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³¹P-Magnetic Resonance Spectroscopic Imaging Detects Regenerative Changes in Human Liver Stimulated by Portal Vein Embolization

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Abstract

Purpose—First, to evaluate hepatocyte phospholipid metabolism and energetics during liver regeneration stimulated by portal vein embolization (PVE) using proton-decoupled ³¹P-magnetic resonance spectroscopic imaging (³¹P-MRSI). Second, to compare the biophysiological differences between hepatic regeneration stimulated by PVE and by partial hepatectomy.

Materials and Methods—Subjects included 6 patients with hepatic metastases from colorectal cancer who were scheduled to undergo right PVE before definitive resection of right-sided tumor. ³¹P-MRSI was performed on the left liver lobe prior to PVE and 48 hours following PVE. Normalized quantities of phosphorus-containing hepatic metabolites were analyzed from both visits. In addition, MRSI data at 48 hours following partial hepatectomy were compared with the data from the PVE patients.

Results—At 48 hours after PVE, the ratio of phosphomonoesters to phosphodiesteres in the non-embolized lobe was significantly elevated. No significant changes were found in NTP and Pi values. The PME to PDE ratio in regenerating liver 48 hours after partial hepatectomy was significantly greater than PME/PDE 48 hours after PVE.

Conclusion—³¹P-MRSI is a valid technique to noninvasively evaluate cell membrane metabolism following PVE. The different degree of biochemical change between PH and PVE indicates that hepatic growth following these two procedures does not follow the same course.

Keywords

spectroscopy; phosphorus; liver; regeneration; portal vein embolization

Liver resection is the only curative therapy for hepatic metastases from colorectal cancer (CRC), and improved surgical techniques have permitted larger resections with acceptable morbidity and mortality (1). The major obstacle in performing large resections in patients with multiple metastases and/or bilobar lesions is insufficient functional remnant liver. In addition, in the past decade, the use of adjuvant systemic chemotherapy agents such as oxaliplatin and irinotecan has become the standard-of-care in CRC patients considered at high risk for metastatic spread. These agents can cause changes to the liver parenchyma which could negatively affect the process of liver regeneration (2,3). In patients with higher risk of liver failure after hepatic resection, portal vein embolization (PVE) has become an accepted technique for increasing the volume of the future remnant liver (4,5). This technique involves embolization of the portal vein supplying the liver lobe which will eventually be resected, resulting in hypertrophy of the contralateral lobe.

While liver regeneration following partial hepatectomy (PH) has been extensively studied in animal models, fewer studies have been performed to investigate the mechanism of liver hypertrophy due to embolization of the contralateral portal vein (6–8). Given the fact that the embolized lobe is still present after PVE and there are differences in the distribution of arterial blood flow after PVE and PH, it has been postulated that the mechanisms of liver regeneration after liver resection and portal vein embolization are different (9,10). The goal of the present study was to determine if proton-decoupled ^{31}P MRSI could detect cellular changes in the regenerating lobe after PVE in human subjects. Furthermore, we assessed the difference between hepatic regeneration stimulated by PVE and by PH using post-surgical data from a prior study. These analyses illustrate the potential of ^{31}P MRSI as a non-invasive probe of liver regeneration.

MATERIALS AND METHODS

Subjects

Twenty-one patients with liver metastases from CRC who presented at our institution between July 2001 and October of 2006 were recruited to this study. All patients were scheduled to undergo portal vein embolization prior to definitive resection of hepatic metastases. Eight patients were excluded from analysis for technical or clinical reasons. Of these, two had low SNR, one had severe motion artifact, one had an incorrectly set flip angle, one did not undergo embolization, and 3 did not undergo followup MRSI. Six of the remaining patients underwent right portal vein embolization and the left lobe (future remnant liver) was studied by MRSI at baseline and 48 hours after PVE. These are the subjects of the current report. Finally, 4 patients whose lobe ipsilateral to the PVE was studied, 2 whose tumor was studied, and one whose followup MRSI was performed at 24 hours are not reported on here. All patients underwent informed consent according to an institutionally approved protocol and in compliance with the Health Information Privacy and Portability Act (HIPPA).

