

## Computed tomography perfusion imaging as a potential imaging biomarker of colorectal cancer

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Author contributions: Hayano K, Fujishiro T and Shuto K contributed to conception and design; all authors contributed to manuscript writing and preparing figures; and all authors reviewed and approved this article to be published.

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Received: February 28, 2014 Revised: April 1, 2014

Accepted: July 22, 2014

Published online: December 14, 2014

radiation therapy

**Core tip:** The importance of angiogenesis, which is an essential process of colorectal cancer (CRC), has been established. Therefore, the *in vivo* measure of angiogenesis such as computed tomography (CT) perfusion (CTP) technique can be a robust imaging biomarker in CRC. Especially, CTP certainly fulfils the criteria necessary for prospective validation as a clinical trial end point, because CT is a stable platform, broadly available, and non-invasive. Therefore, we believe that CTP will play an important role in the management of CRC, providing patients more personalized and effective treatment.

Hayano K, Fujishiro T, Sahani DV, Satoh A, Aoyagi T, Ohira G, Tochigi T, Matsubara H, Shuto K. Computed tomography perfusion imaging as a potential imaging biomarker of colorectal cancer. *World J Gastroenterol* 2014; 20(46): 17345-17351 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i46/17345.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i46.17345>

### Abstract

Neovascularization was reported to arise early in the adenoma-carcinoma sequence in colorectal cancer (CRC), and the importance of angiogenesis in cancer progression has been established. Computed tomography (CT) perfusion (CTP) based on high temporal resolution CT images enables evaluation of hemodynamics of tissue *in vivo* by modeling tracer kinetics. CTP has been reported to characterize tumor angiogenesis, and to be a sensitive marker for predicting recurrence or survival in CRC. In this review, we will discuss the biomarker value of CTP in the management of CRC patients.

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**Key words:** Colorectal cancer; Angiogenesis; Computed tomography perfusion; Antiangiogenic therapy; Chemo-

### INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States<sup>[1]</sup>. About 70% of patients are operated with curative intent; however, up to 30% of these patients will relapse subsequently, usually within 2-3 years<sup>[2,3]</sup>.

In CRC, neovascularization was reported to arise early in the adenoma-carcinoma sequence<sup>[4]</sup>. Angiogenesis is an essential process of CRC, and plays an important role in the process of growth and metastasis<sup>[5,6]</sup>. Previous studies reported that angiogenesis could be a useful prognostic marker in almost all carcinomas, including CRC<sup>[5-7]</sup>. However, currently, the methods for assessing angiogenesis in

**Table 1** Summary of previous reports on computed tomography perfusion and chemoradiation therapy in rectal cancer

Ref.	Year	Number of patients	Parameter changes	Response Prediction
Sahani <i>et al</i> <sup>[13]</sup>	2005	15	BF/decrease; MTT/increase	High baseline BF and low MTT associated with poor response (12 responders <i>vs</i> 3 non-responders)
Bellomi <i>et al</i> <sup>[25]</sup>	2007	20	BF, BV, PS/decrease	High baseline BF and BV associated with good response (17 responders <i>vs</i> 7 non-responders)
Curvo-Semedo <i>et al</i> <sup>[24]</sup>	2012	25	BF, BV, PS/decrease; MTT/increase	High baseline BF and low MTT associated with poor response (5 responders <i>vs</i> 15 non-responders)

BF: Blood flow; BV: Blood volume; MTT: Mean transit time; PS: Permeability surface area product.

clinical practice have relied mainly on immunohistological analysis of postoperative specimens such as microvessel density (MVD) counting. The disadvantage of this analysis is that they assess anatomical data only, and can be used only for postoperative specimens. Therefore, the methods, which enable quantitative measure of angiogenesis in *in vivo*, are highly expected to be a robust biomarker for the management of CRC patients in clinical practice.

