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Spectral CT in evaluating the therapeutic effect of transarterial chemoembolization for hepatocellular carcinoma

A retrospective study

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Abstract

This study aimed to investigate the value of computed tomographic (CT) spectral imaging in evaluating the effect of transarterial chemoembolization (TACE).

The records of 67 patients with hepatocellular carcinoma (HCC) who had undergone dynamic spectral CT before treatment were selected for the study. Iodine concentrations pretreatment in liver parenchyma, the HCC lesion(s), portal vein, and aorta were measured from the decomposition images. The normalized iodine concentrations (NIC) were calculated. All of them underwent plain scan or contrast-enhanced CT post-treatment (approximately 4–6 weeks after TACE).

The values of arterial phase normalized iodine concentrations (AP NIC) before TACE correlated with the grades of lipiodol deposition in tumors ($r = 0.76$, $P < .001$). However, there was no relationship between normalized iodine concentrations in the portal venous phase (PVP NIC) before TACE and the grade of lipiodol deposition ($r = 0.17$, $P = .17$). Values of AP NIC in residual tumors pre-TACE were significantly lower than those in partial lesions with deposition of iodized oil. The threshold AP NIC of 0.18 yielded an AUC of 0.895, 83.33% sensitivity, 81.03% specificity, 83.33% positive predictive value (PPV), and 82.76% negative predictive value, respectively. The survival probability in patients with AP NIC values pre-TACE ≥ 0.18 was higher than those whose AP NIC values pre-TACE were < 0.18 ($P = .028$).

Spectral CT with quantitative analysis of AP NIC may help to evaluate the utility and predict the therapeutic effect of TACE. Values of AP NIC had high sensitivity and specificity for differentiating partial tumors with lipiodol deposition from those without lipiodol deposition.

Abbreviations: AP = arterial phase, AP NIC = normalized iodine concentrations in the arterial phase, AUC = area under the curve, CT = computed tomographic, DESCT = dual energy spectral computed tomography, HCC = hepatocellular carcinoma, NIC = normalized iodine concentrations, NPV = negative predictive value, PPV = positive predictive value, PVP = portal venous phase, PVP NIC = normalized iodine concentrations in the portal venous phase, ROC = receiver operating characteristic, ROIs = regions of interest, TACE = transarterial chemoembolization.

Keywords: carcinoma, hepatocellular, multidetector computed tomography/mt, therapeutic chemoembolization

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide. As most patients are at an advanced stage at the time of diagnosis, they are often unable to undergo surgical resection or transplantation. Transcatheter arterial chemoembolization (TACE) is an important therapeutic alternative for unresectable HCC[1,2] which induces tumor necrosis, precluding tumor growth.[3] However, application of TACE is often complicated by tumor recurrence.[4] Accurate identification of patients who will benefit from TACE, as well as precise assessment of its efficacy, are of great importance.

It has been found that tumor response evaluated by alterations in vascular perfusion instead of by measurement of tumor size may be optimal.[5] Dual energy spectral CT (DESCT) based on the rapid switching between high- and low-energy datasets was introduced to provide both material decomposition images and monochromatic spectral images.[6] This allows generation of iodine maps and monochromatic images that can examine lesion hemodynamics.[7]

This method has been applied in many areas, such as differentiation of hepatic lesions and diagnosis of pulmonary embolism.[6,8,9] We sought to investigate the value of spectral CT in selecting candidates for TACE and evaluating its efficacy.

2. Methods

2.1. Patients

This retrospective study was conducted with the approval of the Institutional Review Board of Renji Hospital affiliated to Shanghai Jiao Tong University and carried out after informed consent was obtained from the patients. From March 2013 to

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Table 1

Basic information of patients.

Patients	67
Age (median age, range, years)	56 (27–75)
Gender (male/female)	42/25
Cirrhosis	67
Etiology of cirrhosis	Alcohol (11)/Hepatitis B (45)/ Hepatitis C (5)/Unknown origin (6)
Child–Pugh	A (47)/ B (20)/ C (0)
Tumor number	
One	39
Two or more	28
Size (in maximum diameter)	
≤3 cm	9
3–5 cm	28
>5 cm	30

April 2017, all cases of hepatocellular carcinoma examined with dynamic CT were reviewed. The diagnosis of HCC was established with typical imaging findings (arterial enhancement with portal venous washout and pseudocapsule appearance) detected on CT during dynamic imaging. Tumors without typical enhancement were subsequently diagnosed by needle biopsy. We analyzed the largest tumor in cases with multifocal disease. Exclusion criteria were as follows: (a) patients had received other treatment previously; (b) thrombi in the portal vein; (c) patients without reviews (plain scan or contrast-enhanced CT) approximately 4 to 6 weeks after TACE; (d) when comparing parameters pretreatment of partial lesions with and without deposition of iodized oil, sizes of tumors changed obviously after TACE were exculded. A total of 67 patients [42 men, 25 women; median age 56 years] who underwent spectral CT imaging pretreatment were included in this study. Detailed data of patients and lesions are listed in Table 1.

