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Utility Of C-Arm CT In Detection Of Hepatocellular Carcinoma Duringtransarterial Chemoembolization

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Abstract:
Background:The development of flat panel detectors has made cone-beam CT feasible for practical use in a clinical setting, the aim of this study isto assess the usefulness of C-arm Cone beam Computed Tomography (CBCT) in conjunction with conventional digital subtraction angiography (DSA) in detection of the tumors and identifying the feeding vessels during transarterial chemoembolization of hepatocellular carcinoma (HCC).
Material and Methods: Between January 2016 and January 2018, cone beam CT was retrospectively used in 19 consecutive patients with HCC tumors, 12 patients (63.2%) done CT as a pre imaging modality and 7 patients (36.8%) done MRI. Detectability of tumors and tumor-feeding subsegmental arteries was compared versus that ofpreimaging CT or MRI and the nonselective digital subtraction angiography (DSA).
Results:DSA depicted additional 14 (38.8 %) lesions were not apparent in the pre imaging (CT/MRI) and CBCT depicted additional 21(58.3%) lesions were not apparent in the pre imaging (CT/MRI). Tumor detectability on DSA was no statistically significant difference from pre imaging (CT/MRI) (P = 0.075), The sensitivity and specificity of DSA in detection of tumors taking the imaging (CT/MRI) as a gold standard was (88.9%), (84.5%) respectively with accuracy (85.53%). Tumor detectability on cone-beam CT was high significantly greater than on preimaging (CT/MRI) modality(p=0.000) .The sensitivity and specificity of CBCT in detection of tumors taking the imaging (CT/MRI) as a gold standard was (94.4%), (71.6%) respectively with accuracy (76.97%). DSA could detect 54 feeding vessels for all tumors detected by DSA. CBCT could detect 101 feeding vessels for all tumors detected by CBCT. The detectability of tumor-feeding branches with CBCT was highly significantly than that with DSA (P= 0.004)
Conclusion:**C-arm CT is a useful collaborative tool in patients undergoing transhepatic arterial chemoembolization **thereby improving the detection of tumor as well as their feeding vessels, We believe the technical success rates of ultraselectivetranscatheter arterial chemoembolization may be improved by chemoembolization guidance software that uses cone-beam CT technology.

Key Words: Cone Beam Computed Tomography – Hepatocellular carcinoma – Transarterial chemoembolization

INTRODUCTION:

Hepatocellular carcinoma (HCC) is the primary liver cancer, which is considered the sixth most common cancer in the world and the second leading cause of cancer related death. Transarterial chemoembolization (TACE) is the officially recommended therapeutic option for many patients. HCC is unique among malignancies in having tumor characteristics on cross-sectional multiphase contrast computed tomography (CT) or magnetic resonance imaging (MRI) that allow for a highly accurate diagnosis of HCC without an invasive biopsy(1).

The diagnosis is based on the qualitative or visual appreciation of differences in attenuation on CT and signal intensities on MRI of the HCC with respect to surrounding liver parenchyma (2). Typical HCC demonstrates arterial enhancement followed by washout at CT(3). By MR imaging HCC usually appears as a hypointense nodule at T1-WI comparing to the surrounding parenchyma, On T2-WI it shows a mild hyperintense signal in post contrast imaging, enhancement is usually arterial with rapid "washout," becoming hypointense to the remainder of the liver with restricted diffusion(4).

One of the most common reasons for early recurrence after treatment is the inability to identify all lesions including the small or occult tumors prior to treatment. Therefore, detection of all tumor nodules, including the smaller HCCs (<3 cm), is essential in achieving best treatment results(5).Unfortunately, angiography frequently cannot detect small HCC lesions. In addition, conventional triphasic contrast enhanced CT and MRI are less sensitive in detecting small lesions(5).

Another area of controversy is the optimal management of patients in whom CT or MRI detects a nodule with some but not all the hallmark features of HCC. The differential diagnosis for such nodules includes HCC, non-HCC malignancy, and non malignantentities(6).

