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Quantitative Measurements of Enhancement on Preprocedure Triphasic CT Can Predict Response of Colorectal Liver Metastases to Radioembolization

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Abstract

Objective—Colorectal liver metastases (CLM) have a variable response to radioembolization.

This may be due at least partly to differences in tumor arterial perfusion. The present study examines whether quantitative measurements of enhancement on preprocedure triphasic CT can be used to predict the response of CLM to radioembolization.

Materials and Methods—We retrospectively reviewed patients with CLM treated with radioembolization who underwent pretreatment PET/CT and triphasic CT examinations and posttreatment PET/CT examinations. A total of 31 consecutive patients with 60 target tumors were included in the present study. For each tumor, we calculated the hepatic artery coefficient (HAC), portal vein coefficient (PVC), and arterial enhancement fraction (AEF) based on enhancement measurements on pretreatment triphasic CT. HAC and PVC are estimates of the hepatic artery and portal vein blood supply. AEF, which is the arterial phase enhancement divided by the portal phase enhancement, provides an estimate of the hepatic artery blood supply as a fraction of the total blood supply. For each tumor, the metabolic response to radioembolization was based on findings from the initial follow-up PET/CT scan obtained at 4–8 weeks after treatment.

Results—A total of 55% of CLM had a complete or partial metabolic response. Arterial phase enhancement, the HAC, and the PVC did not predict which tumors responded to radioembolization. However, the AEF was statistically significantly greater in tumors with a complete or partial metabolic response than in tumors with no metabolic response (i.e., those with stable disease or disease progression) ($p = 0.038$). An AEF of less than 0.4 was associated with a 40% response rate, whereas an AEF greater than 0.75 was associated with a 78% response rate.

Conclusion—Response to radioembolization can be predicted using the AEF calculated from the preprocedure triphasic CT.

Keywords

colorectal cancer; enhancement; liver metastasis; perfusion; yttrium-90

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Radioembolization performed with ^{90}Y -microspheres is used to treat unresectable liver-dominant metastases. However, many colorectal liver metastases (CLM) do not respond to radioembolization [1]. Predicting which patients are unlikely to benefit from radioembolization would allow these patients to avoid the risks of radioembolization, including liver failure [2] and nonhealing gastric ulcers [3]. It would also allow these patients to be directed to other treatment options.

Response to radioembolization can be predicted using invasive or specialized imaging protocols. The enhancement pattern noted on catheter CT angiography [4] and the uptake noted on $^{99\text{m}}\text{Tc}$ -macroaggregated albumin SPECT [5] both predict the response of CLM to radioembolization. Arterial perfusion calculated from a CT perfusion study, which requires a 12-phase contrast-enhanced CT examination, predicts response to radio-embolization in a mixed patient population including both hypovascular and hypervascular metastases [6, 7].

We would ideally like to predict response on the basis of standard noninvasive preprocedure imaging. In the present study, we examine whether quantitative measurements of enhancement on routine preprocedure triphasic CT can be used to predict the metabolic response of CLM to radioembolization. Liver metastases are supplied by both the hepatic artery and the portal vein [8, 9]. Our hypothesis is that liver metastases with greater hepatic arterial blood supply will have a better response to arterially directed therapies, including embolization and radioembolization.

We recently developed a method for estimating the hepatic artery and portal vein blood supply to each portion of the liver, using standard triphasic CT [10]. These perfusion parameters provide an estimate of the fraction of the volume of each pixel that is occupied by microscopic branches of the hepatic artery and portal vein. Using this method, we were able to quantitate the increased hepatic artery perfusion in hepatocellular carcinoma and the decreased portal perfusion in cirrhotic livers [10].

A simpler method for estimating arterial perfusion to a liver tumor involves the use of the arterial enhancement fraction (AEF), which is the arterial phase enhancement divided by the portal venous phase enhancement. Arterial phase enhancement is correlated with arterial perfusion, and portal venous phase enhancement is correlated with both arterial and portal venous perfusion because both the hepatic artery and the portal vein are enhanced in the portal venous phase. The AEF is thus correlated with arterial perfusion as a fraction of total perfusion [11]. A hypovascular tumor will have a high AEF if most of the blood supply comes from the hepatic artery rather than from the portal vein. The AEF predicts the initial response of CLM to chemotherapy [12].

