Supporting Information

Rational design of temperature-sensitive blood-vessel-embolic nanogels for improving hypoxic tumor microenvironment after transcatheter arterial embolization

Ling Li[#,a,c], Yiming Liu[#,b,c], Han Li[#,a,c], Xiaopeng Guo[b], Xiaojun He[b], Shinan Geng[a,c], Hao Zhao[a,c], Xiaole Peng[a,c], Dingwen Shi[a], Bin Xiong[b], Guofeng Zhou[b], Yanbing Zhao[a,c*], Chuansheng Zheng[b,*], Xiangliang Yang[a,*]

[a]: National Engineering Research Center for Nanomedicine, College of Life Science and Technology, Huazhong University of Science and Technology, 430074, Wuhan City, P. R. China.
[b]: Hubei Province Key Laboratory of Molecular Imaging, Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China.
[c:] Shenzhen Institute of Huazhong University of Science and Technology, 518057, Shenzhen, P. R. China

[#]These authors contributed equally to this work.

[*]**Corresponding authors:** Yanbing Zhao (zhaoyb@hust.edu.cn), Chuansheng Zheng (hqzcsxh@sina.com) and Xiangliang Yang (yangxl@hust.edu.cn); Tel: +86-27-87792147, Fax: +86-27-87792234.

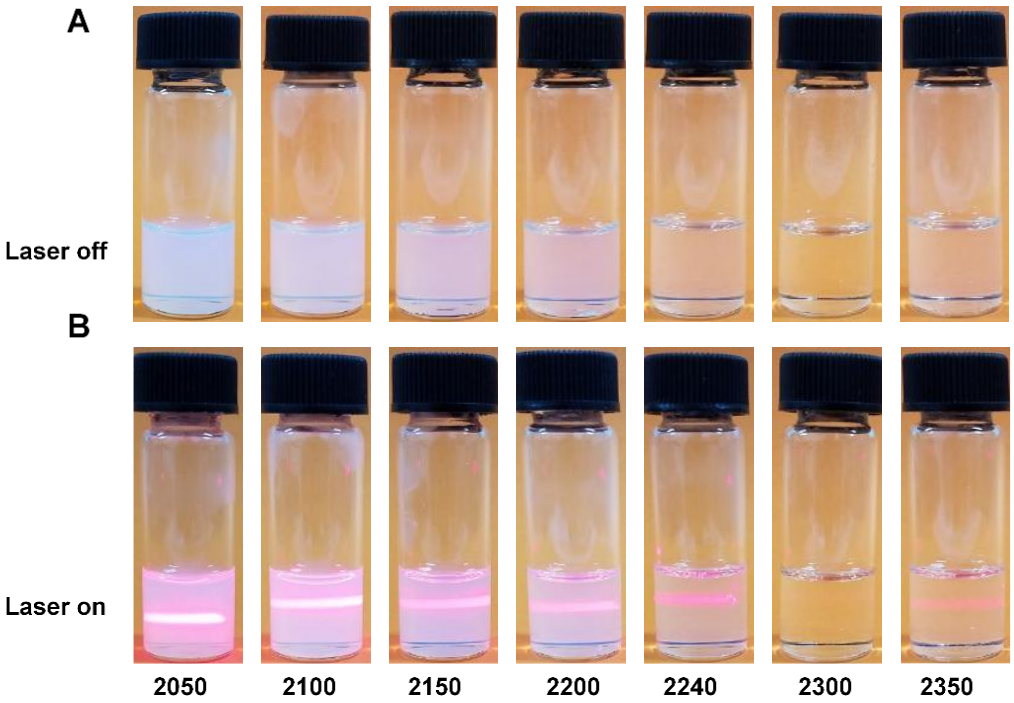

Figure S1. The Tyndall effect of 2% PIB (w/v) dispersed in iohexol solutions with different iohexol concentration (from 50 mg I/ml to 350 mg I/ml).