2.2. Procedure of TACE

The method of TACE was described previously.[10] Briefly, with the method of Seldinger, an 5-F RH arterial catheter (Terumo, Fujinomiya, Japan) was inserted into the femoral artery and placed in the mesenteric artery. Subsequently arteriography was performed to examine the existence of right hepatic artery. Then depending on the location and size of tumor, the catheter was placed in tumor-feeding vessels as far as possible for selective embolization. Microcatheter was also used to achieve this. Then a mixture of Adriamycin (40–50 mg) and 3 to 20 mL of iodized oil (Lipiodol UltraFluid, Laboratoire Guerbet, Aulnay-Sous-Bois, France) was injected through the catheter. The dose of iodized oil and Adriamycin depended on the size of tumor and the liver function of patient.

2.3. CT Examinations

Triple-phase contrast-enhanced CT was performed on every patient using the dual energy spectral imaging mode. Patients were injected with iohexol (500 mg I kg^{-1}, 1.4 mL kg^{-1}) via the antecubital vein at a rate of 3.0 mL/s. The scanning delay for hepatic arterial phase (AP) imaging was determined using automated scan-triggering software (GE Healthcare, Milwaukee WI). AP scanning automatically began 20 s after the trigger attenuation threshold (100 HU) reached at the level of the supraceliac abdominal aorta. Portal venous phase (PVP) scanning began 30 seconds after AP scanning.

CT scanning parameters were as follows: collimation 40 mm, rotation speed 0.6 seconds, and helical pitch 1.375:1. The CT images were reconstructed using projection-based material-decomposition software and a standard reconstruction kernel. The reconstruction thickness was 1.25 mm at an interval of 1.25 mm and a 36-cm display field-of-view. The adaptive statistical iterative reconstruction algorithm was applied to suppress image noise for the decomposition images. The estimated CT dose index was 25.8 mGy for a single phase which was similar to contrast-enhanced liver imaging in a normalized patient at our hospital. Material-decomposition images using iodine and water as the basic material pairs were reconstructed, for analytical purposes, from the single spectral CT acquisition.

2.4. Quantitative analysis

Two radiologists, each with > 3 years of experience in abdominal CT, reviewed the spectral CT images and measured iodine concentration on the pre- and post-TACE examinations. Regions of interest (ROIs) were placed within the lesions. The size, position, and shape of the ROIs were similar between AP and PVP with a constant number of pixels. The iodine content was measured from iodine map images in the AP and VP. The following rules were applied when placing the ROI: (a) the ROI should not include obviously necrotic tissue defined on conventional CT images, and (b) the ROI should not include vessels.

When measuring iodine concentration pretreatment of partial lesions with deposition of iodized oil, lesions with deposition of iodized oil less than 10% were excluded. ROIs were placed on the part of lesions with deposition of iodized oil on pre-TACE images comparing to maps after TACE. Measurements of partial lesions without deposition of iodized oil were similar except for cases with deposition of iodized oil more than 90%.

NIC was calculated to minimize variations caused by the scanning times and patient's status. AP NIC was defined as value dividing the iodine concentration in the ROI by that in the aorta during the AP phase. PVP NIC was defined as value dividing the iodine concentration in the ROI by that in the portal vein during the PVP phase.

2.5. Statistical analysis

When assessing the therapeutic effect of TACE, we divided treated tumors into 3 groups according to the grade of ethiodol uptake: grade I,< 20% of the tumor; grade II, 20%–60%; grade III > 60%,[11,12] (Fig. 1). Statistical analysis was performed with commercial software (SPSS 20.0, SPSS, Inc, Chicago IL). Quantitative values were recorded as mean ± standard deviation (SD).