The purpose of the present study is to examine whether quantitative measurements of perfusion or enhancement on preprocedure triphasic CT can be used to predict the metabolic response of CLM to radioembolization.

Materials and Methods

The institutional review board at Memorial Sloan Kettering Cancer Center approved this retrospective review of patients with CLM treated with radioembolization, all of whom had

undergone PET/CT and triphasic CT within 2 months before treatment and PET/CT within 3 months after treatment (although it was typically performed at 1–2 months after treatment). Thirty-eight radioembolization procedures performed for 31 consecutive patients between November 2009 and June 2014 were included in the study. All patients were treated with ^{90}Y -loaded resin microspheres (SIR-Spheres, Sirtex Medical). For each treatment, the two largest treated tumors were selected as target tumors, resulting in a total of 60 target tumors.

Triphasic liver CT was performed in accordance with our standard clinical protocol. After an unenhanced CT scan was obtained, IV power injection of 150 mL of 300 mg I/mL iohexol (Omnipaque 300, GE Healthcare) was performed at a rate of 4 mL/s. An arterial phase scan was obtained 9 seconds after the abdominal aorta at the level of the celiac artery reached an attenuation of 150 HU. This scan was typically obtained approximately 30 seconds after the start of contrast agent injection. A portal venous phase scan was obtained 40 seconds after the arterial phase scan was obtained. All scans were performed at 120 kVp.

For each target tumor, arterial phase enhancement, portal venous phase enhancement, the hepatic artery coefficient (HAC), the portal vein coefficient (PVC), and the AEF were calculated on the basis of findings from pretreatment triphasic CT. The calculations involve measurements of mean attenuation (measured in Hounsfield units) in ROIs drawn over the tumor, aorta, and portal vein on images from all three phases (Table 1 and Fig. 1). The HAC and PVC provide an estimate of the blood volumes of the hepatic artery and portal vein for each tumor [10]. The AEF provides an estimate of the blood volume of the hepatic artery divided by the total blood volume [11].

For each target tumor, the metabolic response to radioembolization was classified into two categories on the basis of findings from the initial posttreatment PET/CT examination: response (i.e., complete or partial response) and no response (i.e., stable disease or disease progression). Complete response was defined as complete resolution of hypermetabolic activity, whereas partial response was defined as a decrease of 30% or more in the maximum standardized uptake value (SUV_{max}) or a decrease in the size (measured in centimeters) of the region of hypermetabolic activity. Disease progression was defined as an increase of 20% or more in the SUV_{max} or an increase in the size of the region of hypermetabolic activity. Findings that did not fit in one of the three aforementioned categories were considered to denote stable disease [13, 14]. Metabolic response, as noted on PET/CT scans obtained 4–8 weeks after radioembolization of CLM, has been found to predict patient survival [13].

The statistical significance of comparisons of tumors with a complete or partial metabolic response (hereafter referred to as “responders”) and tumors with no metabolic response (i.e., those with stable disease or disease progression; hereafter referred to as “nonresponders”) was calculated using a two-sample *t* test, under the assumption of unequal variances. Cutoff values for predicting response were selected to maximize the accuracy of the classification, as determined by an exhaustive one-dimensional search. Overall survival probabilities after initial radioembolization were estimated using Kaplan-Meier. The date of death was obtained from the Social Security Death Index, records of in-hospital deaths, or

information provided to the hospital billing department or other hospital staff by third parties (e.g., patient family members). Survival curves were compared using the log-rank test.

Results

The mean age of the patients studied was 57 years (range, 23–81 years), and the mean target tumor size was 5.1 cm (range, 1–18 cm). The mean hepatopulmonary shunt fraction was 5.4% (range, 2–14%). The mean dose delivered per procedure was 26.9 mCi (995.3 MBq) (range, 4.7–52.5 mCi [173.9–1942.5 MBq]). The entire liver was treated in 3% of procedures, lobar treatment was performed in 68%, segmental treatment with a single dose was performed in 11%, and segmental treatment involving administration of two or more doses was performed in 18%.