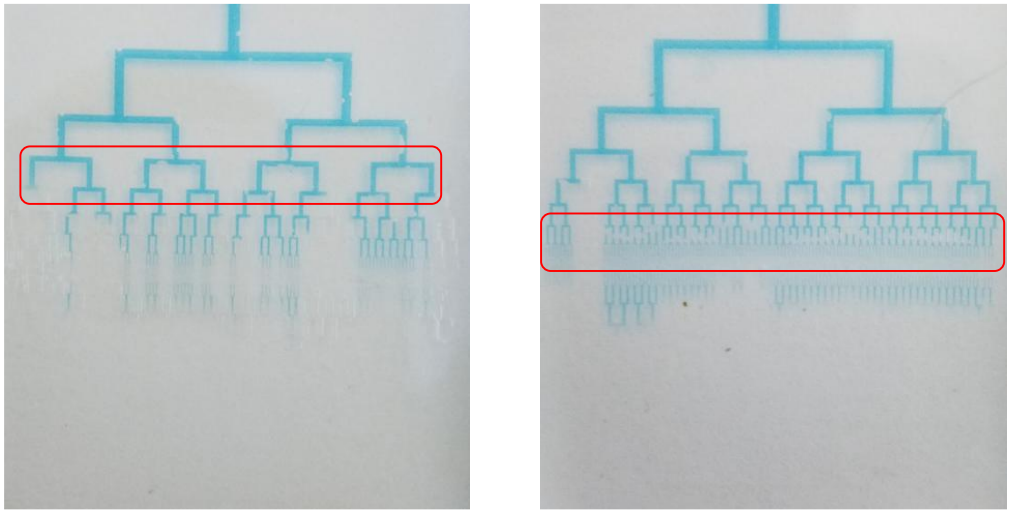

Figure S2. The microfluidic chips after *in vitro* embolization simulated experiment.

Table S1. The formulation of PIBI2050-2350

Sample name	PIBI -2050	PIBI -2100	PIBI -2150	PIBI -2200	PIBI -2240	PIBI -2300	PIBI -2350
Iohexol content (mg I/mL)	50	100	150	200	240	300	350
PIB content (mg/mL)	20	20	20	20	20	20	20

