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Short Communication

Perfusion imaging of colorectal liver metastases treated with bevacizumab and stereotactic body radiotherapy

Jay S. Detsky[a,d,1], Laurent Milot[c,g,1], Yoo-Joung Ko[b,e], Pablo Munoz-Schuffenegger[a,d], William Chu[a,d], Gregory Czarnota[a,d,f], Hans T. Chung[a,d,*]

[a] Department of Radiation Oncology, Odette Cancer Center, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[b] Department of Medical Oncology, Odette Cancer Center, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[c] Department of Medical Imaging, Odette Cancer Center, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[d] Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada
[e] Department of Medical Oncology, University of Toronto, Toronto, Ontario, Canada
[f] Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada
[g] Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada

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ABSTRACT

Stereotactic body radiotherapy (SBRT) and bevacizumab are used in the treatment of colorectal liver metastases. This study prospectively evaluated changes in perfusion of liver metastases in seven patients treated with both bevacizumab and SBRT. Functional imaging using dynamic contrast-enhanced CT perfusion and contrast-enhanced ultrasound were performed at baseline, after bevacizumab, and after SBRT. After bevacizumab, a significant decrease was found in permeability (−28%, $p < .05$) and blood volume (−47%, $p < .05$), while SBRT led to a significant reduction in permeability (−22%, $p < .05$) and blood flow (−37%, $p < .05$). This study demonstrates that changes in perfusion can be detected after bevacizumab and SBRT.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer death worldwide [1]. Approximately 25–50% of patients with colorectal cancer will eventually have tumor recurrence in their liver [2]. In patients with resectable solitary liver metastases, five year survival rates of 30–40% have been reported [3,4]. Stereotactic body radiotherapy (SBRT) is an alternative to surgical resection of liver metastases [5,6] that has an 84% rate of local control at 18 months [7]. Bevacizumab, a vascular endothelial growth receptor (VEGF) inhibitor, when added to conventional chemotherapy has significantly improved overall survival in patients with metastatic colorectal cancer [8–10]. Bevacizumab improves pathological complete response in patients with rectal cancer when combined with neoadjuvant chemoradiation [11].

Conventional morphologic imaging with magnetic resonance imaging (MRI), ultrasound (US) or computed tomography (CT) is the current standard for diagnosing and monitoring colorectal cancer and liver metastases. In the era of high dose radiation and molecular-based targeted therapies, there is increasing interest in the use of functional imaging as a method to both evaluate and predict response to treatment [12–14]. Perfusion imaging with dynamic contrast enhanced computed tomography (DCE-CT) has been used to assess tumor vascularity and has shown promise in identifying tumors that respond poorly to neoadjuvant chemoradiation [15]. In human colon cancer xenografts in mice, DCE-CT has been used to track changes in perfusion over time after treatment with both bevacizumab and radiation [16], but quantitative perfusion changes in colorectal liver metastases in humans has not been reported to date.

Functional imaging using novel ultrasound (US) techniques have more recently been investigated for characterizing malignant lesions. Contrast-enhanced US (CEUS) is a method that uses a microbubble contrast agent to image flow in the capillary microcirculation [17] that has been used to characterize vascular properties of liver lesions [18]. Preliminary data suggests that microbubble-based ultrasound imaging can improve the detection of small colorectal liver metastases [19].

This prospective pilot study was conducted to evaluate the utility of CT and US perfusion imaging in patients with colorectal liver metastases treated with bevacizumab and SBRT.

* Corresponding author at: Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, T-wing, Toronto, Ontario M4N3M5, Canada.
E-mail address: hans.chung@sunnybrook.ca (H.T. Chung).
[1] Co-primary authors.

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Table 1
Perfusion parameters at baseline, after bevacizumab (and prior to SBRT), and after SBRT for all seven patients. Also shown is the initial tumor volume as well as local or distant recurrence by patient.

Patient #	Tumor size (cc)	Permeability (mL/100 g/mL)				Blood volume (mL/100 g)				Blood flow (mL/100 g/min)				Tumor recurrence
		Baseline T1	Pre SBRT T2	Post SBRT T3	Change (%) (T1-T2/T2-T3)	Baseline T1	Pre SBRT T2	Post SBRT T3	Change (%) (T1-T2/T2-T3)	Baseline T1	Pre SBRT T2	Post SBRT T3	Change (%) (T1-T2/T2-T3)	
1	29	48	43	29	−10/−33	21	17	6	−21/−61	267	125	79	−53/−37	None
2	154	70	69	64	−1/−7	44	24	58	−45/142	197	141	117	−29/−17	Local, distant
3	28	19	14	11	−27/−22	23	12	12	−48/0	120	99	36	−18/−64	Local
4	52	25	18	13	−28/−28	100	20	8	−80/−80	114	113	42	−1/−63	None
5	26	xx	42	12	xx/−70	xx	29	11	xx/−63	xx	394	196	xx/−50	Distant
6	68	32	25	25	−22/1	14	10	14	−27/43	76	116	90	52/−23	Local
7	14	25	6	17	−75/166	11	5	5	−55/0	117	74	64	−37/−13	Distant
				Median change	−28/−22				−47/0				−24/−37	
				W-value	0*/1.5*				0*/6				3/0*	

* Indicates statistical significance at $p < .05$.