Portal Vein Embolization

All patients were referred for portal vein embolization when a small future liver remnant after partial hepatectomy was anticipated. The right portal vein branches were embolized through an ipsilateral percutaneous puncture using PVA particles or embospheres. Details of the procedure are described in reference (11).

Proton decoupled ^{31}P MRSI

All 6 PVE patients underwent baseline MRSI within 7 days prior to PVE and at 48 hours following PVE. Additional MRSI studies were carried out in three patients prior to liver

resection: one at day 20, one at day 35, and one at day 39. Two patients had followup MRSI evaluations after PH: one on day 6 post-resection and one on days 6 and 22.

To compare liver metabolism after PVE and PH, we introduced data from 4 patients who underwent ^{31}P MRSI 48 hours after PH. These patients were part of a previously published study of liver regeneration after PH (12). The ^{31}P -MRSI data from these 4 patients were compared with the present 48-hour PVE data. Pre-surgical MRSI data from the PH patients was not obtained due to difficulties in scheduling these patients prior to surgery.

Experiments were performed on a 1.5 Tesla Signa scanner equipped with a stand-alone proton decoupler (GE, Milwaukee, WI) and running either the 5x or 12x software platforms. Initially, the entire liver was imaged for volume calculations using the torso phased array coil with a breath-held, multislice, T_2 -weighted fast spin-echo (FSE) sequence (TR = 4000 ms, TE = 102 ms, echo train length = 12, averages = 2, slice thickness 10 or 12 mm, gap = 2 mm). Following whole-liver imaging, a dual $^1\text{H}/^{31}\text{P}$ coil pair (IGC Medical Advances, Milwaukee, WI) was placed adjacent to the patient's torso.

The coil pair was positioned atop the abdomen, adjacent to the left lobe of the liver. A detailed description of ^{31}P MRS acquisition has been reported elsewhere (13). In brief, T_2 -weighted FSE images were first acquired in two orthogonal planes using the proton coil. The water signal in the liver was shimmed over the volume of interest using automated software. On the ^{31}P channel, the 90° flip angle power for a rectangular pulse was determined using a triphenylphosphite (TPP) standard attached to the coil, and a fully relaxed free induction decay (FID) from the standard was acquired for metabolite quantitation. Proton-decoupled three-dimensional ^{31}P MRS was performed using a pulse-and-acquire sequence with the following parameters: matrix = $8 \times 8 \times 8$, FOV = 24, 28 or 32 cm, TR = 1 s, averages = 4, points = 1024 and spectral width = 8000 (5x platform) or points = 512 and spectral width = 2000 Hz (12x platform), flip angle = $\sim 45^\circ$, scan time = 34 minutes. Waltz 4 proton-decoupling was applied during data acquisition and low level continuous wave power was applied in the remainder of the TR interval to maintain nuclear Overhauser enhancement (NOE). Fiducial markers on the coil permitted retrospective assessment of the coil position in space for field mapping. Although the same average flip angle was targeted in each patient (45° at voxel center), the resulting flip angles could vary once the voxel location was chosen retrospectively and this was accounted for in the post-processing analysis.

Spectroscopic Data Processing

MRSI data were processed using SAGE/IDL (GE, Milwaukee WI, RSI, Boulder, CO) or 3DiCSI (courtesy of T. Brown, Columbia University) for voxel shifting, Fourier transform, and single voxel FID extraction from the voxel-of-interest. The FID was fit in the time domain using MRUI-AMARES (14). In liver spectra at 1.5 Tesla, there is a broad hump underlying the PDE region corresponding to semi-mobile membrane phospholipids (15). This peak was incorporated into the fit as a broad peak using the prior knowledge option in MRUI-AMARES. Both raw peak area ratios and normalized quantities relative to the TPP standard were calculated. The quantitative procedure has been described elsewhere (16). Briefly, the B_1 distribution over the voxel-of-interest was calculated and used for sensitivity and flip angle distributions. Metabolite peak areas were corrected for 1) T_1 saturation using published T_1 values for the normal liver (17), and 2) receive sensitivity over the voxel relative to the standard (16). Metabolite concentrations relative to the standard are reported as normalized units (n.u.). No corrections were made for NOE or point spread function. Normalized values are reported for phosphorylethanolamine (PE), phosphorylcholine (PC), inorganic phosphate (Pi), glycerophosphorylethanolamine (GPE), glycerophosphorylcholine (GPC), and nucleoside triphosphates (NTP). The beta-NTP triplet was used for NTP concentration calculations. Phosphomonoester (PME) was calculated as the sum of the PE