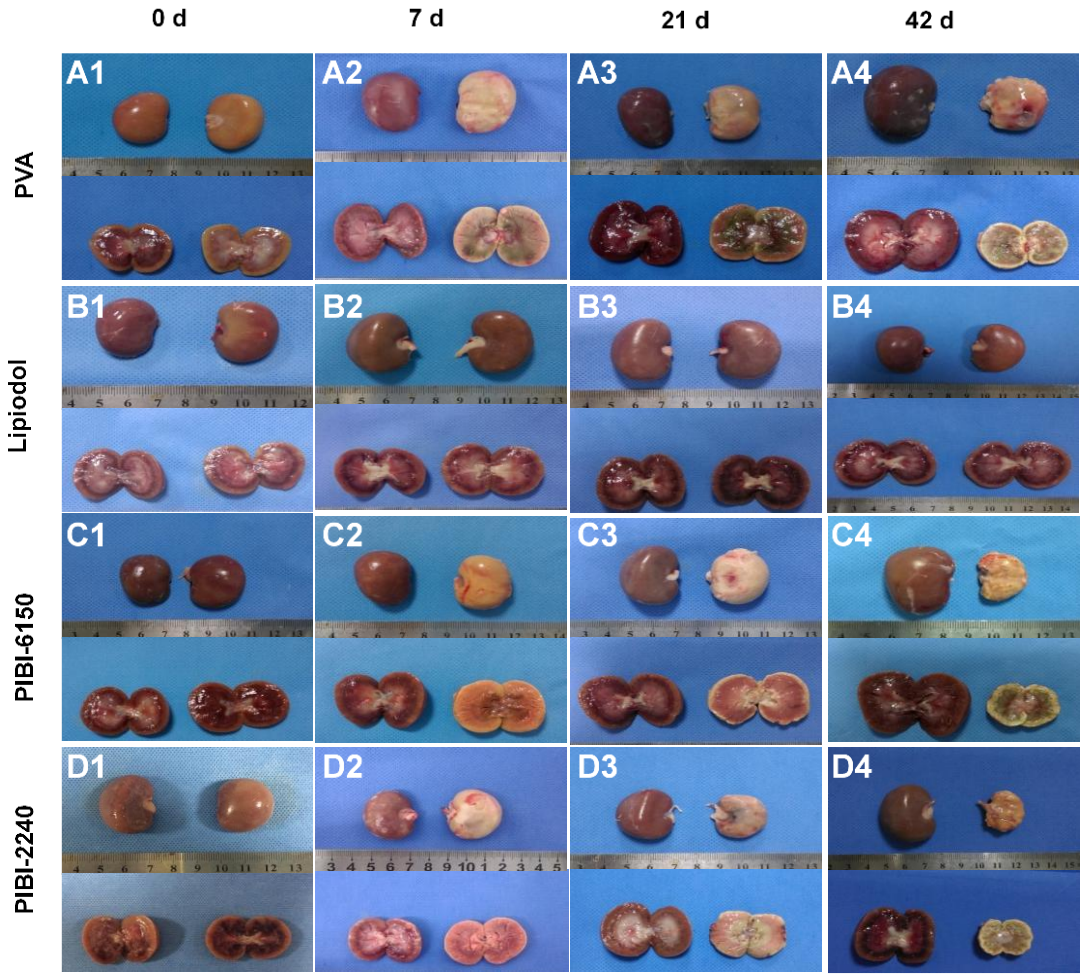

Figure S3. The gross photos of rabbit kidneys after 0, 7, 21, and 42 days of embolization. The dose of embolic agents was 2.5 mL.

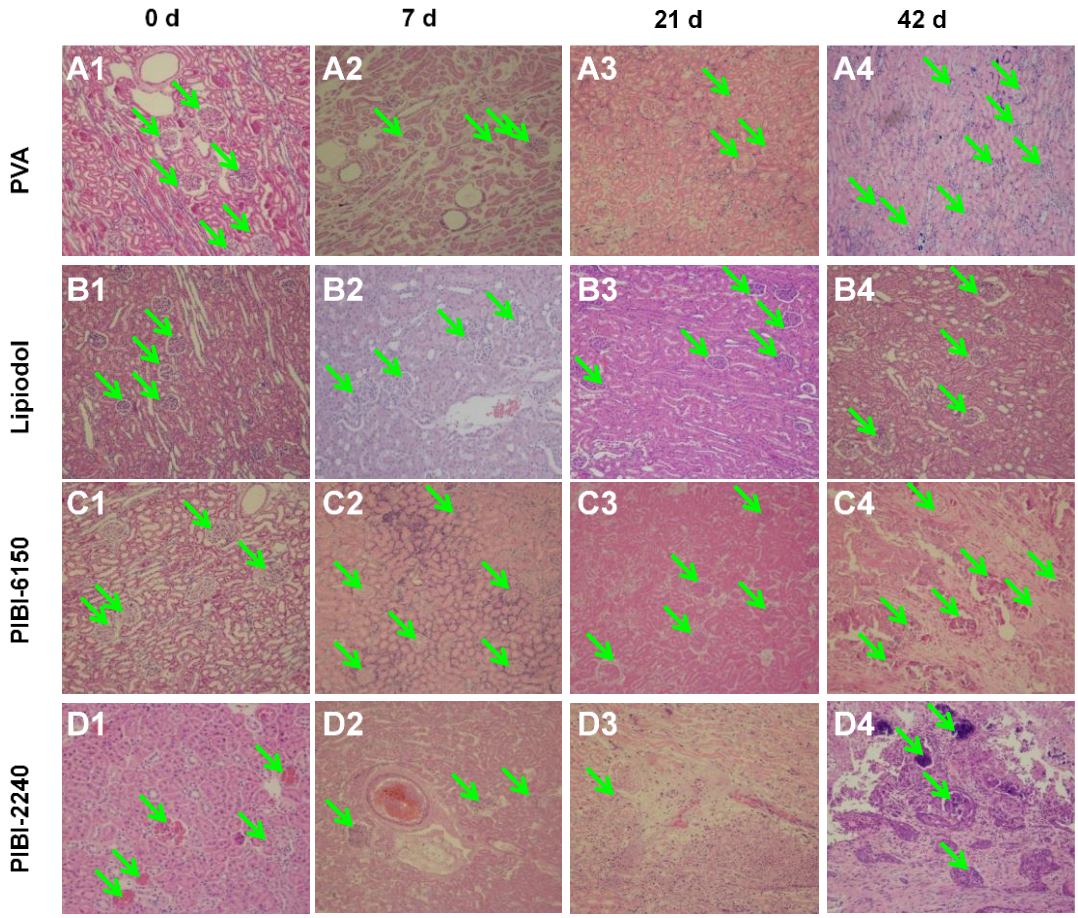

Figure S4. H&E staining of rabbit kidney (original magnification, ×100) after 0, 7, 21, and 42 days of embolization (the region where green arrow pointed at was glomerulus). Scale bar: 200 μm. The dose of embolic agents was 2.5 mL.

