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Usefulness of tumor perfusion on cone-beam CT after hepatic arterial infusion port implantation for evaluating tumor response to hepatic arterial infusion chemotherapy in hepatocellular carcinoma treatment

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PURPOSE

To compare tumor perfusion on cone-beam computed tomography (CBCT) after hepatic artery infusion port implantation with the tumor response to hepatic arterial infusion chemotherapy (HAIC) in patients with hepatocellular carcinoma (HCC).

METHODS

This retrospective study was conducted in patients with advanced HCC treated with HAIC from 2015 to 2020. We performed CBCT with contrast injection via a port on the day following implantation. We classified tumor perfusion on CBCT into three groups: hyperperfusion, isoperfusion, and hypoperfusion. We also evaluated tumor response to HAIC on follow-up images using RECIST 1.1 and compared it with tumor perfusion on CBCT.

RESULTS

This study included 206 tumors in 193 patients (mean: 60.5 years) with HCC. There were 100 hyperperfusion tumors (48.5%), 92 isoperfusion tumors (44.7%), and 14 hypoperfusion tumors (6.8%). The tumor response to HAIC included 10 tumors with a complete response (CR) (4.9%), 66 tumors with a partial response (32%), 60 tumors with stable disease (29.1%), and 70 tumors with progressive disease (34%). Hyperperfusion tumors had a 65% objective response rate (ORR) and a 92% disease control rate (DCR). Isoperfusion tumors had a 12% ORR and a 46.8% DCR, while hypoperfusion tumors had a 0% ORR and a 7.1% DCR. A CR was shown only in hyperperfusion tumors. The ORR and DCR of the three groups were different, with statistical significance ($P < 0.001$).

CONCLUSION

Hyperperfusion tumors on CBCT showed a better tumor response to HAIC, with a 65% ORR in patients with HCC. Tumor perfusion on CBCT after implantation of the hepatic arterial infusion port was associated with the tumor response to HAIC.

KEYWORDS

Cone-beam CT, hepatic arterial infusion chemotherapy, hepatocellular carcinoma, tumor perfusion, tumor response

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Hepatocellular carcinoma (HCC) is among the world's main causes of cancer-related deaths.[1] Many patients (42%–50%) are diagnosed at late stages, with short overall survival (OS) of only 4.2–7.9 months due to a lack of effective treatment. In recent years, the explosive development of systemic therapies has brought about increased treatment opportunities for patients with advanced HCC. However, the results have not been consistently effective, and significant side effects have been recorded.[2-5]

Hepatic arterial infusion chemotherapy (HAIC) has been widely approved as a monotherapy or combination therapy for treating patients with advanced HCC in East Asian countries.

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The practical guidelines for HCC treatment in these countries recommend HAIC for treating patients with HCC and portal vein tumor thrombosis (PVTT) and for HCCs refractory to transarterial chemoembolization (TACE).[6-8] The primary purpose of HAIC treatment is to transport high concentrations of chemotherapeutic agents to tumors; accordingly, the distribution of such agents via infusion ports directly affects tumor responses.[9] Although there have been several studies on the distribution of chemotherapeutic agents in tumors after the placement of a HAIC port, none have investigated the relationship between this tumor perfusion and tumor response after treatment.[10-12] In our study, the contrast distribution pattern on cone-beam computed tomography (CBCT) after the insertion of a HAIC port was evaluated the day after port insertion to assess the relationship between tumor perfusion on CBCT and tumor response to HAIC treatment.