The relationship between the parameters before TACE and the post-TACE grades of lipiodol deposition in tumors was analyzed with Spearman's correlation. Group-sample *t*-test or nonparametric test was performed to compare the quantitative parameters between partial lesions with and without deposition of iodized oil. A receiver operating characteristic (ROC) analysis was used to assess the diagnostic performance of AP NIC values in distinguishing partial lesions with deposition of iodized oil from those without lipiodol deposition. Survival curves were calculated by the Kaplan–Meier method. The statistical significance of the differences in the curves was analyzed with the log-rank test. Statistical significance was set at $P < .05$.

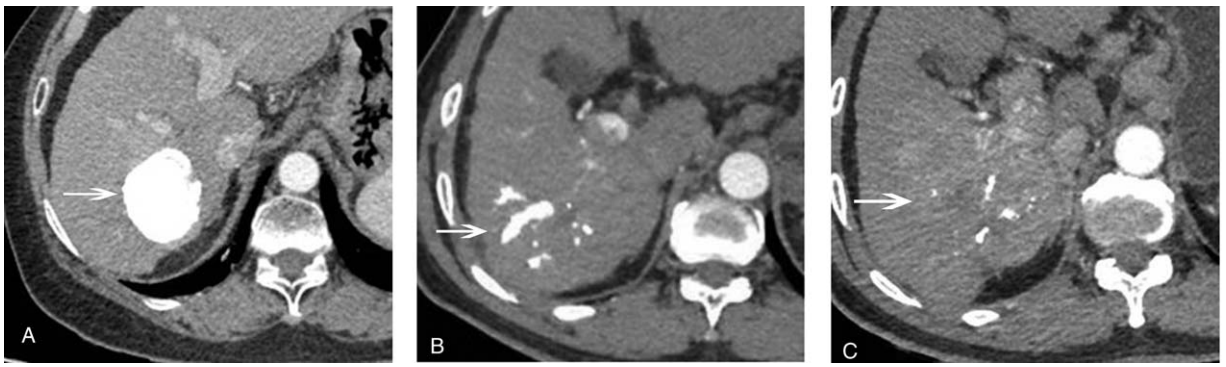

Figure 1. Images after transarterial chemoembolization showed different types of iodine deposition. (A) Image showed complete accumulation which was assigned to grade III. (B) Image showed lipiodol deposition in some area of the tumor which was assigned to grade II. (C) Image after TACE showed little accumulation of iodine which was assigned to grade I. TACE = transarterial chemoembolization.

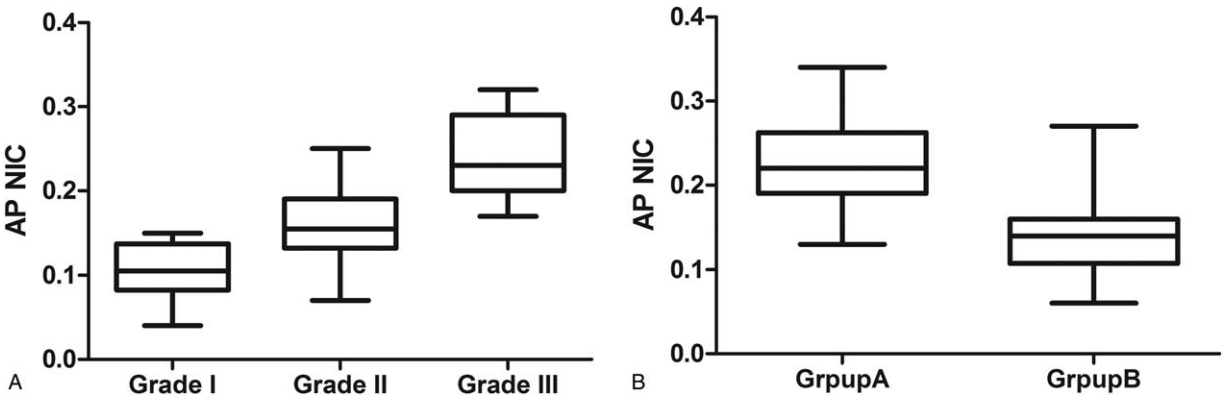

Figure 2. Box plots of the differences in parameters of spectral CT in different groups. CT = computed tomographic.

3. Results

A total of 16, 32, and 19 tumors were assigned to grade I, grade II, and grade III groups, respectively. The values of AP NIC before TACE were proved to be closely correlated with the grades of post-TACE lipiodol deposition in tumors ($r = 0.76$, $P < .001$) (Fig. 2), whereas the values of PVP NIC before TACE showed no relationship with the grades of post-TACE lipiodol deposition ($r = 0.17$, $P = .17$, Table 2).