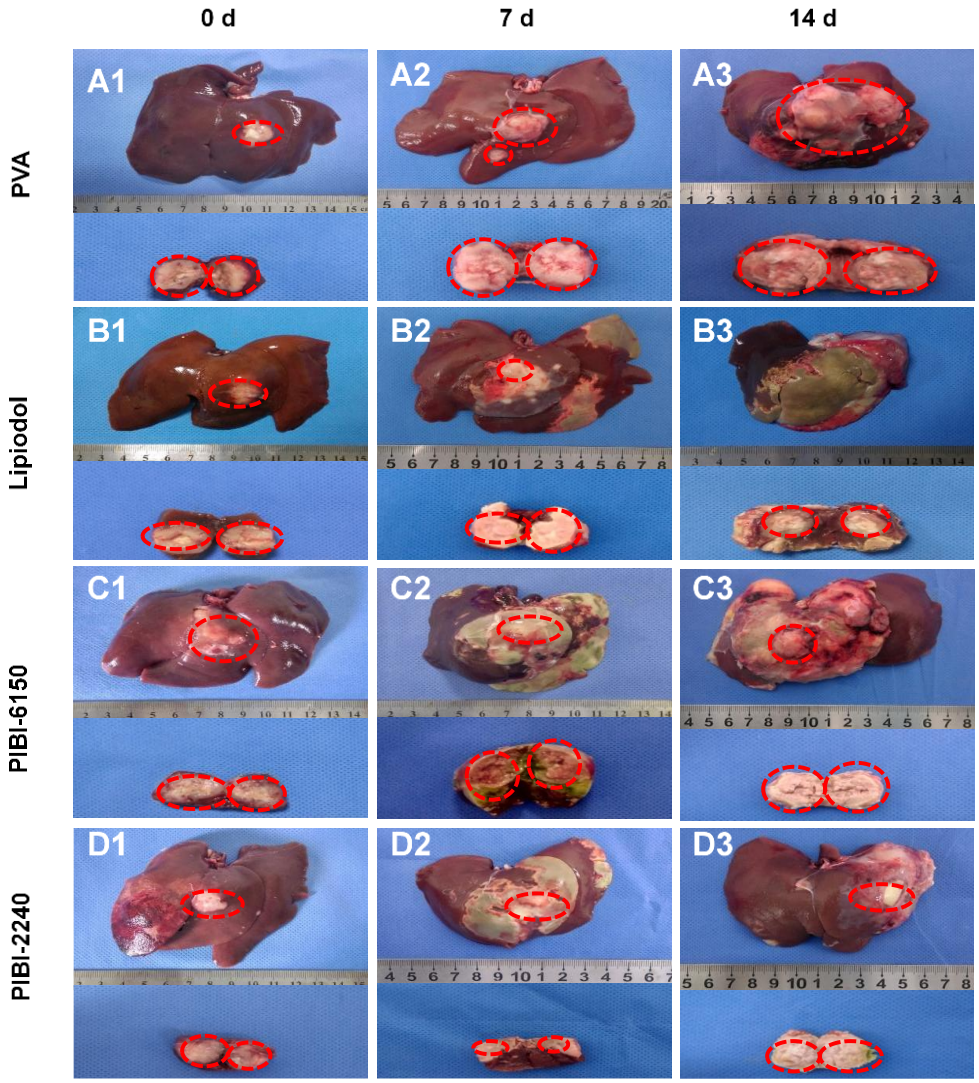

Figure S5. The photos of liver and tumor after 0, 7, and 14 days of embolization (red circle indicates the tumor region).