and PC peaks and phosphodiester (PDE) as the sum of the GPE and GPC peaks. In patients where PE and PC and/or GPE and GPC could not be resolved, only PME and PDE values were reported. Metabolite raw peak area ratios were also calculated for comparison. In one patient, the reference information needed to perform individual peak quantitation was not available and only peak area ratios were reported.

Liver volume analysis in PVE patients

MR volumetry in PVE patients was carried out using the public-domain Java-based image-processing program ImageJ (<http://rsb.info.nih.gov/ij/>). Total liver volume and left lobe volume were measured at baseline and at 48 hours after PVE on T2-weighted MR images. Regions of interest (ROI) were drawn in consecutive axial images and volume was calculated as the sum over all slices of [area $\times$ (slice thickness + gap)]. The left liver was delineated from the right liver using the middle hepatic vein. Tumor volume was measured and deducted from total liver volume. Gallbladder and inferior vena cava were excluded from liver contours.

Statistical analysis

Phosphorus metabolite values at 48 hours after PVE were compared to baseline values using the signed-ranks test, the standard non-parametric test for paired data. Metabolite values at 48 hours post-PVE and 48 hrs post-PH were compared using the Wilcoxon rank-sum test. Only the metabolites with sample number greater than 4 were analyzed. Two-tailed p-values < 0.05 were used to define statistical significance.

RESULTS

Clinical information

Information about prior chemotherapy and serum liver function tests for all patients is shown in Table 1. All patients but one were exposed to prior chemotherapy. Chemotherapy was halted at least 7 days prior to PVE in that group and at least 180 days prior to surgery in the PH group. All of the patients in the PVE group had at least one abnormal serum liver function value at baseline, while two PH patients had abnormal serum liver function tests (alkaline phosphatase) prior to surgery. After PVE, bilirubin increased in 5 patients and was abnormally high in 3. In this group, AST and ALT did not change markedly or show a particular trend, and alkaline phosphatase tended to decrease at 48 hours. In the PH group at 48 hours, bilirubin increased in the 3 patients where measurements were available, AST and ALT increased in two cases, and alkaline phosphatase results were mixed.

Changes in phosphorus metabolism at 48 hours after PVE detected by ^{31}P MRS

Examples of ^1H -decoupled ^{31}P MR spectra from the liver of one patient at baseline and 48 hours post-PVE are shown in Figs. 1a and 1b. Spectra were acquired from the left liver and the patient underwent right portal vein embolization. These spectra demonstrate the ability of ^1H -decoupled ^{31}P MRSI at 1.5T to detect changes in ^{31}P metabolites after PVE. On inspection, changes were seen in the PME region. Figure 1b shows increased levels of PE and PC relative to other metabolites at 48 hours post-PVE, although resolution of the two peaks in the baseline spectrum is limited. Because resolution of PE and PC as well as GPE and GPC was not consistent throughout the study, our quantitative analysis includes only the results for the sum of PE and PC (PME) and the sum of GPE and GPC (PDE).

A graphical representation of the changes seen in the hypertrophying lobe at 48 hours is shown in Figure 2. Figures 2a and 2b contain PME and PDE levels quantified relative to the standard, while Figs. 2c and 2d contain raw peak area ratios. The changes in all ^{31}P metabolites at 48 hours after PVE are shown in Table 2 along with P values for the

difference with respect to the baseline values. Because saturation factor information for patient 6 was not available, only peak area ratios were reported for this patient. Five patients showed increased PME and decreased PDE at 48 hours following the PVE procedure although P values for the trends were borderline significant ($P = 0.06$ for both metabolites). The values of NTP and P_i did not change significantly after PVE. Metabolite ratios calculated from raw peak areas showed that PME/PDE increased by a mean value of $59\% \pm 40\%$ after PVE ($P = 0.03$), accounting for the greatest change among all parameters. The ratio of PME to NTP was $48\% \pm 41\%$ higher after PVE compared to baseline ($P = 0.06$). NTP/ P_i and PDE/NTP were unchanged at 48 hours after PVE.