When assessing parameters pretreatment of partial lesions with and without deposition of iodized oil, 54 and 58 partial tumors were assigned to group A (partial tumors with lipiodol deposition) and group B (partial tumors without lipiodol deposition). AP NIC values in group A were obviously higher than those in group B ($P < .001$, Table 3) (Fig. 2). No significant difference was found between PVP NIC values in 2 groups ($P = .10$).

The ROC curves of AP NIC for differentiating partial tumors in group A from those in group B are shown in Figure 3, with an area under the curve (AUC) of 0.895. A threshold AP NIC of 0.18 would yield a sensitivity of 83.33%, specificity of 81.03%, positive predictive value (PPV) of 83.33%, and negative predictive value (NPV) of 82.76%, respectively.

Forty-five patients with follow-up period more than 2 years were divided into 2 groups: those whose AP NIC values pre-TACE were < 0.18 (group C) and those with AP NIC values pre-TACE ≥ 0.18 (group D). The survival probability was significantly increased ($P = .028$) in patients with AP NIC values

Table 2

Correlation between grades of lipiodol deposition in tumors and dynamic spectral CT parameters.

Parameters	AP NIC	PVP NIC
Grade I	0.11 ± 0.03	0.43 ± 0.06
Grade II	0.16 ± 0.05	0.48 ± 0.07
Grade III	0.24 ± 0.05	0.47 ± 0.07
r	0.76	0.17
P	<.001	.17

AP NIC = the normalized iodine concentration during arterial phase, CT = computed tomographic, NIC = the normalized iodine concentration during portal venous phase, PVP = portal venous phase.

Table 3

Parameters differences in partial lesions with and without deposition of iodized oil.

Parameters	N	AP NIC	PVP NIC
Group A	54	0.23 ± 0.01	0.50 ± 0.01
Group B	58	0.14 ± 0.01	0.47 ± 0.02
P	–	<.001	.10

AP NIC = the normalized iodine concentration during arterial phase, NIC = the normalized iodine concentration during portal venous phase, PVP = portal venous phase.

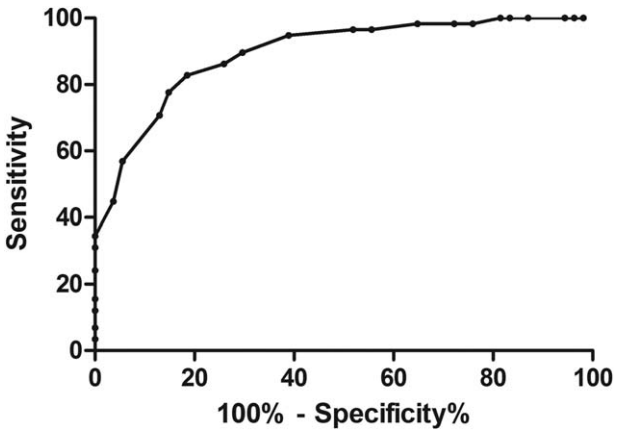

Figure 3. ROC curves for AP NIC in differentiating group A from group B. AP NIC = normalized iodine concentrations in the arterial phase, ROC = receiver operating characteristic.

pre-TACE ≥ 0.18 versus those whose AP NIC values pre-TACE were < 0.18 (Fig. 4).

4. Discussion

The recent introduction of spectral CT affords the ability to eliminate beam hardening caused by preferential absorption and analyze hemodynamic changes quantitatively.[8,13] It has been found that the values of AP NIC and PVP NIC of hepatic tumors had close relationships with hepatic blood flow and permeability of capillary vessel surface measured from perfusion CT, which both play an important role in assessing the effect of TACE.[14,15] This study was focused on investigating the potential of spectral imaging in evaluating the effect of transarterial chemoembolization.