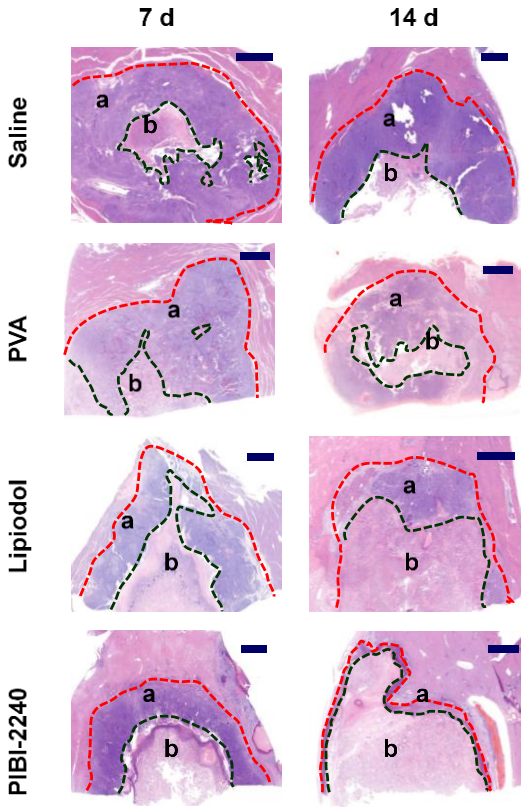

Figure S6. Histopathology with H&E staining after 7 and 14 days of VX2-tumor-bearing rabbits, (a) areas of tumor (b) areas of necrosis. Scale bar: 2 mm.

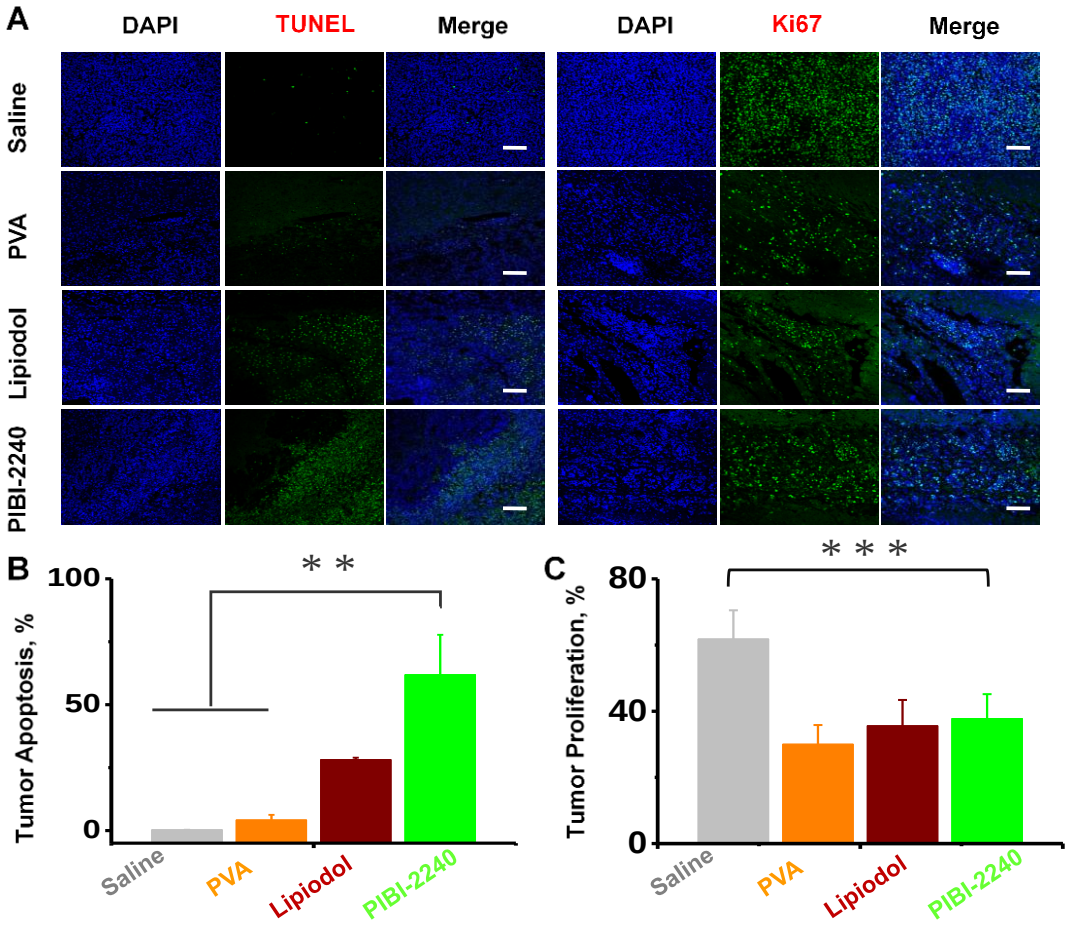

Figure S7. Confocal fluorescence microscopy images of cell apoptosis (stained by TUNEL) and cell proliferation (stained by Ki67) in histology sections of VX2-tumors following TAE therapies for 7 days. (A) Fluorescence images comparison of VX2-tumor-bearing rabbit with various treatments for 7 days (original magnification, ×200). Scale bar: 100 μm. (B) and (C) were quantitative analysis on the fluorescence intensities of the images in Plot A with TUNEL and Ki67 staining, respectively. **$p < 0.01$, and ***$p < 0.001$.