Generally, C-arm Cone beam CT (CBCT) shows additional HCCs that are not evident on CT, MRI, and angiography, so the sensitivity of HCC detection is increased through the use of CBCT. But, non-tumorous lesions mimicking HCCs are frequently seen on C-arm CBCT, resulting in reduced specificity(7). C-arm hepatic artriography the most common technique for intraprocedural HCC detection and is recommended as part of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE)/Society of Interventional Radiology (SIR) protocol guidelines for selective TACE due to it provides substantially more information than digital subtraction angiography (DSA) because it delineates the exact location of a target tumor in relation with the surrounding structures, and direct injection of contrast material into the hepatic artery allows easy and accurate tracing of the tumor feeders on the CT images (7).The purpose of this study is to evaluate the usefulness of CBCT in detecting hepatocellular carcinoma (HCC) tumors and their feeding vessels during transarterial chemoembolization (TACE).

MATERIAL AND METHODS

Between January 2016 and January 2018, CBCT was used in 19 consecutive patients with HCC tumors in Theodor Bilharz Research Institute. Written informed consent was obtained from all patients before each procedure. The institutional review board of our institute approved the study. The study included 13 men and 6 women, with a mean age of 65.47 ± 7.90 (standard deviation; range, 55 – 80 years), 8 patients (42.1%) were below 60 years and 11 patients (57.9%) were above 60 years . All patients had liver cirrhosis, which was related to hepatitis C. 12 patients (63.2%) done CT as a pre imaging modality and 7 patients (36.8%) done MRI.

All patients were confirmed to have HCC on the basis of clinical history, underlying liver disease and/or viral infection and imaging findings. Inclusion criteria are initial presentation of HCC without previous treatments, hypervascular nodules satisfying the imaging diagnosis criteria of HCC and stage A or B according to Barcelona Clinic Liver Cancer (BCLC) staging system. The imaging criteria for the diagnosis of HCC according to European Association for the Study of the Liver (EASL) or The American Association for the Study of Liver Diseases (AASLD) criteria for the radiologic diagnosis of HCC can be made at either CT or MR imaging, provided that a multiphasic contrast material–enhanced study is used. If the lesion demonstrates characteristic features of hepatocellular carcinoma that is, arterial phase hyperenhancement and portal venous or delayed phase washout—with a single modality, the diagnosis can be made and no further investigation is required(8).Exclusion Criteria are diffuse infiltrative HCC, malignant portal vein thrombosis, patient with decompensated cirrhosis (Child-Pugh B, score >8), including jaundice, clinical hepatic encephalopathy, and refractory ascites and/hepatorenal syndrome and contraindication to contrast medium (Impaired renal function creatinine ≥1.5 mg/dl or creatinine clearance <30 ml/min).

Technique:
All procedures were done by an experienced team, with local anesthesia and standardized techniques using SeimensArtis Zee interventional angiography system with CBCT device, Visceral angiography was performed via the common femoral artery with a 4 or 5-F angiographic catheter to establish hepatic arterial anatomy, tumor location, and vascular supply. Feeding arteries supplying the target tumor were catheterized as selectively as possible using microcatheters(9).

Angiography Protocol
Two-dimensional DSA of the common hepatic or proper hepatic artery was achieved with a 5 French catheter (Cobra or Simon) with injection of 14-21mL of contrast material at a rate of 2-3mL/s(10).

Cone Beam CT Hepatic Arteriography
It's a technique involves a single CBCT acquisition with one contrast medium injection through a catheter or a microcatheter positioned in the common hepatic artery in case of the normal hepatic anatomy, in case of the any variant hepatic artery, the variant vessel will be catheterized and CBCT will be done from that vessel. Nonetheless, an acquisition delay after injection start of 2–10 seconds, and an injection rate of 2 mL/sec of non –ionic iodinated contrast medium diluted to 150mg/ml concentration (50%) (Omnipaque 300, Mallinckrodt, St .Lois, Missori) were injected. CBCT hepatic arteriography has the ability to depict occult HCC lesions unseen on nonselective DSA images during TACE.

Definition Of Tumor-Feeding Branches
We evaluated tumor-feeding branches at the segmental or sub-segmental artery of the hepatic artery. A microcatheter was advanced into any branch that was suspected to be a tumor-feeding branch. Selective catheterization into the tumor-feeding branch was attempted under a postero - anterior fluoroscopic view with reference to 3D reconstructed images with the feeding branches. If the orifice of the feeding branch was unclear, selective catheterization was attempted under the optimal oblique view determined by 3D reconstructed images. The selected branch was determined as a tumor-feeding branch when partial or entire tumor staining was demonstrated on DSA and/or selective CBCT hepatic arteriography .

