns after radiofrequency ablation of hepatic malignancies. *J Gastrointest Surg* 2002;6(2):255-263.
- Lu DSK, Raman SS, Limanond P, et al. Influence of large peritumoral vessels on outcome of radiofrequency ablation of liver tumors. *J Vasc Interv Radiol* 2003;14(10):1267-1274.
- Kang TW, Lim HK, Lee MW, Kim YS, Choi D, Rhim H. Perivascular versus nonperivascular small HCC treated with percutaneous RF ablation: retrospective comparison of long-term therapeutic outcomes. *Radiology* 2014; 270(3):888-899.
- Meloni MF, Andreano A, Bovo G, et al. Acute portal venous injury after microwave ablation in an in vivo porcine model: a rare possible complication. *J Vasc Interv Radiol* 2011; 22(7):947-951.
- Meloni MF, Andreano A, Lava M, Lazzaroni S, Okolicsanyi S, Sironi S. Segmental portal vein thrombosis after microwave ablation of liver tumors: Report of two cases. *Eur J Radiol Extra* 2010;76(3):e95-e98.
- Livraghi T, Meloni F, Solbiati L, Zanusi G; Collaborative Italian Group using AMICA system. Complications of microwave ablation for liver tumors: results of a multicenter study. *Cardiovasc Intervent Radiol* 2012; 35(4):868-874.
- Lu DSK, Raman SS, Vodopich DJ, Wang M, Sayre J, Lassman C. Effect of vessel size on creation of hepatic radiofrequency lesions in pigs: assessment of the "heat sink" effect. *AJR Am J Roentgenol* 2002;178(1):47-51.
- Yu NC, Raman SS, Kim YJ, Lassman C, Chang X, Lu DSK. Microwave liver ablation: influence of hepatic vein size on heat-sink effect in a porcine model. *J Vasc Interv Radiol* 2008; 19(7):1087-1092.
- Chiang J, Hynes K, Brace CL. Flow-dependent vascular heat transfer during microwave thermal ablation. *Conf Proc IEEE Eng Med Biol Soc* 2012;2012:5582-5585.
- Chiang J, Willey BJ, Del Rio AM, Hinshaw JL, Lee FT, Brace CL. Predictors of thrombosis in hepatic vasculature during microwave tumor ablation of an in vivo porcine model. *J Vasc Interv Radiol* 2014;25(12):1965-1971.e2.
- Wald C, Russo MW, Heimbach JK, Husain HK, Pomfret EA, Bruix J. New OPTN/ UNOS policy for liver transplant allocation: standardization of liver imaging, diagnosis, classification, and reporting of hepatocellular carcinoma. *Radiology* 2013;266(2):376-382.
- Ziemlewicz TJ, Hinshaw JL, Lubner MG, et al. Percutaneous microwave ablation of hepatocellular carcinoma with a gas-cooled system: initial clinical results with 107 tumors. *J Vasc Interv Radiol* 2015;26(1):62-68.
- Ahmed M, Solbiati L, Brace CL, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria--a 10-year update. *Radiology* 2014;273(1):241-260.
- Perisic M, Ilic-Mostic T, Stojkovic M, Culafic D, Sarenac R. Doppler hemodynamic study in portal hypertension and hepatic encephalopathy. *Hepatogastroenterology* 2005;52(61):156-160.
- McNaughton DA, Abu-Yousef MM. Doppler US of the liver made simple. *RadioGraphics* 2011;31(1):161-188.
- Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. *Nat Rev Cancer* 2014;14(3):199-208.
- Park Y, Kim Y-S, Rhim H, Lim HK, Choi D, Lee WJ. Arterial enhancement of hepatocellular carcinoma before radiofrequency ablation as a predictor of postablation local tumor progression. *AJR Am J Roentgenol* 2009;193(3):757-763.
- Nakashima Y, Nakashima O, Hsia CC, Kojiro M, Tabor E. Vascularization of small hepatocellular carcinomas: correlation with differentiation. *Liver* 1999;19(1):12-18.
- Brace CL, Laeseke PF, Sampson LA, Frey TM, van der Weide DW, Lee FT Jr. Microwave ablation with multiple simultaneously powered small-gauge triaxial antennas: results from an in vivo swine liver model. *Radiology* 2007;244(1):151-156.
- Harari CM, Magagna M, Bedoya M, et al. Microwave ablation: comparison of simultaneous and sequential activation of multiple antennas in liver model systems. *Radiology* 2016;278(1):95-103.
- Mertyna P, Goldberg W, Yang W, Goldberg SN. Thermal ablation: a comparison of thermal dose required for radiofrequency-, microwave-, and laser-induced coagulation in an ex vivo bovine liver model. *Acad Radiol* 2009;16(12):1539-1548.