Methods

Patients

This retrospective study's protocol was approved by Seoul St. Mary's Hospital's Institutional Review Board (approval number: KC22RISI0706). Due to the study's design, we were permitted to remove the requirement for patient consent. Our study collected data on patients treated with HAIC from January 2015 to December 2020. HAIC was performed in patients with HCC plus PVTT or refractory TACE and in those unsuitable for local therapies because of tumor spread in both hemilivers. In this study, the inclusion criteria included the following: (a) patients who had undergone at least two cycles of HAIC after insertion, (b) age ≥18 years, (c) patients with full pre- and post-treatment images [CT or magnetic resonance imaging (MRI)], (d) contrast-enhanced CBCT performed on the day following implantation, and (e) patients presenting with at least one measurable hepatic lesion. The exclusion criteria included (a) patients with Barcelona Clinic Liver Cancer (BCLC) grade D, (b) those with a insufficient pre- and post-treatment images (CT or MRI), (c) those without CBCT after HAIC port implantation, (d) patients who underwent TACE or other local therapies combined with HAIC simultaneously, and (e) patients with fewer than two HAIC cycles after port implantation. All tumors were diagnosed as HCC based on biopsy or imaging criteria CT and/or MRI combined with tumor markers.

Main points

- Tumor perfusion on cone-beam computed tomography after the implantation of a hepatic arterial infusion port was associated with the tumor's response to hepatic arterial infusion chemotherapy (HAIC).
- The hyperperfusion tumor had the best tumor response. A complete response was shown only in hyperperfusion tumors.
- Most hypoperfusion tumors exhibited disease progression following treatment with HAIC. Hypoperfusion-type tumors were found predominantly in patients with hepatic artery anatomical variations or extrahepatic circulation that specifically involved the right inferior phrenic artery supplying the tumor.

Procedures

The procedure was performed by two interventional radiologists with over 10 years of experience. With the patient under local anesthesia, the procedure was performed via the right femoral artery or the left subclavian artery. The Seldinger technique was utilized to puncture the common femoral artery using a guide wire (Terumo, 0.035-inch diameter) and an Angiocath 18G catheter. Selective angiography was performed on the celiac artery, superior mesenteric artery, and the extrahepatic arteries feeding the tumor [right inferior phrenic artery (RIPA), internal mammary artery, etc.]. Before the infusion port was inserted, the collateral branches from the extrahepatic arteries were embolized to increase the effectiveness of the treatment. The left gastric artery was embolized by a pushable microcoil (Tornado, Cook, USA) or detachable microcoils (Concerto, Medtronic, USA) to prevent the reflux of chemotherapeutic agents into the stomach during treatment. Following the placement of a port catheter (Celsite® port and catheters, B. Braun Medical, USA) in the common hepatic artery, the distal end of the catheter was fixed to the gastroduodenal artery using microcoils (Concerto, Medtronic, USA). Sixteen patients had variant hepatic artery anatomy, with each main blood supplying artery in both hemilivers; therefore, two ports were required.[12] To prevent catheter occlusion after each cycle of HAIC therapy, 3,000–5,000 units of heparin were packed into the port chamber and catheter.

On the day following implantation, we routinely performed CBCT with contrast enhancement to evaluate both port performance and contrast distribution. Contrast media (Visipaque 270, GE Healthcare, USA) was infused via the port. A CT scan was started 40 sec after the injection of 40 mL of contrast media at a rate of 1 mL/sec.

Tumor perfusion

We classified contrast perfusion of the tumor on CBCT into the following three perfusion types: (1) hyperperfusion type: the tumor was more contrast-enhanced than the rest of the hepatic parenchyma; (2) isoperfusion type: the tumor enhancement was homogeneous and indistinguishable from the rest of the hepatic parenchyma; (3) hypoperfusion type: the tumor had less contrast enhancement than the remaining hepatic parenchyma or no enhancement on CBCT (Figure 1). In each patient, each tumor perfusion type was selected based only on the largest tumor that could be measured.

Chemotherapy

We adopted the following chemotherapy protocol for HAIC: an epirubicin–cisplatin-5-fluorouracil (ECF) chemotherapy regimen was repeated approximately every month. The ECF chemotherapy regimen consisted of 35 mg/m^2 of epirubicin on day 1, 60 mg/m^2 of cisplatin over 2 hours on day 2, and 500 mg/m^2 of 5-fluorouracil over 5 hours on days 1 to 3.