Computed tomography perfusion (CTP), which can quantify tumor vascularity by measuring the temporal changes in tissue attenuation following intravenous contrast administration, is readily incorporated into the existing CT protocol, and enables evaluation of hemodynamics of tissue *in vivo* by modeling tracer kinetics<sup>[8,9]</sup>. Generally, a small volume of contrast material (40-70 mL depending on concentration) is injected at high flow injection rate (> 4 mL/s), and followed by 20-40 mL of saline flush at a similar flow rate to obtain a narrow bolus for optimal CTP analysis. Both tissue and vascular enhancement by contrast material can be measured and traced over time (45-120 s depending on kinetic model and parameter), and mathematic models such as compartmental or deconvolution analysis for contrast material exchange have been applied to quantify the tissue vascular physiology<sup>[10]</sup>. Perfusion parameters are dependent on the scan protocol and the kinetic model for perfusion analysis<sup>[9,11]</sup>, but the common CTP parameters were blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability surface area product (PS)<sup>[12-16]</sup>. CTP has emerged as an important imaging biomarker to evaluate tissue vascular physiology and tumor biology, which has been reported to associate with tumor characterization, survival, and therapy response in CRC<sup>[13-15,17,18]</sup>. Furthermore, with the increasing use of the neoadjuvant chemoradiation therapy (CRT) for rectal cancer and the targeted therapy including antiangiogenic therapy in recent various oncology trials, there is a renewed interest in the use of CTP as a surrogate endpoint for monitoring early therapeutic response or predicting treatment outcome<sup>[18-22]</sup>. Although still considered a research tool in the realm of oncology, CTP offers several potential clinical applications; and therefore, its integration into routine clinical practice is a distinct possibility because most CT scanners now come equipped with sophisticated hardware platforms coupled with powerful and user-friendly software packages for tissue perfusion analysis.

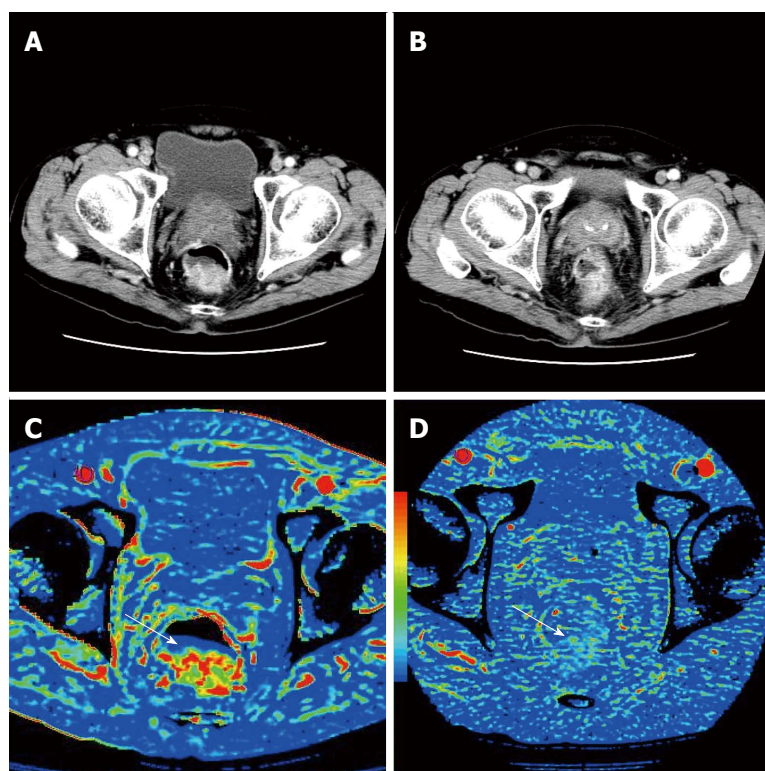
Needless to say, imaging plays an important role in the management of patients with CRC. And CT has become the main diagnostic tool in tumor evaluation, including diagnosis, staging, or monitoring of anticancer therapies because of the relatively low cost and wide availability. In this review, we discuss how CTP can be applied to the management of CRC as an imaging biomarker, reviewing novel clinical approaches of CTP in assessing response to the treatment or predicting survival in CRC patients.