2. Material and methods

Our Institutional Research Ethics Committee approved this study, and informed consent was obtained from each patient. Patients were included if they had one to three liver metastases and histological confirmation of colorectal cancer. Ten patients were enrolled and a total of seven patients (each with a solitary metastasis) were included in the final CT perfusion parametric analysis. CEUS images were acquired in four patients. Baseline patient characteristics are shown in Supplementary Table S1.

Bevacizumab was administered at a dose of 5 mg/kg IV for two doses two weeks apart, starting two weeks before SBRT; the second dose was administered no more than 48 h before starting SBRT. The radiation simulation process has been described previously and contouring was performed on a 4D-CT simulation scan (in the portal-venous phase) to account for respiratory motion [20]. The prescription dose was determined by the volume of liver receiving less than 15 Gy and dose constraints to surrounding organs at risk (median dose 54 Gy, range 36–60 Gy).

All imaging studies were performed at three time points. A baseline scan was performed prior to any treatment. A second scan, after bevacizumab but before SBRT, was obtained within 48 h after the second dose of bevacizumab. The last scan was performed within seven days after completion of SBRT. The DCE-CT was acquired using a 64-slice clinical CT (VCT Lightspeed, GE Medical Systems, Milwaukee, WI) with a field-of-view of 40 cm. Patients then received bolus intravenous CT contrast (Ultravist 370) at a dose of 100 mL at a rate of 4 mL/s, and high temporal resolution scans and time attenuation curves were collected. Data were analyzed using commercially available software (CT Perfusion 4.0, GE Medical Systems). The metastases being treated were contoured on conventional contrast-enhanced CT images by an experienced abdominal radiologist (LM). The Johnson and Wilson model for distribution of CT contrast medium was used [21]. The perfusion analysis is described in detail elsewhere [15]. The DCE-CT output parameters are the following: blood volume (mL/100 g), blood flow (mL blood/100 g/min) and permeability surface area (mL/100 g/mL).

For CEUS, microvascular volume was measured using an approved microbubble agent, Definity (Bristol-Myers Squibb, Boston MA), using bolus and disruption-replenishment methods with pulse inversion contrast-specific imaging software (iU22, Philips Medical Systems or Aplio 80, Toshiba Medical Systems). Following bubble disruption, replenishment into the imaging plane of interest in the tumor was used to calculate the integrated contrast signal, normalized with respect to the signal in the adjacent normal liver. A quantitative perfusion index was calculated as the ratio of the integrated signal to the mean transit time.

The perfusion parameters were averaged over the tumor of interest for each patient and compared longitudinally over the three time points (comparing baseline to post-bevacizumab, and pre-SBRT to post-SBRT) using the Wilcoxon Signed-Rank test as the limited sample size does not allow for the assumption of normality. The output W from the Wilcoxon test is considered to demonstrate a statistically significant difference at a level of 0.05 if W is less than or equal to zero (for $n = 6$) or W less than or equal to two (for $n = 7$) [22]. All statistical tests were performed using Matlab (The Mathworks, Natick, MA).

3. Results

The median age of the enrolled patients was 70 years. The mean target volume was 43 cc (range from 14 to 154 cc). During treatment, two patients experienced grade 2 toxicities (fatigue and nausea), while one patient developed grade 3 hypertension. Otherwise there were no other acute or late grade 3–5 toxicities observe during a median follow-up of 412 days. Of the seven evaluable patients with CT perfusion data, three had local failure at the time of last follow up. One of three patients with local failure had simultaneous distant failure; two of the four patients with no local failure developed distant failure. Median overall survival was not reached during follow-up.

The mean permeability decreased in all six patients from baseline to post-bevacizumab (median change −28%, $W = 0$, $p < .05$), as did the blood volume (median change −47%, $W = 0$, $p < .05$). Blood flow decreased in five of six patients in this cohort (median change −24%, $W = 3$, $p > .05$); the one patient that had an increase in blood flow after bevacizumab was one of the three patients that had local failure. CT perfusion data at baseline and after bevacizumab for all patients is shown in Table 1. The changes in perfusion parameters before and after SBRT are shown in Table 2. Radiation caused a decrease in permeability

Table 2
Contrast-enhanced ultrasound (CEUS) perfusion index for individual patients at baseline, after bevacizumab, and after SBRT.

Patient	Baseline (T1)	Post bevacizumab (T2)	Post SBRT (T3)	% change (T1-T2)	% change (T2-T3)
1	0.160	0.090	0.070	−46%	−14%
2	0.070	0.004	0.001	−95%	−79%
3	0.060	0.008	0.005	−86%	−41%
4	0.007	0.001	0.001	−82%	−2%
Median change				−84%	−28%