After radioembolization, 8% of CLM had a complete metabolic response, 47% had a partial response, 15% had stable disease, and 30% had disease progression. Arterial phase enhancement, the HAC, and the PVC did not predict metabolic response to radioembolization (Table 2). However, the AEF was statistically significantly greater in responders than in nonresponders (Table 2 and Fig. 2). Use of an AEF cutoff of 0.4 maximized the accuracy of predicting metabolic response to radioembolization, resulting in sensitivity of 70%, specificity of 56%, and accuracy of 63%.

The AEF of a tumor is related to the arterial blood supply as a fraction of total blood supply of that tumor. The AEF depends only on enhancement of a metastasis in the arterial and portal venous phases. Theoretically, a more accurate estimate of arterial blood supply as a fraction of total blood supply could be calculated using the equation $HAC / (HAC + PVC)$, which accounts for differences in hepatic artery and portal vein enhancement curves in different patients. In the present study, AEF and $HAC / (HAC + PVC)$ were highly correlated, with a correlation coefficient of 0.87. However, only AEF showed a statistically significant difference between responders and nonresponders, likely as a result of insufficient statistical power. The estimate of arterial blood supply as a fraction of total blood supply obtained using the aforementioned equation was higher in responders than in nonresponders, as was expected, with a trend toward statistical significance ($p = 0.17$, two-tailed t test; $p = 0.087$, onetailed t test).

Patients with target lesions for which the mean AEF was less than 0.4 had a mean overall survival of 15.7 months after initial radio-embolization. Patients with target lesions for which the mean AEF was greater than 0.4 had an average overall survival of 22.0 months after initial radioembolization (Fig. 3). However, no statistically significant difference between the survival curves was noted for the two groups of patients ($p = 0.53$).

Discussion

The AEF calculated on the basis of enhancement measurements on pretreatment triphasic liver CT predicts which CLM will have a metabolic response after radioembolization. The AEF is easy to measure and does not require any special software or imaging protocols (Fig. 1). This could enable better patient selection for radioembolization procedures. However, the AEF was not correlated with overall survival.

A previous study that used qualitative assessment of enhancement on triphasic CT revealed no difference in survival after radioembolization of hypervascular versus hypovascular metastases in a mixed population of colorectal, neuroendocrine, and other metastases [15]. This finding agrees with the observation in the present study that arterial and portal phase enhancement on triphasic CT is not correlated with metabolic response after radioembolization.

The AEF is related to the arterial blood supply as a fraction of total blood supply. The AEF predicts the response to radioembolization, but arterial phase enhancement alone does not. This suggests that hypovascular tumors can respond to radioembolization as long as the blood supply comes mostly from the hepatic artery. On the other hand, a more vascular tumor might not respond to radioembolization if the vascularity is mostly supplied by the portal vein. In other words, the data suggest that tumors with more arterial blood supply than portal vein blood supply are more likely to respond to radioembolization.

These results provide some insight into the mechanism of treatment failure. It is somewhat surprising that arterial enhancement and perfusion alone were not correlated with the response to an arterially directed therapy, at least for the CLM examined in the present study. Patients with tumors with a low AEF, which corresponds to high portal vein perfusion relative to hepatic artery perfusion, were less likely to respond to radioembolization. This finding suggests that portal vein blood flow plays an important role in determining the response to radioembolization, and it raises the possibility that reducing portal vein blood flow might improve the response to radioembolization in tumors with low AEF.

AEF also predicts the initial response of CLM to chemotherapy [12]. A comparison of the AEF versus response curves for different treatments could enable selection of the optimal treatment modality for each patient, on the basis of the AEF of their metastases. Future studies should also examine the use of AEF in combination with other imaging biomarkers, in addition to the clinical and genetic characteristics of each tumor, to select the optimal treatment modality.

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Fig. 1.