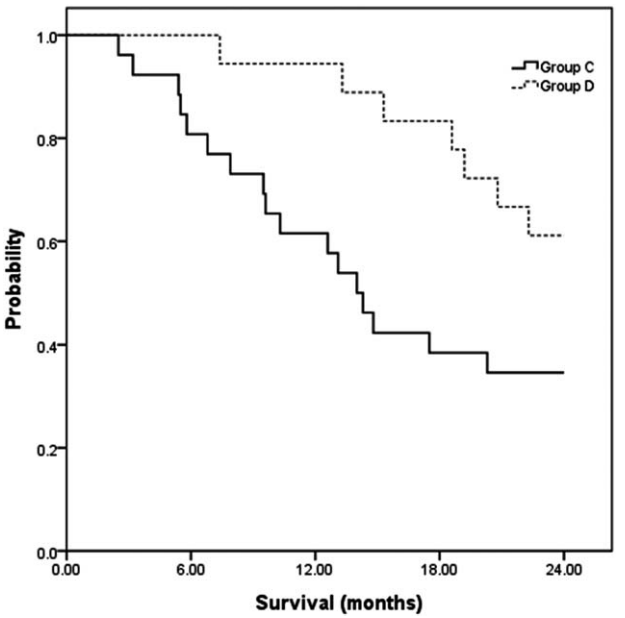

Figure 4. Kaplan–Meier estimates of survival in both groups. Patients whose AP NIC values pre-TACE were ≥ 0.18 (group D) survived significantly longer than those with AP NIC values pre-TACE < 0.18 (group C) ($P = .028$). AP NIC = normalized iodine concentrations in the arterial phase, TACE = transarterial chemoembolization.

It is usually acknowledged that the antitumor effect of TACE is associated with the grade of iodized lipiodol deposition in the lesions.[16] In this study, the value of normalized iodine concentration was introduced to minimize variations among individuals, thereby increasing the validity of the results. Values of AP NIC before TACE closely correlated with the grade of ethiodol accumulation. Lin et al[6] analyzed 24 HCC patients who underwent chemoembolization and found hepatic arterial perfusion measured from perfusion images correlated well with ethiodol accumulation. However, their results were obtained by assessing a relatively restricted number of cases and the increased radiation exposure associated with perfusion CT remains problematic. Thus, spectral CT has the potential to be a quantitative method to select candidates for TACE procedures so as to maximize the success of the treatment.

PVP NIC obtained in the different groups did not correlate with the grades of lipiodol deposition in tumors. We found some tumors with relatively low PVP NIC also showed satisfactory lipiodol deposition. Recent studies[17,18] have found that typical HCCs with obvious enhancement on AP followed by washout during PVP had a more abundant arterial blood supply. Increased arterial BF may explain TACE's higher efficacy in these cases. Moreover, obvious washout in PVP underestimates the blood flow of tumor distinctly, which may have been the reason for the poor correlation between PVP NIC and grades of lipiodol deposition.

Our results also showed than AP NIC values in group A were obviously higher than those in group B. This reflected that partial tumors with lipiodol deposition had more abundant arterial supply pretreatment than those without lipiodol deposition. Previous study[19] had found that the presence of heterogeneity in tumor differentiation is common within 1 tumor especially in tumors >5 cm. This accounted for the heterogeneity of arterial supply and lipiodol deposition in an identical tumor. ROC curves in this study indicated that the values of AP NIC had high sensitivity and specificity for differentiating partial tumors with lipiodol deposition from those without lipiodol deposition. The threshold AP NIC of 0.18 yielded a sensitivity of 83.33%, specificity of 81.03%, PPV of 83.33%, and NPV of 82.76%, respectively. Therefore, spectral CT may have the potential to predict the situation of lipiodol deposition after TACE.

Furthermore, the survival probability was significantly increased ($P = .028$) in patients with AP NIC values pre-TACE ≥ 0.18 versus those whose AP NIC values pre-TACE were < 0.18. The survival rates for the patients with higher AP NIC at 12 and 24 months were 94.44% and 61.11%, respectively. For patients with relatively lower AP NIC, the survival rates at 12 and 24 months were 61.54% and 34.61%, respectively.

The measurement of iodine concentrations may be influenced by some factors. Timing of arterial and portal venous phase was thought to be a vital factor to guarantee the precision of the measurement. The results could be affected if the HAP initiate too early or too late. According to previous study,[20] optimal initial time of HAP should range from 19 to 21 s after the trigger attenuation threshold (100 HU) reached at the level of the supraceliac abdominal aorta based on pharmacokinetic and clinical analysis. Another 30 s delay after HAP was thought to be appropriate for PVP.[20,21] These regulations of contrast medium injection were considered in this study. Moreover, NIC was used to minimize variations caused by the scanning times and patient's status.

5. Limitations

There were several limitations of our study. The parameters analyzed were based on a relatively small number of patients. Thus, the accuracy of values needs to be confirmed by larger samples in further studies. Second, according to previous studies,[12,22] types of accumulation are classified into four grades. HCCs in the present study were not classified rigorously by acknowledged criteria because of the limited number of cases.

6. Conclusions

In conclusion, quantitative analysis of iodine concentration measured from CT spectral imaging may be helpful to select candidates for treatment with TACE and for evaluating the effectiveness of treatment.

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