

## Perfusion CT findings in liver of patients with tumor during chemotherapy

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Received: April 4, 2010 Revised: April 26, 2010

Accepted: May 3, 2010

Published online: July 7, 2010

### Abstract

**AIM:** To investigate the microcirculation changes in liver of patients with tumor during chemotherapy by perfusion computed tomography (CT).

**METHODS:** Sixty patients with tumor and 20 controls were enrolled in this study. Perfusion CT parameters of patients and controls were compared, including hepatic perfusion index (HPI), mean transit time (MTT), and permeability-surface area product (PS). Correlation between perfusion CT parameters, treatment cycle and alanine aminotransferase (ALT) level was studied.

**RESULTS:** No difference was found in HPI ( $25.68\% \pm 7.38\%$  vs  $26.82\% \pm 5.13\%$ ), MTT ( $19.67 \pm 5.68$  s vs

$21.70 \pm 5.43$  s) and PS ( $17.00 \pm 4.56$  mL/100 mL per min vs  $19.92 \pm 6.35$  mL/100 mL per min) between patients and controls. The HPI and MTT were significantly higher in patients undergoing 2 cycles of chemotherapy than in controls and those undergoing 1 cycle of chemotherapy ( $29.76\% \pm 5.87\%$  vs  $25.68\% \pm 7.38\%$  and  $25.35\% \pm 4.05\%$ , and  $25.61 \pm 5.01$  s vs  $19.67 \pm 5.68$  s and  $19.74 \pm 4.54$  s, respectively,  $P < 0.05$ ). The HPI was higher in patients with hepatic steatosis than in controls and those without hepatic steatosis ( $30.85\% \pm 6.17\%$  vs  $25.68\% \pm 7.38\%$  and  $25.70\% \pm 4.24\%$ ,  $P < 0.05$ ). Treatment cycle was well correlated with HPI and MTT ( $r = 0.40$ ,  $r = 0.50$ ,  $P < 0.01$ ). ALT level was not correlated with perfusion CT parameters.

**CONCLUSION:** HPI and MTT are significantly increased in patients with tumor during chemotherapy and well correlated with treatment cycle. Chemotherapy affects hepatic microcirculation in patients with tumor. Changes in hepatic microcirculation can be quantitatively assessed by perfusion CT.

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**Key words:** Liver; Microcirculation; Chemotherapy; Tomography, X-ray computed; Perfusion imaging

**Peer reviewer:** Paul E Sijens, PhD, Associate Professor, Radiology, UMCG, Hanzeplein 1, 9713GZ Groningen, The Netherlands

Zhang Q, Yuan ZG, Wang DQ, Yan ZH, Tang J, Liu ZQ. Perfusion CT findings in liver of patients with tumor during chemotherapy. *World J Gastroenterol* 2010; 16(25): 3202-3205 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v16/i25/3202.htm> DOI: <http://dx.doi.org/10.3748/wjg.v16.i25.3202>

### INTRODUCTION

Liver damage secondary to chemotherapy in patients with

tumor is common, and hepatic toxicity differs from mild inflammatory changes of nonspecific hepatitis to fibrosis and marked cirrhosis<sup>[1,2]</sup>. Although early liver damage causes no symptoms and is reversible in most patients, it occasionally progresses to more severe liver impairment, which may be irreversible. It is, therefore, necessary to demonstrate the presence and severity of drug-related parenchymal changes with effective imaging.

Early liver damage cannot be demonstrated by traditional computed tomography (CT). Perfusion CT is a noninvasive method showing hemodynamic changes in living tissue and has been used in evaluation of liver diseases. However, microcirculation changes in liver on perfusion CT image during chemotherapy have not been described. In this study, we investigated the hemodynamic changes in liver during chemotherapy, and estimated the correlation between the perfusion CT parameters and alanine aminotransferase (ALT) level.