Tumor response

Contrast-enhanced CT or MRI was performed after every two cycles of HAIC before

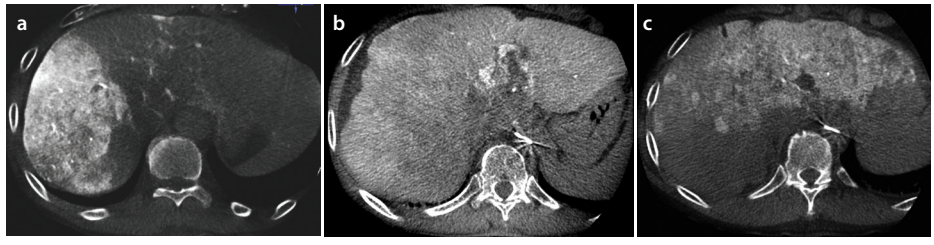

Figure 1. Tumor perfusion type on cone-beam computed tomography. **(a)** Hyperperfusion type: the right hepatic tumor must be more enhanced with contrast media than the remaining hepatic parenchyma. **(b)** The isoperfusion-type tumor and hepatic parenchyma are heterogeneous, with no difference between the tumor and the normal hepatic parenchyma. **(c)** A hypoperfusion type observed at the posterior segment without contrast enhancement.

initiating the next cycle, with each cycle repeated every month. We used the Response Assessment Criteria in Solid Tumors (RECIST) version 1.1 instead of the modified RECIST guideline because the latter is unsuitable for use in cases of infiltrative tumors.[13-15] We selected the best overall tumor response to assess tumor response in comparison with tumor perfusion. The best overall tumor response was defined as the most favorable response observed from the start of HAIC treatment until the final follow-up time point collected for each patient. The overall response rate (ORR) was defined as a complete response (CR) or a partial response (PR). The disease control rate (DCR) was defined as CR, PR, and stable disease (SD).

Statistical analysis

We expressed data for continuous variables as means ± standard deviations and data for categorical variables as frequencies. Fisher's exact test or the chi-squared test was used to compare tumor responses between groups. A value of $P \leq 0.05$ was regarded as significant. Statistical analyses were conducted using SPSS v.25.0 software (IBM Corp, Armonk, NY, USA).

Results

We collected data between January 2014 and December 2021. A total of 193 patients with 206 tumors were selected, and the patients' characteristics are summarized in Table 1. The mean age was 60.5 ± 10.4 years (26–89 years), 171 patients were male (88.6%), and 22 patients were female (11.4%). A total of 145 patients were infected with hepatitis B (75.1%). The majority of patients were Child–Pugh stage A or B, with 153 patients at Child–Pugh stage A (79.3%). In our study, 180 patients were BCLC stage C (93.3%). One hundred seventy-two patients had PVTT (89.1%), of which 82 patients had PVTT in both hemilivers (42.5%). There were 121 patients (62.7%) with infiltrative tumors and 30 patients (15.5%) with solitary tumors.

The technical characteristics of HAIC and tumor perfusion on CBCT after port implantation are summarized in Table 2. Among the 193 patients with HAIC were 43 patients with hepatic arterial variations, of which 16 patients had dual ports inserted. The predominant anatomical variant observed was the right hepatic artery originating from the superior mesenteric artery in 29 patients (15%). All patients received contrast-enhanced CBCT on the day following port implantation.

Table 1. Basic characteristics of the patients

Characteristic	Value n (%)
Age (years) ± standard deviation	60.5 ± 10.4
Gender	
Male	171 (88.6)
Female	22 (11.4)
Cause of cirrhosis	
HBV	139 (72)
HCV	9 (4.7)
HBV + HCV	5 (2.6)
Alcohol	6 (3.1)
Child–Pugh class	
A	153 (79.3)
B	39 (20.2)
C	1 (0.5)
BCLC class	
A	0 (0)
B	13 (6.7)
C	180 (93.3)
PVTT	
No	21 (10.9)
Segmental	20 (10.4)
Lobar	70 (36.3)
Bilobar	82 (4.5)
HCC type	
Multifocal nodular	42 (21.8)
Focal massive	30 (15.5)
Infiltrative	121 (62.7)

HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombosis; HCC: hepatocellular carcinoma.