Volume Measurements at baseline and 48 hours post PVE

MR volumetric measurements showed that total liver volume did not change significantly between baseline and 48 hours post-PVE. In addition, the mean percent change in the volume of the future remnant (left) lobe for the 6 patients was not significant after 48 hours ($2.53 \pm 8.68\%$), indicating that an appreciable increase in volume had not yet occurred.

Comparison of liver phosphorus metabolites after PVE and PH

An example of a ^1H -decoupled ^{31}P MR spectrum acquired at 48 hours after partial hepatectomy is shown in Figure 1c. The patient had undergone a right trisegmentectomy involving removal of approximately 75% of the liver. Compared to the PVE-48 hr spectrum in Fig. 1b, the PH patient had a strikingly elevated PE peak, with PC detected as a small shoulder on the upfield side of the PE. This tendency toward elevation in PE after PH was previously reported (12). Metabolites in the PDE region also appear reduced after PH. Comparative data from patients at 48 hours post PVE and 48 hours post PH are contained in Table 3. Only measurements with $N \geq 4$ for both groups were compared. Phosphodiesteres were significantly lower in the PH-48 hr patients ($p = 0.049$) while PME/PDE was higher. PME was not significantly different between PH-48 hr and PVE-48 hr subjects.

Serial evaluation of liver regeneration following PVE and PH using ^{31}P MRS

Patients 4 and 5 underwent PVE as well as subsequent partial hepatectomies with concomitant MRSI examinations. Figure 3 shows serial data from patient No. 4 at baseline, 48 hours post-PVE, 20 days post-PVE, 6 days after right lobectomy and 22 days after right lobectomy. Increased PME and decreased PDE in the left lobe at 48 hrs post-PVE appeared to resolve by day 20 post-PVE. The regenerative changes resulting from the partial liver resection then induced an elevation in PE and reduction of PDE at day 6 which approached normalization at 22 days. Patient No. 5 showed the same pattern of changes.

DISCUSSION

The goal of the current study was to explore the changes in ^{31}P -containing metabolites in the regenerating liver lobe at 48 hours following portal vein embolization of the contralateral lobe. In addition, we compared these changes to those seen in the regenerating lobe of patients at 48 hours after partial hepatectomy. Metabolites in the phosphomonoester and phosphodiester regions of the MR spectrum exhibited alterations at 48 hours following PVE. The PME and PDE peaks underwent borderline significant elevation and reduction, respectively, while PME/PDE increased significantly compared to baseline values. Although PME/PDE was elevated after PVE, the value did not reach approach the average PME/PDE in the regenerating lobe at 48 hours post-PH. These data indicate that 1) *in vivo* ^{31}P MRSI can detect regenerative changes in the left lobe of the liver due to right portal vein embolization, and 2) the changes in ^{31}P MRS-detectable metabolites in the regenerating lobe at 48 hours after partial hepatectomy are more obvious.

The metabolites which were most altered after PVE, PME and PDE, are comprised of precursors and breakdown products of cell membrane phospholipids. PE and PC which comprise the PME peak are precursors of phosphatidylethanolamine (PtdEth) and phosphatidylcholine (PtdCho), respectively. PE is metabolized to CDP-ethanolamine which is converted to PtdEth. There are multiple paths for the breakdown of PtdEth, one of which involves the generation of glycerophosphorylethanolamine (GPE) which can be recycled to PE. Similarly, choline is converted to phosphorylcholine and then CDP-choline which is converted to the PtdCho. Glycerophosphorylcholine (GPC) is a breakdown product of PtdCho which can be recycled to PC. PtdCho can also be synthesized by methylation of PtdEth; thus there is interaction between the pathways. Alterations in PME and PDE levels suggest upregulation of cell membrane phospholipid synthesis, which would be expected with hepatocyte proliferation. Animal models of liver regeneration after partial hepatectomy have demonstrated alterations in membrane metabolism. In ex vivo samples of regenerating rat liver, phosphorylethanolamine (PE) levels and synthesis of PtdEth have been shown to be elevated (18,19). Phosphatidylcholine synthesis has also been shown to increase in regenerating rat liver, while phosphorylcholine decreased transiently and normalized at 48 hours (19). In humans, Zakian and Mann have shown changes in PME, PDE and NTP after partial hepatectomy (12,20).