## CTP FOR MONITORING AND PREDICTING THE RESPONSE TO THE CHEMORADIATION THERAPY

In patients with a locally advanced rectal cancer, neoadjuvant CRT has been recommended, and such neoadjuvant therapy is useful for decreasing the tumor stage to facilitate curative resection and to decrease the rate of recurrence<sup>[22,23]</sup>. Thus, it is highly desirable and beneficial to develop the noninvasive diagnostic tool to monitor or predict the response to CRT.

There are several CTP studies reporting perfusion changes of rectal cancer during CRT (Table 1)<sup>[13,24,25]</sup>. These previous reports demonstrated that BF and BV decreased, whereas MTT increased after CRT (Figure 1). Similar perfusion changes were also reported in CTP studies of head and neck cancer and esophageal cancer treated with CRT<sup>[26,27]</sup>. These changes may reflect the fibrosis induced by CRT. The tissue fibrosis leads directly to compression of tumor capillaries and increased flow resistance, which leads to decrease in BF and BV, and increase in MTT<sup>[14,28]</sup>. Another assumption is that these perfusion changes may reflect reduction in MVD. Johansson *et al*<sup>[29]</sup> showed that irradiation caused decrease in MVD in a rat glioma model.

Previous papers also reported that baseline perfusion values could predict the response to the CRT<sup>[24,25]</sup>. However, their results are controversial. Bellomi *et al*<sup>[25]</sup> showed baseline BF and BV in non-responders to be significantly lower and MTT significantly higher than in responders, while Curvo-Semedo *et al*<sup>[24]</sup> showed baseline BF in non-responder to be significantly higher and MTT significantly lower than in responders. The reasons for these discrepancies might be because they used different reference standards to assess response, different patient selection criteria and different kinetic models. The small



**Figure 1** Perfusion change after chemoradiation therapy. Contrast enhanced CT images at baseline (A) and post-CRT (B). BF maps at baseline (C) and post-CRT (D). After CRT, tumor showed significant decrease in BF (arrows). CRT: Chemoradiation therapy; CT: Computed tomography; BF: Blood flow.

**Table 2** Summary of previous reports on computed tomography perfusion and antiangiogenic therapy in colorectal cancer

Ref.	Year	Number of patients	Time of CTP after the treatment	Parameter changes
Willet <i>et al</i> <sup>[18]</sup>	2004	6 (primary)	After 12 d of administration of bevacizumab	BF, BV/decrease
Willet <i>et al</i> <sup>[32]</sup>	2009	32 (primary)	After 12 d of administration of bevacizumab	BF, PS/decrease
Anzidei <i>et al</i> <sup>[33]</sup>	2011	18 (liver metastases)	After 181 d of the treatment (including bevacizumab)	BF, BV/slightly decrease (not significant)

CTP: Computed tomography perfusion; BF: Blood flow; BV: Blood volume; PS: Permeability surface area product.