Table 2. Features of port implantation and tumor classification

Characteristic	Value n (%)
Hepatic artery variations	
No	150 (77.7)
Yes	43 (22.3)
Number of ports	
Mono	177 (91.7)
Dual	16 (8.3)
Tumor perfusion type	
Hyperperfusion	100 (48.5)
Isoperfusion	92 (44.7)
Hypoperfusion	14 (6.8)
Best tumor response	
CR	10 (4.9)
PR	66 (32)
SD	60 (29.1)
PD	70 (34)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The perfusion of 206 tumors was analyzed after CBCT, of which 100 were hyperperfusion tumors (48.5%), 92 were isoperfusion tumors (44.7%), and 14 were hypoperfusion tumors (6.8%). There was no association between tumor perfusion types after CBCT and the number of ports (P = 0.114) or hepatic arterial variations (P = 0.427) (Table 3). The most common locations for hypoperfusion tumors were in the posterior segment and the left hemiliver. Among the patients with hypoperfusion tumors, we encountered nine cases of variant hepatic arterial anatomy. In six of these patients, RIPA embolization was not performed prior to port implantation for hepatic perfusion redistribution, and in one case, a significant arterial portal venous shunt was identified within the right hepatic artery.

Tumor response and the relationship with tumor perfusion on CBCT: there were 10 tumors with a CR (4.9%), 66 tumors with a PR (32%), 60 tumors with SD (29.1%), and 70 tumors with PD (34%). Seventy-six tumors had an ORR of 36.9%, and 136 tumors had a DCR of 66%. Tumor response differed according to tumor perfusion on CBCT: the CR, PR, SD, and PD values in the hyperperfusion tumor group were 10%, 55%, 27%, and 8%, respectively; the values in the isoperfusion tumor group were 0%, 12%, 34.8%, and 53.2%, respectively; and the values in the hypoperfusion tumor group were 0%, 0%, 7.1%, and 92.9%, respectively (Figure 2). The hyperperfusion tumor group had a 65% ORR and a 92% DCR, the isoperfusion group had a 12% ORR and a 46.8% DCR, and the hypoperfusion group had a 0% ORR and a 7.1% DCR. All (100%) tumors with CR were of the hyperperfusion type. The ORR and DCR values among the three groups were different, with statistical significance (P < 0.001) (Table 3). There was no difference in ORR between the isoperfusion and hypoperfusion groups (P = 0.171); however, the DCR of these two groups differed (P = 0.007).

Table 3. Comparative analysis of tumor perfusion types

Tumor perfusion type	Hyperperfusion	Isoperfusion	Hypoperfusion	*P*
HCC type				
Multifocal nodular	23 (23)	20 (21.7)	2 (14.3)	0.833
Focal massive	17 (17)	12 (13)	3 (21.4)	
Infiltrative	60 (60)	60 (65.2)	9 (64.3)	
PVTT				
No	14 (14)	8 (8.7)	0 (0)	0.065
Segmental	13 (13)	7 (7.6)	1 (7.1)	
Lobar	41 (41)	29 (31.5)	4 (28.6)	
Bilobar	32 (32)	48 (52.2)	9 (64.3)	
Hepatic artery variations				
No	81 (81)	68 (73.9)	8 (57.1)	0.114
Yes	19 (19)	24 (26.1)	6 (42.9)	
Number of ports				
Mono	93 (93)	81 (88)	12 (85.7)	0.427
Dual	7 (7)	11 (12)	2 (14.3)	
Best tumor response				
CR	10 (10)	0 (0)	0 (0)	*P* < 0.001
PR	55 (55)	11 (12)	0 (0)	
SD	27 (27)	32 (34.8)	1 (7.1)	
PD	8 (8)	49 (53.2)	13 (92.9)	
ORR (%)	65	12	0	*P* < 0.001
DCR (%)	92	46.8	7.1	*P* < 0.001

HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

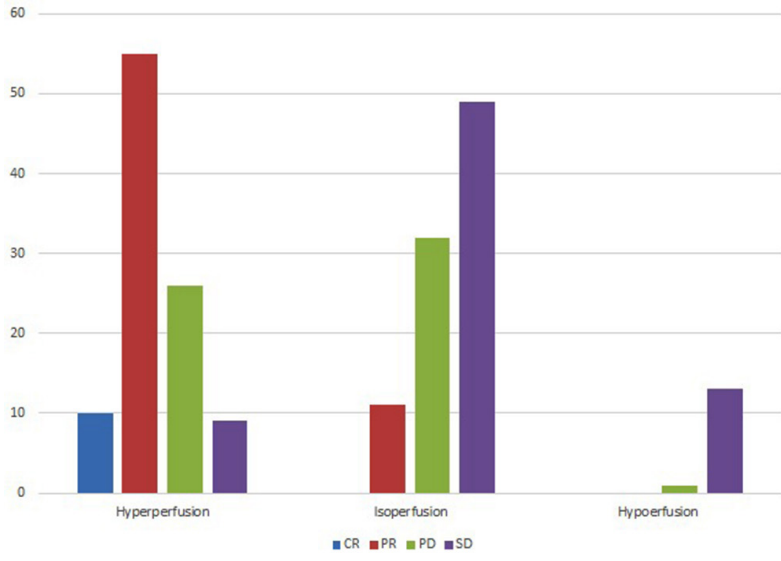

Figure 2. Comparison of tumor response in tumor perfusion types. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Discussion

The factors affecting the OS of patients treated with HAIC include patients' status according to the Child–Pugh score, BCLC stage, the classification of PVTT, and tumor size and number. HCC with infiltrative characteristics or rim-like enhancement indicates a poor prognosis.[13,14] Several studies have shown that the response of a tumor to HAIC is related directly to OS. According to Kim et al.[13], when tumor did not initially respond to HAIC, which indicated a poor prognosis. The early prediction of tumor response based on tumor perfusion assessment immediately after HAIC port placement can facilitate the timely selection of optimal combined treatments or alternative therapies for tumors with poor response prognoses.

The initial tumor response to HAIC depends on a tumor's histological differentiation, its invasion and metastasis, and the distribution of chemotherapeutic agents within the tumor. The initial response assessment is usually performed after at least two cycles of HAIC.[13] The purpose of HAIC is to concentrate chemotherapeutic agents in the tumor rather than in the normal parenchyma, which increases the tumor's response to chemotherapy and reduces the side effects of chemotherapy on the normal liver parenchyma. To evaluate the distribution of chemotherapeutic agents in the liver parenchyma, several studies used the injection of tech-

netium-99m-labeled macroaggregated albumin via a port followed by single-photon emission CT. This method accurately determined chemotherapeutic agent distribution throughout the liver parenchyma.[10,11] Seki et al.[16] utilized slow-infusion MR arteriography to reflect the actual distribution of infused drugs. Meanwhile, CBCT can be performed following port implantation to check the port's function and detect the recanalization of embolized arteries and new anastomoses that could prevent chemotherapeutic agents from spreading to the surrounding organs, especially the stomach. Additionally, CBCT has been used following TACE to predict tumor response and prognosis and guide subsequent investigations.[17,18] As in some previous studies that have utilized CBCT to analyze perfusion patterns after port implantation, the technique may be useful for predicting tumor response to HAIC.[19,20]

In the present study, contrast-enhanced CBCT showed three tumor perfusion types, including 100 hyperperfusion tumors (48.5%), 92 isoperfusion tumors (44.7%), and 14 hypoperfusion tumors (6.3%). Ikeda et al.[11] classified intrahepatic perfusion into six groups according to lobes and segments, with three main types: homogeneous distribution, hyperperfusion, and perfusion defect. This classification method is similar to our method for classifying tumor perfusion types. The tumor responses in our study varied on CBCT according to the different types. Figure 2 shows a better tumor response in the hyperperfusion group (65% ORR, 92% DCR); the isoperfusion type had a 12% ORR and a 46.8% DCR, while the hypoperfusion type had a 0% ORR and a 7.1% DCR. A CR was demonstrated only in the hyperperfusion group (Figure 3). The ORR and DCR values of the three groups were significantly different ($P < 0.001$). There was no difference in ORR between the isoperfusion and hypoperfusion groups ($P = 0.171$); however, the DCR of these two groups differed significantly ($P = 0.007$). Unlike in our study, where all patients had HCC, Ikeda et al.[11] conducted their study on a heterogeneous group of patients, including those with primary and secondary liver tumors. They suggested that the homogeneous type had the best prognostic characteristics for HAIC for liver malignancies and was better than the hypoperfusion type and the perfusion defect type.[11]