The distinct advantages of ^{31}P MRSI are that it is non-invasive, requires neither ionizing radiation nor contrast agents, and permits serial studies to be performed without perturbing physiology. As shown in Figure 3, this technique has the potential to follow the time course of biophysical changes after PVE and PH to help in our understanding of the regenerative process. The process of liver growth after PVE of the contralateral lobe is not completely understood. It is widely accepted that hemodynamic changes resulting from shunting of total portal vein flow to the remaining functional liver lobe play an important role in the induction of liver growth (21,22). Thereafter, levels of cytokines and growth factors increase and induce hepatocyte proliferation and hypertrophy of the lobe. It has been hypothesized that the mechanical stress on the endothelium of the portal vessels in the non-embolized lobe induces elevated levels of interleukin-6 (IL-6), a cytokine active in hepatocyte proliferation (23). It is not clear whether the mechanism of liver regeneration after PVE is the same as that after PH, but to a lesser degree, or whether there are intrinsic differences. Kawai, et al, suggest that after PH, TNF- α initiates hepatocyte proliferation, but after PVE, IL-6 plays a more important part (23).

To our knowledge, there are no prior human studies which compared cell proliferative changes in regenerating liver at the same time point after PVE and PH. Multiple rodent studies have been performed, although many use portal branch ligation (PBL or PVL) which is not necessarily a surrogate for PVE, but which is easier to perform in small animals (7,9). In rats the levels of proliferative markers such as Ki-67, ^3H -thymidine incorporation into DNA and the mitotic index in regenerating liver are elevated compared to control subjects in the first 24–48 hours (7,9,24,25). Most studies show higher levels of these markers after PH than after PVE or PBL (7,24,25). In rodents, there have been conflicting reports as to whether the proliferative peak occurs earlier after PH than PVE (7,9). In a porcine model of 60–70% PVE, peak proliferation occurred on day 7 and comprised 14% of hepatocytes (6) while in a PH model, peak proliferation occurred on day 3 (26). Comparison of these two results suggests that, in pigs, the PVE proliferation response is delayed compared to the response to PH. This tends to agree with our study.

Human studies of metabolic and proliferative changes in regenerating tissue after PVE are limited in number. Analysis of cell proliferation has been performed on tissue samples obtained at the time of partial hepatectomy using markers such as Ki-67, PCNA, and mitotic index. These studies, usually performed between 8 days and 3 weeks after PVE, have shown

elevated Ki-67 labeling, increased PCNA staining, and increased mitotic index in the non-embolized lobe compared to quiescent tissue (27–29). One study found that ATP concentration at 25 days after PVE did not differ from control values (30). To our knowledge there have been no direct comparisons between proliferative markers measured after PVE and PH in humans. Non-invasive ^{31}P MRSI permits investigation of proliferation at time points of interest to the investigator.

Other investigators have reported a number of potential sources of changes in liver PME levels. An *in vitro* study carried out by Bell et al. (31) showed increased PE and PC in histologically normal liver tissue within tumor-bearing liver lobe. We cannot rule out altered PME levels in liver parenchyma due to the presence of tumor in the liver, although our spectra were obtained from the lobe contralateral to the tumor-bearing lobe. However, our patients served as their own controls and we compared only the changes from baseline to 48 hours. Therefore, pre-existing abnormalities would not be expected to influence our results. Gluconeogenesis stimulated by alanine has been shown to cause an increase in the PME region of the ^{31}P spectrum possibly due to increased 3-glycerophosphate (31,32). While there is very limited data on glucose metabolism in the liver following PVE, Mueller, et. al. found that the ligated lobe in a mouse liver model initially maintains its functional capacity with respect to glucose homeostasis (33). They suggest that the presence of the remnant lobe after PVE may reduce the need for upregulation of gluconeogenesis in the hypertrophying lobe. Fibrosis and particularly, cirrhosis, have been shown to increase liver PME levels (34–36). However, none of our patients had clinical or pathological evidence of these conditions.