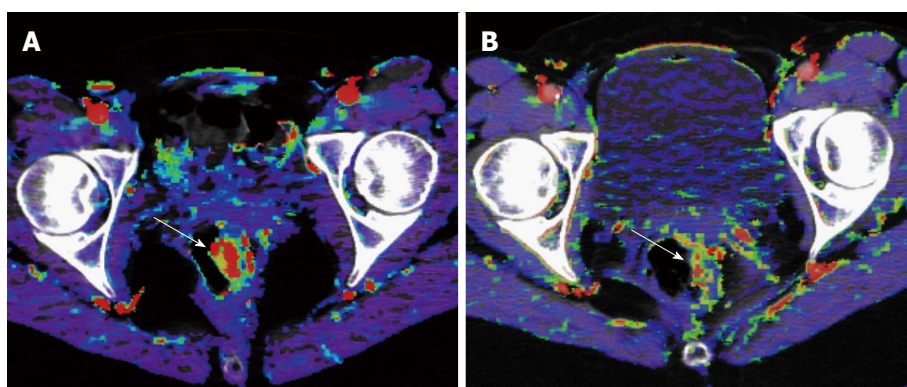
sample size of these studies also might affect their results. It is highly beneficial to predict the response to CRT so that non-responders could avoid the side effects associated with intensive therapeutic regimens, and therefore, predictive value of CTP in the response to CRT should be evaluated in a prospective study with a larger sample size.

## CTP AND ANTIANGIOGENIC THERAPY

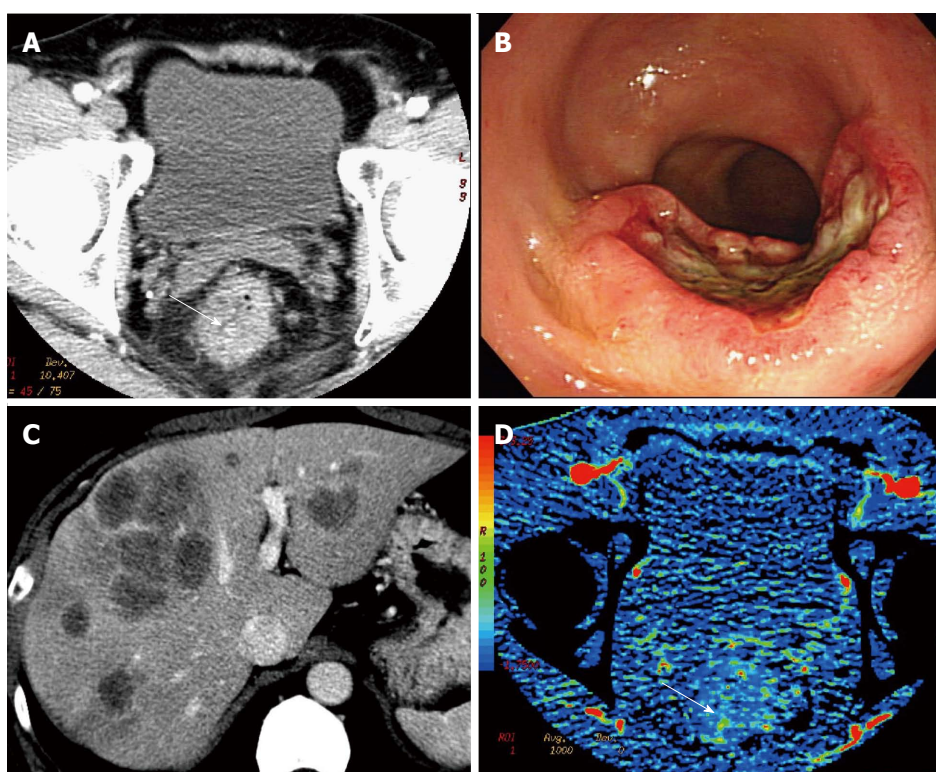
Tumor angiogenesis provides an attractive target for anticancer therapy. Previous clinical trials have established that the addition of antiangiogenic agents to chemotherapy significantly improves survival compared with chemotherapy alone in first-line and second-line treatment of metastatic CRC<sup>[30,31]</sup>. These studies have shown followings: (1) in the treatment of metastatic CRC, the addition of the VEGF-directed antibody, bevacizumab, to chemotherapy significantly improve outcome in comparison with chemotherapy alone; and (2) bevacizumab has minimum activity as a single agent. Based on these findings, further understanding of the mechanism of the interaction between antiangiogenic agents and chemotherapy