Definition Of Technical Success
The technical success means that all the tumor feeding vessels which detected should be reached, targeted andembolized during the procedure.

Statistical Analysis
The detectability of the tumors by pre imaging (CT/MRI), DSA and CBCT was assessed. The comparison of DSA and CBCT taking the preimaging (CT/MRI) as a gold standard was calculated. The detectability of the tumor-feeding branch with non-selective DSA and CBCT images was compared. A X^2 test was used to compare the detection rate of the tumors and tumor-feeding branches with non-selective DSA versus CBCT, with calculation of the *P* - value of significance: *P* value more than 0.05: non-significant. *P* value less than 0.05: statistically significant. A commercial statistical software package (SPSS version 22; SPSS, Chicago, Illinois) was used for data analysis.

Results:

Detectability of HCC

Additional tumor detected by DSA and CACT in comparison to pre imaging (CT/MRI) seen in Table 1. Overall, DSA depicted additional 14 (38.8 %) lesions were not apparent in the pre imaging (CT/MRI). Also CBCT depicted additional 21(58.3%) lesions were not apparent in the pre imaging (CT/MRI).

Table 1. Additional tumor detected by DSA and CBCT in comparison to pre imaging (CT/MRI)

	Pre imaging (CT/MRI)	**DSA**	**CBCT**
No. of tumor detected	36	50	67
Additional tumor detected in comparison topreimaging (CT/MRI)		14 (38.8 %)	21(58.3%)

Table 2 shows the segmental location of tumors seen in the pre imaging (CT /MRI) modalities among the studied cases. Thirty six tumors were seen in the pre imaging modalities, as following: two within segment I (5.6%), two in segment II (5.6%), two in segment III (5.6%), two in segment VI (5.6%), six in segment V (16.7%), eight in segment VI (22.2%), four is segment VII (11.1%) and ten for segment VIII (27.8%). while the segmental location of tumors seen in the DSA modality among the studied cases was as follow, Fifty tumors were seen in the DSA modality, as following: Four within segment I (8.0%), Five in segment II (10.0%), Three in segment III (6.0%), Five in segment VI (10.0%), three in segment V(6.0%), twelve in segment VI (24.0%),six is segment VII (24.0%) and twelve for segment VIII (24.0%). the segmental location of tumors seen in the CBCT modality was as follow, sixty seven tumors were seen in the CBCT modality, as following: Five within segment I (7.5%), Seven in segment II (10.4%), Five in segment III (7.5%), Six in segment VI (9.0%), Ten in segment V (14.9%), Fourteen in segment VI(20.9%), Eight is segment VII(11.9%) and Twelve for segment VIII (17.9%).

Table 2. The segmental location of tumors seen by preimaging CT/MRI, DSA and CBCT modalities among the studied cases

	pre imaging CT/MRI		**DSA**		**Cone beam CT**	
Segments	No. of tumordetected (total no. = 36)		No. of tumordetected (total no. = 50)		No. of tumordetected (total no. = 67)	
I	2	5.6%	4	8.0%	5	7.5%
II	2	5.6%	5	10.0%	7	10.4%
III	2	5.6%	3	6.0%	5	7.5%
IV	2	5.6%	5	10.0%	6	9.0%
V	6	16.7%	3	6.0%	10	14.9%
VI	8	22.2%	12	24.0%	14	20.9%
VII	4	11.1%	6	24.0%	8	11.9%
VIII	10	27.8%	12	24.0%	12	17.9%
Total no. of tumors detected	36		50		67	

Table 3. Comparison between results by pre imaging (CT/MRI) and results by DSA among the studied cases