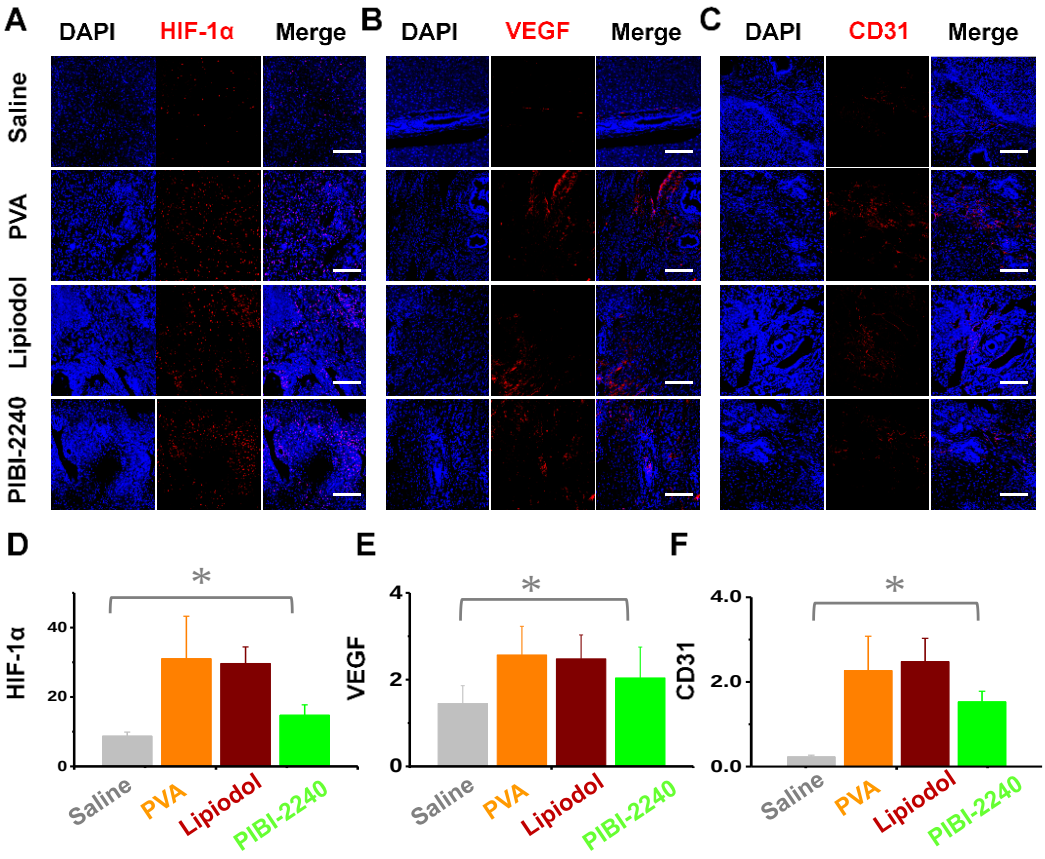

Figure S8. Immunofluorescence evaluations of neovascularization and collateral circulation in VX2 tumor-bearing rabbits after 7 days of blood-vessel-embolization with various materials (Saline, PVA, Lipiodol, and PIBI-2240). (A) Confocal fluorescence microscopy images of HIF-1α staining. (B) Confocal fluorescence microscopy images of VEGF staining. (C) Confocal fluorescence microscopy images of CD31 staining. Scale bar: 100 μm. (D), (E), and (F) are a quantitative comparison of fluorescence intensities in the slices of HIF-1α staining from plot A, VEGF staining from plot B, and CD31 staining from plot C, respectively. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