is highly beneficial for the personalized therapy in CRC. In addition, the morphologic assessment has a difficulty in distinguishing viable tumor from necrotic or fibrotic tissue because molecular targeted agents suppress tumor growth by downregulating angiogenesis without causing much morphologic change. Thus, there is an increasing interest in the *in vivo* quantification of angiogenesis based on images such as CTP. A few CTP papers concerning antiangiogenic therapy have been published in CRC (Table 2)<sup>[18,32,33]</sup>. Willett *et al*<sup>[18,32]</sup> reported that tumor BF and BV decreased within two weeks of the initiation of bevacizumab alone, which is a monoclonal antibody that targets VEGF, and they also reported reduction in MVD after the administration of bevacizumab (Figure 2). Anzidei *et al*<sup>[33]</sup> reported a CTP study of liver metastases in CRC treated with chemotherapy and bevacizumab. Their study showed reduction in BF and PS after the therapy, but this tendency was not statistically significant. It is assumed that these perfusion changes may reflect the change of MVD, because several previous reports demonstrated positive correlations of BF, BV and PS with MVD<sup>[15,34,35]</sup>. However, exploitation of the ability of this technique in predicting response to antiangiogenic therapy is still in





**Figure 2** Perfusion change after antiangiogenic therapy. After 2 wk of antiangiogenic therapy (bevacizumab), tumor BF decreased significantly (arrows). A: Baseline; and B: Post-therapy BF map. BF: Blood flow.



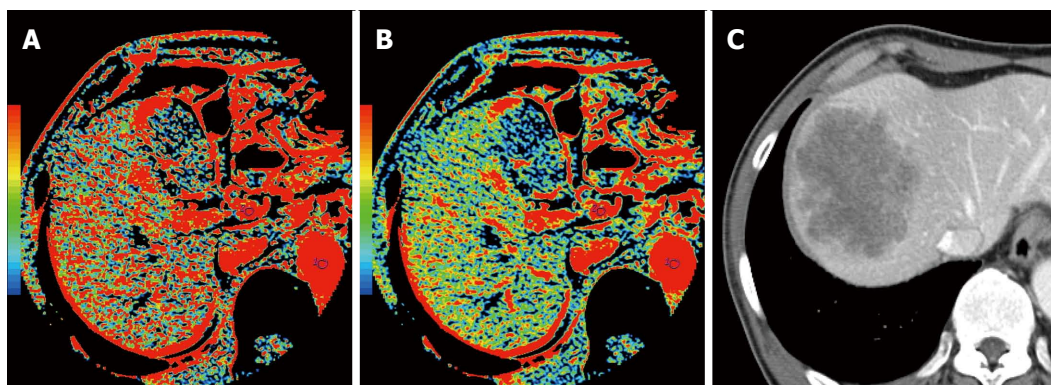
**Figure 3** Tumor perfusion and distant metastases. A-C: Rectal cancer patient with synchronous multiple liver metastases; D: Computed tomography perfusion demonstrated low tumor BF (35.3 mL/100 g per minute) (arrow). BF: Blood flow.

early stages of development.

## CTP AND SURVIVAL IN CRC PATIENTS

Angiogenesis plays an important role in cancer progression, and could be a useful prognostic marker in almost all carcinomas, including CRC<sup>[5-7]</sup>. Thus, CTP that can assess angiogenesis of the tumor *in vivo*, is highly expected to be an imaging biomarker that can reflect clinical outcome of CRC. CTP has been reported to be a sensitive marker for predicting recurrence or outcome in CRC<sup>[14,16]</sup>. Goh *et al*<sup>[16]</sup> reported that tumor BF measured by perfusion CT was significantly lower in CRC patients who ultimately developed metastatic disease. Our previous CTP