We identified 14 tumors as the hypoperfusion type, and 13 out of those 14 tumors (92.9%) exhibited PD following HAIC treatment (Figure 4). Hypoperfusion-type tumors were found predominantly in patients with

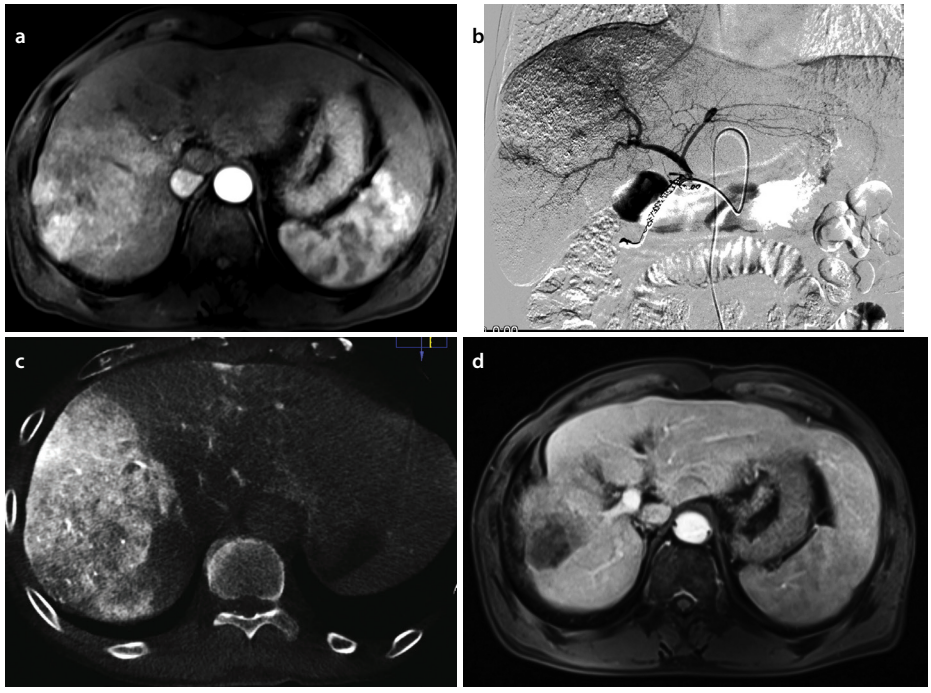

Figure 3. A 55-year-old male with hepatitis B virus, a Child–Pugh score of 5A, and refractory TACE. **(a)** An infiltrative right hepatic tumor with right portal vein tumor thrombosis. **(b)** Hepatic angiography via port when treated with hepatic arterial infusion chemotherapy (HAIC). **(c)** Contrast-enhanced cone-beam computed tomography (CT) on the day after port implantation: a right hyperperfusion tumor. **(d)** Follow-up contrast CT after five cycles of HAIC showing a complete response. TACE, transarterial chemoembolization.