Examples of ROIs used to measure mean tumor enhancement of colorectal liver metastasis on pretreatment triphasic liver CT scans. Elliptical ROIs were placed in same location on images obtained in all three phases. ROIs (*ovals*) were drawn to cover as much of tumor as possible while avoiding large necrotic portions of tumor and large blood vessels. **A–C**, 51-year-old woman with colorectal liver metastases. Pretreatment triphasic liver CT scans show tumor in unenhanced (mean attenuation, 46 HU) phase (**A**), with minimal arterial phase enhancement (1 HU) (**B**), and with more portal venous phase enhancement (13 HU) (**C**), corresponding to low arterial enhancement fraction (AEF) of 0.08. This colorectal metastasis showed disease progression after radioembolization. **D–F**, 52-year-old woman with colorectal liver metastases. Pretreatment triphasic liver CT scans show tumor in unenhanced (mean attenuation, 30 HU) phase (**D**), with arterial phase enhancement of 17 HU (**E**), and with a plateau in portal venous phase enhancement (23 HU) (**F**), corresponding to high AEF of 0.74. This colorectal metastasis showed partial response after radioembolization.

Fig. 2. Probability of metabolic response to radioembolization as function of arterial enhancement fraction (AEF). Statistically significant difference in AEF was noted in tumors with complete or partial metabolic response, compared with tumors with no metabolic response (i.e., those with stable disease or disease progression).

Fig. 3.

Overall survival after initial radioembolization of colorectal liver metastases, as stratified by mean arterial enhancement fraction (AEF) of target tumors. Mean survival was 22.0 months when mean AEF was greater than 0.4 (*black line*) and 15.7 months when mean AEF was 0.4 or less (*gray line*). However, this difference was not statistically significant.

Table 1
Enhancement and Perfusion Parameters

Parameter	Equation	Interpretation [Reference]
Hepatic artery coefficient	$[v_1(x_3 - x_2) + v_2(x_1 - x_3) + v_3(x_2 - x_1)] / [a_1(v_2 - v_3) + a_2(v_3 - v_1) + a_3(v_1 - v_2)]$	Hepatic artery blood volume [10]
Portal vein coefficient	$[a_1(x_3 - x_2) + a_2(x_1 - x_3) + a_3(x_2 - x_1)] / [a_1(v_3 - v_2) + a_2(v_1 - v_3) + a_3(v_2 - v_1)]$	Portal vein blood volume [10]
Arterial enhancement fraction	$(x_2 - x_1) / (x_3 - x_1)$	Hepatic artery blood volume divided by total blood volume [11]
Arterial phase enhancement	$x_2 - x_1$	
Portal venous phase enhancement	$x_3 - x_1$	

Note—The hepatic artery coefficient and the portal vein coefficient describe the enhancement curve of a liver lesion as a linear combination of the aortic and portal venous enhancement curves. The variables a_1 , a_2 , and a_3 are the mean attenuation values (measured in Hounsfield units) in the aorta (at the level of the celiac artery) in the unenhanced, arterial, and portal venous phases, respectively; v_1 , v_2 , and v_3 are the mean attenuation values (measured in Hounsfield units) in the portal vein (near the bifurcation) in the unenhanced, arterial, and portal venous phases, respectively; and x_1 , x_2 , and x_3 are the mean attenuation values (measured in Hounsfield units) in the colorectal liver metastases in the unenhanced, arterial, and portal venous phases, respectively. Mean attenuation values were measured in elliptical ROIs with a length of at least 5 mm. Each ROI was drawn to cover as much of the tumor as possible while avoiding large necrotic portions of the tumor and large blood vessels. The same portion of the tumor was measured on CT scans obtained in all three phases.

Table 2
Characteristics of Target Tumors Before Radioembolization

Characteristic	Tumors Without Metabolic Response	Tumors With Metabolic Response	<i>p</i>
Size (cm)	5.1 ± 3.8	5.1 ± 3.6	0.95
Arterial phase enhancement (HU)	11 ± 11	14 ± 14	0.32
Portal venous phase enhancement (HU)	29 ± 17	26 ± 19	0.64
Arterial enhancement fraction	0.29 ± 0.59	0.74 ± 1.02	0.038 ^a
HAC	-0.025 ± 0.039	-0.018 ± 0.069	0.62
PVC	0.24 ± 0.15	0.22 ± 0.14	0.66
HAC / (HAC + PVC)	-0.20 ± 0.48	0.00 ± 0.62	0.17

Note —Metabolic response was defined as a complete or partial response to treatment. Data are mean ± SD. HAC = hepatic artery coefficient, PVC = portal vein coefficient.

^aDenotes statistical significance.