study demonstrated that rectal cancer with low BF, which tended to be accompanied by synchronous metastatic lymphnodes or distant metastases (Figure 3), associated with poor overall survival<sup>[14]</sup>. These authors hypothesized that reduced BF are related to increasing interstitial fluid pressure and hypoxia in tumor tissue<sup>[14,16]</sup>. Accumulation of excess fluid in the interstitium of tumor and excessive tumor growth in a confined space also leads to increased solid tissue pressure and elevated interstitial fluid pressure, which in turn cause capillary compression, and may reduce blood flow<sup>[36,37]</sup>. Regarding to relationship between CTP and tissue oxygenation, Haider *et al*<sup>[38]</sup> reported that the tumor blood flow on CTP correlated positively with tumor oxygenation in cervical cancer. Hypoxic environ-



**Figure 4 Hepatic perfusion and recurrence.** This patient underwent curative surgery, and was diagnosed as stage II colon cancer (no distant and lymphnode metastases). Preoperative hepatic BF (A) and hepatic arterial fraction (B) was high (BF = 191 mL/min per 100 g, HAF = 32%). After 6 mo of surgery, this patient developed a liver metastasis (C). BF: Blood flow.

ment plays an important role in cancer progression with promoting oncogenic mutations, cell survival, and more aggressive behavior in tumors<sup>[39]</sup>. Therefore, low BF tumor may correlate with poor survival. But we have to say that CTP measurements to clinical outcomes remain limited. These reports are based on small and single center studies. Therefore, we need to confirm these results with larger multicenter trials.

## LIVER PERFUSION AND METASTASES

Several studies have suggested the relationship between tumor progression and hemodynamic changes in the liver. In 1983, Leveson *et al*<sup>[40,41]</sup> reported that gastrointestinal cancer patients with simultaneous liver metastasis exhibited a higher hepatic arterial blood flow measured with scintigraphy. In CRC with simultaneous liver metastases, Leen *et al*<sup>[42]</sup> demonstrated a significant increase in the hepatic arterial blood flow and a significant decrease in the portal blood flow compared with those observed in healthy volunteers using doppler ultrasonography study. The CTP technique was also applied to this investigation of the relationship between tumor progression and hemodynamic changes in the liver. In liver CTP studies of patients with known metastatic disease, increased arterial perfusion has been shown by Miles *et al*<sup>[43]</sup> and Blomley *et al*<sup>[44]</sup>. Cuenod *et al*<sup>[45]</sup> reported that hemodynamic changes, including decrease in the portal blood flow and increase in the mean transit time, could be detected using CTP in the rats with occult liver metastases. In CRC with simultaneous liver metastases, Leggett *et al*<sup>[46]</sup> reported that the hepatic arterial blood flow significantly increased and the portal blood flow decreased by using CTP. In CTP study of esophageal cancer, Fujishiro *et al*<sup>[47]</sup> reported that the preoperative hepatic arterial blood flow might be a useful predictive marker for the future metastases. Therefore, CTP derived hemodynamic change in the hepatic blood flow has a potential to become a novel imaging biomarker to predict recurrence or metastases in CRC patients (Figure 4). A tumor-related circulating vasoactive mediator may contribute to this global perfusion change<sup>[48]</sup>, and

further supportive work is necessary<sup>[49]</sup>.

## CONCLUSION

Data relating CTP to clinical outcomes in CRC still remain limited. Relatively small, single center studies have suggested that CTP parameters may reflect clinical outcome in CRC<sup>[14,16]</sup>. Thus, there is a need to confirm these results with prospective and larger multicenter trials. As CT technology has reached maturity, further consideration has to be given to the direction of CTP research. As an imaging biomarker, CTP certainly fulfils the criteria necessary for prospective validation as a clinical trial end point, because CT is a stable platform, widely available, and non-invasive. Therefore, we believe that CTP technique will play an important role in the management of patients with CRC as a key imaging technique in clinical practice, providing patients more personalized treatment.

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**P- Reviewer:** Caboclo LF, Cai SJ, Kato J **S- Editor:** Ma YJ

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ISSN 1007-9327