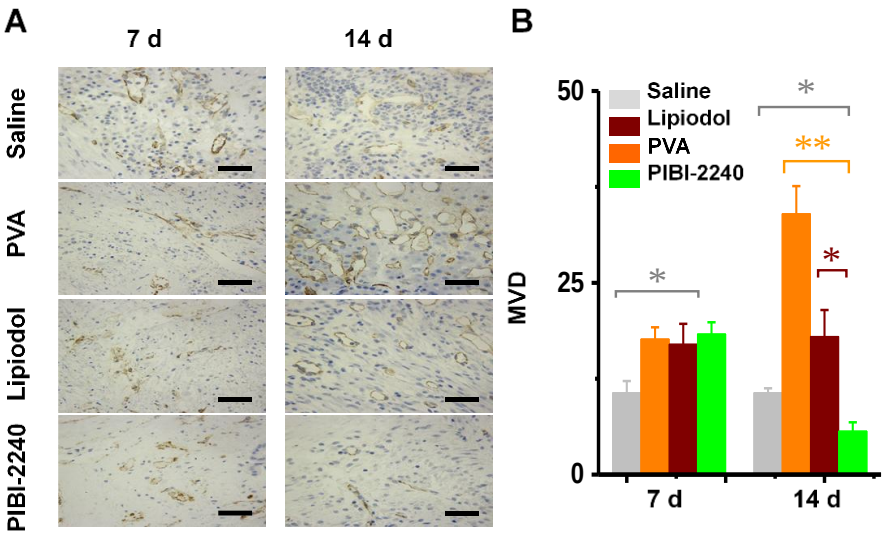

Figure S9. Immunohistochemistry of CD31 in VX2-tumor-bearing rabbits at 7 days and 14 days. (A) Immunohistochemistry images of CD31 on VX2 tumor-bearing rabbits (original magnification, ×400). Scale bar: 50 μm. (B) MVD. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

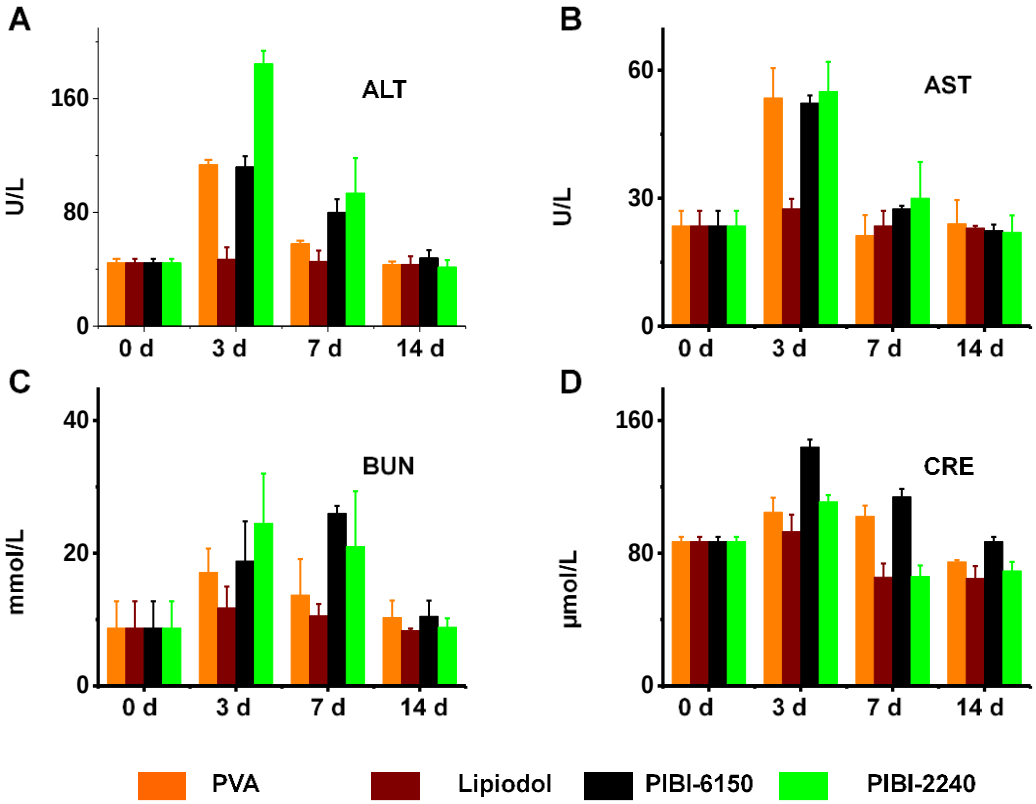

Figure S10. Hepatorenal function of renal arterial embolization rabbits at various time points after treatments. PVA (orange), Lipiodol (burgundy), PIBI-6150 (black), PIBI-2240 (green).