One interesting qualitative observation in this study was that both PE and PC appeared to increase at 48 hours after PVE while the trend in PH patients was a highly elevated PE peak and a low PC peak (see Fig. 1). This finding could explain why the total PME values in PH and PME did not differ significantly. Elevation of PE has been demonstrated in *in vitro* rodent studies after PH (19). Elevation in PC requires further investigation. One hypothesis is a contribution from erythrocyte 2, 3-diphosphoglycerate (2, 3-DPG). The PE and PC peaks are located at 4.36 ppm and 3.85 ppm respectively. Erythrocyte 2,3-DPG peaks are located at 3.8 and 2.8 ppm and can contribute 45% of the PC signal under normal conditions when the vascular volume of human liver is approximately 25% (37). The total blood volume of left liver would increase after right PVE, resulting in a higher fraction of 2, 3-DPG and thus might account for the elevated PC peak. However, the blood volume of the regenerating liver would also increase after PH and an increase in PC was not observed in these patients. This question requires further investigation.

DNA synthesis and cell mitosis during regeneration demand energy expenditure, and NTP/Pi is considered a measure of cellular energy reserve. NTP values in the PVE-48 group were unchanged compared to baseline. While we could not compare to our NTP values at 48 hours post-PH due to low sample size, human data from Mann, et. al. suggest that NTP is not significantly changed at 48 hours post-PH (38). Thus, it is unlikely that hepatic energy stores are depleted at 48 hours after PVE.

To our knowledge, there are no published measures of volume change in the non-embolized lobe at 48 hours after PVE in humans. In our study, neither the future liver remnant volume, nor the total liver volume changed significantly at 48 hours after PVE. Most likely, 48 hours is too early in the regenerative process for a substantial change in FLR volume. Total liver volume is not expected to change since PVE leads to the hypertrophy of the future remnant liver and concomitant atrophy of the embolized lobe without a significant change in the total liver volume (39,40).

The main weakness in this study was the limited number of subjects. This was governed by the difficulty in obtaining the baseline and, particularly, the 48 hour post-PVE MRSI data without disrupting the clinical care of the patient or delaying discharge from the hospital. The low signal-to-noise ratio inherent to ^{31}P studies due to the low sensitivity of the nucleus also reduced the number of data points for certain metabolites. This problem could be ameliorated by performing studies on a 3 Tesla scanner. Because the patients were pre-treated by multiple chemotherapy regimes (Table 1), analysis of ^{31}P changes segregated by prior chemotherapy regimen would have been of interest. However, the low number of patients precluded such an analysis.

In conclusion, ^{31}P -MRS is a promising technique for monitoring liver growth after PVE and other interventions. Alterations in cell membrane metabolism following portal vein embolization of the contralateral lobe are detectable at 48 hours by proton-decoupled ^{31}P -MRSI. The magnitude of metabolic alterations is lower after PVE than it is in the regenerating lobe at 48 hours after partial hepatectomy reflecting different processes and kinetics with growth after PVE and PH. Building on these findings, future studies should correlate subsequent liver growth with changes seen or not seen initially on ^{31}P MRSI.

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Figure 1.

^1H decoupled- ^{31}P MR spectra from tumor free liver at baseline (a) and 48 hours after PVE (b) from one patient. A spectrum from a different patient acquired at 48 hours post-partial hepatectomy (c) is shown for comparison. MRSI parameters: matrix = $8 \times 8 \times 8$, voxel size 48 mm^3 , TR = 1 s, averages = 4, points sampled = 1024, spectral width = 8000 Hz, flip angle = $\sim 45^\circ$, scan time = 34 min, apodization 2 Hz.

Figure 2.

Phosphorus metabolites in individual patients at baseline and 48 hours post-PVE. (a) normalized metabolite values for phosphomonoesters (PME), (b) normalized metabolite values for phosphodiester (PDE), (c) PME/PDE peak area ratio, and (d) PME/ β -NTP peak area ratio.