## MATERIALS AND METHODS

### Patients and study design

Eighty consecutive individuals including 60 patients with tumor and 20 controls were enrolled in this study. Although history, physical examination, laboratory test, and Doppler sonography of liver showed that the 20 controls including 8 women at a mean age of  $47.3 \pm 8.6$  years (range 35-64 years) had no evidence of liver disease, they underwent abdominal perfusion CT for unrelated causes. Inclusion criteria included patients with tumor confirmed by appropriate clinical and laboratory examinations, those still on chemotherapy when perfusion CT was performed, those with hepatic carcinoma or metastasis who had an adequate space in liver parenchyma for later calculation, those who had no history of alcohol abuse, viral hepatitis, liver cirrhosis or other hepatic/biliary diseases, and those who had adequate heart, renal and liver function for perfusion CT. The 60 patients including 24 women at a mean age of  $53.2 \pm 7.1$  years (range 25-71 years) met the criteria. All patients received 1-2 cycles of chemotherapy (6-8 courses in one treatment cycle). Perfusion CT parameters were compared between controls and patients. The diagnostic criteria for hepatic steatosis were the density of liver parenchyma lower than that of spleen or the CT value of liver parenchyma less than 40 Hu on CT image without contrast agent.

The study was approved by the institutional ethics committee. Written informed consent was obtained from each patient or his or her family members after the nature of procedures was fully explained.

### Perfusion CT imaging and data processing

Perfusion CT was performed for patients at the end of each treatment cycle. After an overnight fast, patients and controls lying supine on a table underwent perfusion CT with a 64-row multi-detector CT scanner (Light Speed VCT, GE Healthcare, Chalfont St. Giles, UK). Before perfusion CT, patients underwent an abdominal scan without contrast medium during a breath hold at the end of

expiration. We selected a slice with the right hepatic lobe, spleen and portal trunk clearly visualized. Then, multiple-slice dynamic sequences lasting 80 s were scanned 8 s after injection of a contrast material (iohexol, 350 mg I/mL, Changfujiejing Pharmaceutical Co. Ltd., Shandong, China). The CT perfusion protocol comprised 80 scans, for 320 images. Because blood vessels of patients with tumor during chemotherapy became too fragile to endure a high injection pressure, a bolus infusion of 40 mL contrast material was given at a speed of 2.5-3.0 mL/s *via* a 20-gauge intravenous catheter in the antecubital vein with a power injector (SCT-210, Medrad Inc., Indianola, PA, USA). The patients kept normal respiration during the perfusion study. The CT parameters used in this study were 120 kV, 250 mA, 5-mm slice thickness, 1-s cycle time and standard reconstruction algorithm.

After image acquisition, the data were transferred to an image processing workstation (AW4.1, GE Healthcare, Chalfont St. Giles, UK) and analyzed with the integrated software of CT Perfusion 3. Four regions of interest (ROI) were set on the abdominal aorta, portal vein trunk, spleen and right liver lobe. The ROI of right liver lobe was drawn on the whole visible right lobe carefully, avoiding blood vessels, margin of liver parenchyma and possible lesions. Hepatic perfusion index (HPI), mean transit time (MTT), and permeability-surface area product (PS) were calculated.

### Statistical analysis

All data were expressed as mean  $\pm$  SD. Independent-sample *t* test was used to determine differences between patients and controls. Data about controls and patients were compared by one-way ANOVA. Spearman correlation coefficient was used to assess the correlation between perfusion parameters, treatment cycle and ALT level. All tests were two-tailed.  $P < 0.05$  was considered statistically significant. Data processing and analysis involved use of SPSS v11.5 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Differences in perfusion parameters

No significant difference was found in HPI ( $25.68\% \pm 7.38\%$  *vs*  $26.82\% \pm 5.13\%$ ,  $t = 0.77$ ,  $P = 0.44$ ), MTT ( $19.67 \pm 5.68$  s *vs*  $21.70 \pm 5.43$  s,  $t = 1.43$ ,  $P = 0.16$ ) and PS ( $17.00 \pm 4.56$  mL/100 mL per min *vs*  $19.92 \pm 6.35$  mL/100 mL per min,  $t = 1.90$ ,  $P = 0.06$ ) between patients and controls.