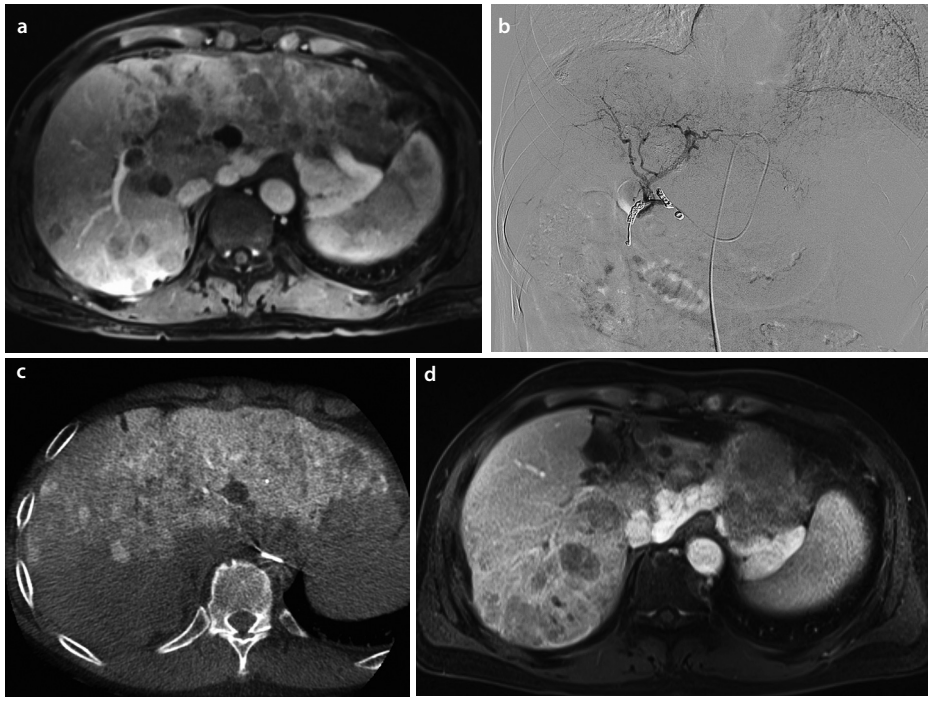

Figure 4. A 75-year-old male with hepatitis C virus and a Child–Pugh score of 7B. **(a)** Computed tomography (CT) image with multiple hepatocellular carcinoma nodes focusing mainly on the left hepatic lobe and the right posterior hepatic segment. **(b)** Hepatic angiography via port when treated with hepatic arterial infusion chemotherapy (HAIC). **(c)** Cone-beam CT on the day following port implantation: Hypoperfusion of the tumor was observed in the posterior segment and a segment of the left lobe located adjacent to the spleen, with isoperfusion tumors in the remaining liver parenchyma. **(d)** Follow-up contrast CT after four cycles of HAIC: the hypoperfusion tumor increased in size (progressive disease). A left hepatic tumor of the isoperfusion type, with decreased size and no enhanced-contrast media (partial response).

hepatic artery anatomical variations or extrahepatic circulation that specifically involved the RIPA supplying the tumor. Yamagami et al.[9] reported that for patients with multiple hepatic arteries, redistribution was achieved by a single HAIC port implantation in the main artery and occluding the remaining arteries, thus maintaining the distribution of chemotherapeutic agents throughout the liver parenchyma. The authors also suggested that embolization of the RIPA is necessary to achieve the best distribution pattern.[9] Kobe et al.[20] reported that in patients with hepatic artery variants with a single port, redistribution after port placement did not alter the differences in reperfusion or change the tumor response to HAIC treatment when comparing both hemilivers. Kim et al.[19] also reported that patients with hepatic artery anatomical variations and two main blood supply sources could be implanted with dual ports, although there was no statistically significant difference in tumor response between monoport and dual-port groups.

Two limitations affected the present study. First, we used contrast injection on CBCT (1 mL/sec of contrast agent for 40 sec) to simulate the actual distribution of chemotherapeutic agents during HAIC as closely as possible; however, this injection condition still differed from the actual distribution of chemotherapeutic agents delivered via a port. Furthermore, the difference in viscosity between the contrast media and chemotherapeutic agents used may have led to discrepancies in the results. Second, the image quality on CBCT was not as good as that of conventional CT scanners, which may have reduced the accuracy of the evaluation. However, the utilization of CBCT following intervention has become increasingly prevalent and convenient in medical practice.

In conclusion, the hyperperfusion tumor type on CBCT had the best tumor response to HAIC, with a 65% ORR and a 92% DCR; of these, 10 tumors (10%) had a CR after HAIC treatment in patients with HCC. Tumor perfusion on CBCT after the implantation of a HAIC port in patients with HCC was associated with tumor response in HAIC-treated patients.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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