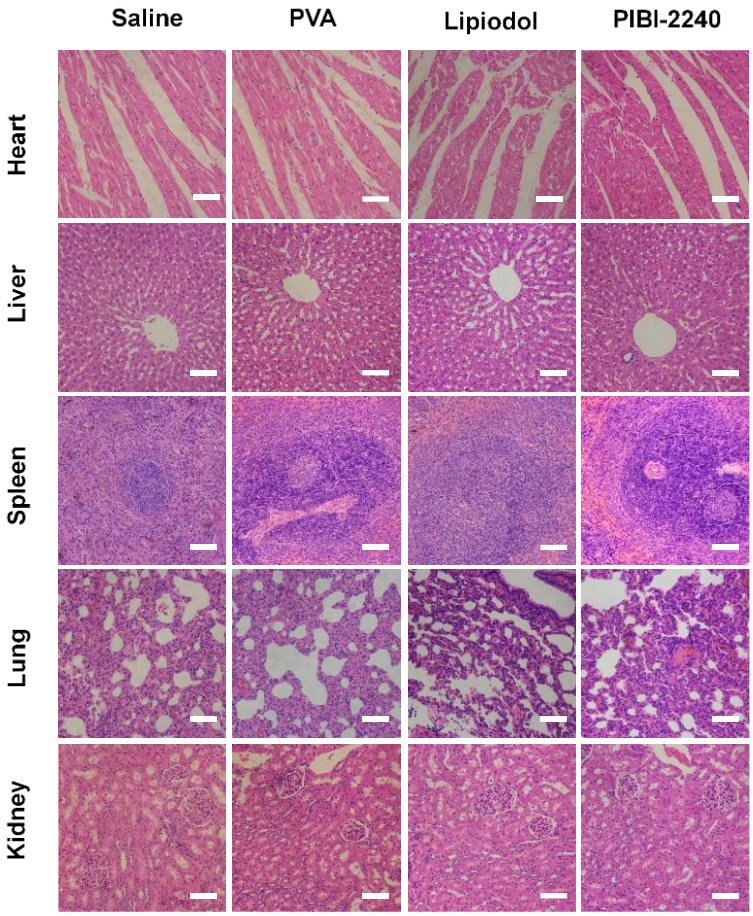

Figure S11. Histological sections of heart, liver, spleen, lung and kidney stained using H&E after 14 days of treatment by saline, PVA, Lipiodol, and PIBI-2240 (×200). Scale bar: 100 μm.

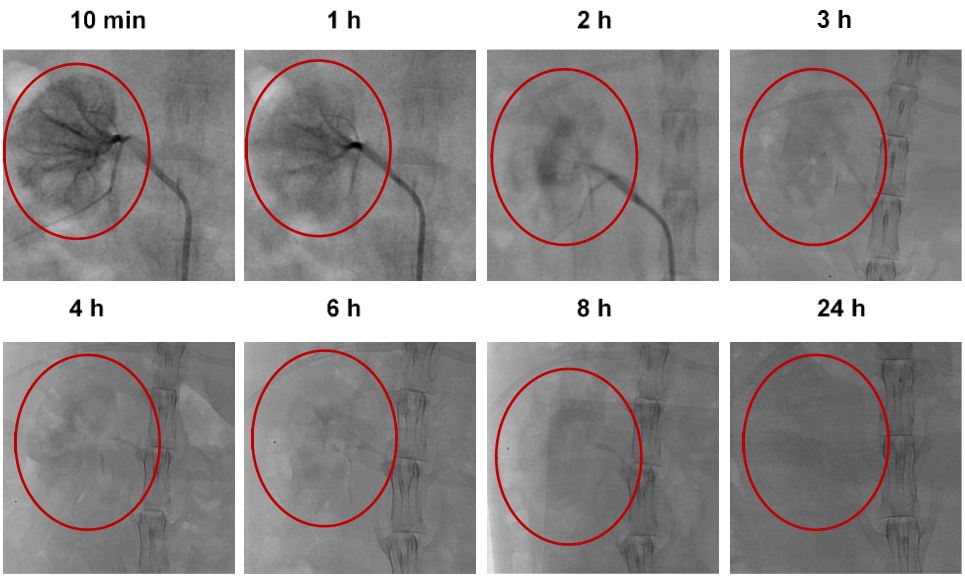

Figure S12. Digital radiography images of a rabbit's abdomen at designated time intervals after embolization of the right kidney with the PIBI-2240.

Supporting Movies

Movie 1 Representative video recording of Lipiodol.
Movie 2 Representative video recording of PVA.
Movie 3 Representative video recording of PIBI-6150.
Movie 4 Representative video recording of PIBI-2240.