Patients were divided into two subgroups: one receiving 1 cycle of chemotherapy ( $n = 40$ ) and the other receiving 2 cycles of chemotherapy ( $n = 20$ ). The HPI and MTT were higher in patients receiving 2 cycles of chemotherapy than in those receiving 1 cycle of chemotherapy and controls ( $29.76\% \pm 5.87\%$  *vs*  $25.35\% \pm 4.05\%$  and  $25.68\% \pm 7.38\%$ , and  $25.61 \pm 5.01$  s *vs*  $19.74 \pm 4.54$  s and  $19.67 \pm 5.68$  s,  $P < 0.05$ ). No significant difference was observed in HPI and MTT between patients receiving 1 cycle of chemotherapy and controls, and in PS between patients and controls ( $F = 1.78$ ,  $P = 0.18$ ) (Table 1).

**Table 1** Comparison of perfusion parameters between controls and patients by treatment cycle (mean  $\pm$  SD)

Parameters	Controls (n = 20)	1 cycle (n = 20)	2 cycles (n = 40)	F value	P value
HPI (%)	25.68 $\pm$ 7.38	25.35 $\pm$ 4.05	29.76 $\pm$ 5.87	4.62	0.01
MTT (s)	19.67 $\pm$ 5.68	19.74 $\pm$ 4.54	25.61 $\pm$ 5.01	10.59	< 0.01
PS (mL/100 mL per min)	17.00 $\pm$ 4.56	19.95 $\pm$ 6.76	19.86 $\pm$ 5.60	1.78	0.18

Of the 60 patients, 13 (21.7%) showed hepatic steatosis. The incidence of hepatic steatosis was higher in patients receiving 2 cycles of chemotherapy than in those receiving 1 cycle of chemotherapy ( $P = 0.01$ ). The HPI was higher in patients with hepatic steatosis than in those without hepatic steatosis and controls (30.85%  $\pm$  6.17% *vs* 25.70%  $\pm$  4.24% and 25.68%  $\pm$  7.38%,  $P < 0.05$ ). No significant difference was found in HPI between patients without hepatic steatosis and controls, and in MTT or in PS between patients and controls (Table 2).

#### Correlation between CT perfusion parameters, treatment cycle and ALT level

Treatment cycle was well correlated with HPI ( $r = 0.40$ ,  $P < 0.01$ ) and MTT ( $r = 0.50$ ,  $P < 0.01$ ) but not with PS ( $r = 0.02$ ,  $P = 0.89$ ). ALT level was not correlated with treatment cycle ( $r = -0.05$ ), HPI ( $r = -0.06$ ), MTT ( $r = 0.19$ ), and PS ( $r = 0.18$ ).

## DISCUSSION

Hepatic toxicity is often encountered in patients with tumor following chemotherapy. Chemotherapy agents can impair many vital functions of liver cells and cause their death<sup>[3]</sup>. Severe cell death is followed by nodular regeneration and obstruction of sinusoids, including transformation of fenestrated sinusoids into continuous capillaries and deposition of collagen in extravascular tissue spaces located between sinusoidal endothelium and hepatocytes<sup>[4,5]</sup>. These morphologic alterations modify blood transit time and distribution volume of small and large molecules<sup>[6,7]</sup>, increase vascular resistance and reduce portal perfusion<sup>[8,9]</sup>. The reduction in portal perfusion is then buffered by liver arterialization, thereby increasing the arterial fraction of liver perfusion<sup>[8,10,11]</sup>. These alterations following chemotherapy are non-specific and can mimic any form of acute or chronic liver disease.

Perfusion CT can be used to evaluate the hemodynamic changes in liver disease. However, since the results of previous studies are varied<sup>[12-14]</sup>, no established conclusion is available on the change in liver perfusion, especially in early chronic liver disease. Some studies showed that HPI and MTT values are significantly increased in patients or rats with chronic liver disease<sup>[12,13]</sup>. However, another study showed that the MTT is lower while the PS is higher in patients than in controls<sup>[14]</sup>. In the present study, the hepatic HPI and MTT values were higher in

**Table 2** Comparison of perfusion parameters between controls and patients with or without hepatic steatosis (mean  $\pm$  SD)

Parameters	Controls (n = 20)	Patients without steatosis (n = 47)	Patients with steatosis (n = 13)	F value	P value
HPI (%)	25.68 $\pm$ 7.38	25.70 $\pm$ 4.24	30.85 $\pm$ 6.17	4.79	0.01
MTT (s)	19.67 $\pm$ 5.68	21.33 $\pm$ 5.31	23.03 $\pm$ 5.83	1.52	0.23
PS (mL/100 mL per min)	17.00 $\pm$ 4.56	20.23 $\pm$ 6.08	18.79 $\pm$ 7.43	2.09	0.13

patients during chemotherapy than in controls, and well correlated with treatment cycle. No significant difference was observed in PS between patients and controls.