Figure 3.

^{31}P MRS spectra acquired from left liver lobe of patient No. 4 at baseline, 48 hours following PVE, 20 days after PVE, 6 days after right lobe hepatectomy, and 22 days after resection. MRSI acquisition parameters were identical through the 5 serial studies. Matrix = $8 \times 8 \times 8$, FOV = $320 \times 240 \times 280$ (voxel size 42 mm^3), TR = 1 s, averages = 4, points sampled = 1024, spectral width = 8000 Hz, flip angle = $\sim 45^\circ$, scan time = 34 min.

Clinical information and serum liver function results for 6 PVE patients and 4 PH patients studied at 48 hours after embolization or surgery.

Table 1

Pt No.	Sex	age	Prior chemo therapy	Chemo duration (d)	Tx free interval (d)	Baseline				48 hours after PVE or PH			
						Bilirubin (0–1 mg/dl)	AST (10– 37U/L)	ALT (5–37 U/L)	Alk phos (30– 88U/L)	Bilirubin (0–1 mg/dl)	AST (10–37U/L)	ALT (5–37U/L)	Alk phos (30– 88U/L)
Portal vein embolization patients (PVE)													
1	m	46	FOLFIRI	303	66	0.6	66	32	174	1.2	66	32	154
2	m	32	5FU/LV/CPT11/Oxali/FUDR	373	14	0.6	45	98	210	1.2	42	86	186
3	f	55	FOLFIRI	357	7	0.5	28	45	79	0.9	35	51	72
4	f	54	FOLFOX	113	8	0.8	51	67	92	1.0	41	46	82
5	f	50	FUDR/CPT11/Oxali	147	8	1.1	42	55	197	1.4	53	79	138
6	m	66	FOLFOX/FOLFIRI/Bev	300	120	0.8	47	13	10	---	---	---	---
Partial hepatectomy patients (PH)													
1	m	67	5 FU/LV	180	120	0.4	17	28	60	0.6	25	N/A	125
2	f	45	FOLFIRI	180	200	0.4	25	22	183	N/A	555	329	61
3	f	39	NO CHEMO	0		0.4	15	29	78	2.3	24	75	81
4	f	84	5 FU/LV	360	300	0.4	22	21	108	0.8	148	199	66

Abbreviations: 5FU =5-fluorouracil, LV = leucovorin, oxali = oxaliplatin, CPT11 = irinotecan, FUDR = floxuridine given by hepatic arterial infusion, Bev = bevacizumab, FOLFOX = 5FU+LV+oxaliplatin, FOLFIRI = 5FU+LV+irinotecan. Treatment free interval is the time between the end of chemotherapy and the PVE or surgical resection. N/A = data not available.

Changes in phosphorus metabolites at 48 hours following PVE. Bold lettering indicates a significant change from baseline to 48 hours.

Table 2

	PME	PDE	NTP	PME/PDE	PME/NTP	PDE/NTP	NTP/Pi
Observations(n)	5	5	4	6	5	5	5
Change from baseline (mean)	27±12%	-21±15%	-15±17%	59±40%	48±41%	-8±13%	-4±18%
P value	0.06	0.06	0.25	0.03	0.06	0.31	0.81

Table 3

Phosphorus metabolites at 48 hours after PVE and PH.

	PME	PDE	PME/PDE	Pi	GPE	GPC	GPE/GPC
PVE 48 hrs	7.22 ± 1.18 (n = 5)	25.01 ± 8.27 (n = 5)	0.51 ± 0.13 (n = 6)	4.68 ± 0.78 (n = 5)	9.57 ± 3.43 (n = 4)	11.58 ± 3.29 (n = 4)	0.91 ± 0.28 (n = 5)
PH 48 hrs	7.85 ± 2.57 (n = 4)	13.32 ± 5.91 (n = 4)	0.97 ± 0.25 (n = 4)	5.97 ± 2.80 (n = 4)	5.73 ± 1.68 (n = 4)	9.45 ± 4.56 (n = 4)	0.99 ± 0.55 (n = 4)
P value	0.63	0.049	0.004	0.35	0.06	0.17	0.77