Steatosis is a common manifestation of drug hepatotoxicity and a form of liver damage most readily recognized on CT image. Several studies have shown that the incidence of hepatic steatosis is increased in patients undergoing chemotherapy<sup>[15-18]</sup>. In this study, hepatic steatosis was observed in 13 (21.7%) of the 60 patients, which was higher in patients receiving 2 cycles of chemotherapy than in those receiving 1 cycle of chemotherapy. The HPI was higher in patients with hepatic steatosis than in those without hepatic steatosis and controls. No difference was found in MTT or in PS between patients and controls.

At present, ALT level is the main index of drug-induced hepatic damage<sup>[19]</sup>. However, the ALT level was found to be a less sensitive index of hepatic damage and could not thoroughly reflect hepatic toxicity in this study. In clinical practice, many liver function tests remain normal despite obvious liver changes seen on CT images. In the present study, only 4 of 13 patients with hepatic steatosis had abnormal ALT, which was not correlated with HPI, MTT or PS. However, it has been shown that perfusion CT parameters are correlated with the severity of hepatic disease<sup>[13]</sup>, indicating that further study is needed to classify the severity of liver damage with perfusion CT parameters.

Our study has some limitations. First, the injection rate of contrast agent was low. Because the detection of perfusion parameters is affected by many factors such as the type and injection rate of contrast agent, drawing of ROI and calculation method<sup>[20,21]</sup>, the low injection rate may be a major obstacle to comparison with other results. Second, our sample size was small. Third, we only investigated the changes in perfusion CT in liver of patients during chemotherapy, and did not observe the entire changing characteristics of hepatic microcirculation during and after chemotherapy.

In conclusion, hepatic microcirculation is changed in patients with tumor during chemotherapy and can be quantitatively assessed by perfusion CT. Perfusion CT may be used as a noninvasive tool in detection of hepatic toxicity.

## ACKNOWLEDGMENTS

The authors thank Ji-Quan Du, Hospital of Shandong Armed Police Forces for his efforts in the research, and

Gui-Lin Liu, Affiliated Hospital of Shandong Academy of Medical Science for her invaluable help in data processing and manuscript preparation.

## COMMENTS

### Background

Liver damage is common in patients with tumor following chemotherapy. Although early liver damage causes no symptoms and is reversible in most patients, it occasionally progresses to more severe liver impairment, which may be irreversible, it is thus necessary to demonstrate the presence and severity of drug-related parenchymal changes.

### Research frontiers

Hepatic microcirculation changes in patients with tumor during chemotherapy were evaluated by perfusion computed tomography (CT). The hotspot of this research is whether hepatic microvascular changes can be quantified with perfusion CT and what kind of modifications can be detected.

### Innovations and breakthroughs

At present, alanine aminotransferase (ALT) level is the main index in diagnosis of drug-induced hepatic damage. In this study, however, ALT level was found to be a less sensitive index and could not thoroughly reflect hepatic toxicity. The aim of this study was to investigate the microcirculation changes in liver of patients with tumor during chemotherapy, showing that hepatic perfusion index and mean transit time are significantly increased in patients undergoing 2 cycles chemotherapy.

### Applications

The findings of this study may underscore the possibility of using perfusion CT parameters as indicators of hepatic microcirculation alteration in drug-induced liver damage. Perfusion CT may be used as a noninvasive tool in detection of hepatic toxicity.

### Peer review

The paper is a concise documentation of a good study.

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S- Editor Tian L L- Editor Wang XL E- Editor Ma WH