	Pre imaging (CT/MRI)		**DSA**		**Test value**	**P-value**	**Sig.**
	No. of tumor detected	**%**	**No. of tumor Detected**	**%**			
I	2	10.50%	4	21.10%	0.792	0.373	NS
II	2	10.50%	5	26.30%	1.576	0.209	NS
III	2	10.50%	3	15.80%	0.230	0.632	NS
IV	2	10.50%	5	26.30%	1.576	0.209	NS
V	6	31.60%	3	15.80%	1.31	0.252	NS
VI	8	42.10%	12	63.20%	1.689	0.193	NS
VII	4	21.10%	6	31.60%	0.543	0.461	NS
VIII	10	52.60%	12	63.20%	0.432	0.511	NS
Total no. of tumor detected	36	23.7%	50	32.9%	3.178	0.0	NS

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DSA could depict 50 tumors from all 67 tumors detected and pre-imaging (CT/MRI) could depict only 36 tumors. Tumor detectability on DSA was no statistically significant difference from pre imaging (CT/MRI) (P = 0.075) as seen in Table 3, The sensitivity and specificity of DSA in detection of tumors taking the imaging (CT/MRI) as a gold standard was (88.9%), (84.5%) respectively with accuracy (85.53%) (Table 4).

Table 4. Predictive value of DSA taking pre imaging (CT/MRI) as a gold standard

DSA	**Sensitivity**	**Specificity**	**TP**	**FN**	**TN**	**FP**	**PPV**	**NPV**	**Accuracy**
I	100%	88.2%	2	0	15	2	50%	100%	89.5%
II	50%	76.50%	1	1	13	4	20%	92.86%	73.7%
III	100%	94.10%	2	0	16	1	66.70%	100%	94.7%
IV	100%	82.40%	2	0	14	3	40%	100%	84.2%
V	50%	100%	3	3	13	0	100%	81.25%	84.2%
VI	100%	63.60%	8	0	7	4	66.67%	100%	78.9%
VII	100%	86.70%	4	0	13	2	66.70%	100%	89.5%
VIII	100%	77.80%	10	0	7	2	83.30%	100%	89.5%
Total	**88.9%**	**84.5%**	**32**	**4**	**98**	**18**	**64.0%**	**96.1%**	**85.53%**

CBCT could depict 67 tumors and pre imaging (CT/MRI) could depict only 36 tumors. Tumor detectability on cone-beam CT was high significantly greater than on preimaging (CT/MRI) modality (*p*=0.000) as seen in Table 5. The sensitivity and specificity of CBCT in detection of tumors taking the imaging (CT/MRI) as a gold standard was (94.4%), (71.6%) respectively with accuracy (76.97%) (Table 6)(Fig. 1).

Table 5. Comparison between results by pre imaging (CT/MRI) and results by cone beam CT among the studied cases.

	Pre imaging (CT/MRI)		**Cone beam CT**		**Test value**	**P-value**	**Sig.**
	No. of tumor detected	**%**	**No. of tumor detected**	**%**			
I	2	10.50%	5	26.30%	1.576	0.209	NS
II	2	10.50%	7	36.80%	3.64	0.056	NS
III	2	10.50%	5	26.30%	1.576	0.209	NS
IV	2	10.50%	6	31.60%	2.533	0.111	NS
V	6	31.60%	10	52.60%	1.232	0.267	NS
VI	8	42.10%	14	73.70%	3.886	0.048	**S**
VII	4	21.10%	8	42.10%	1.949	0.163	NS
VIII	10	52.60%	12	63.20%	0.432	0.511	NS
Total no.	36	23.7%	67	44.1%	14.1	0.000	**HS**

of tumor detected					11		

Table 6. Predictive value of cone beam CT taking pre imaging (CT/MRI) as a gold standard.

CB CT	Sensitivity	Specificity	TP	FN	TN	FP	PPV	NPV	Accuracy
I	50%	76.50%	1	1	13	4	20%	92.86%	73.7%
II	50%	64.70%	1	1	11	6	14.29%	91.67%	63.2%
III	100%	82.40%	2	0	14	3	40%	100%	84.2%
IV	100%	76.50%	2	0	13	4	33.33%	100%	78.9%
V	100%	69.20%	6	0	9	4	60%	100%	78.9%
VI	100%	45.50%	8	0	5	6	57.14%	100%	68.4%
VII	100%	73.30%	4	0	11	4	50%	100%	78.9%
VIII	100%	77.80%	10	0	7	2	83.30%	100%	89.5%
Total	**94.4%**	**71.6%**	**34**	**2**	**83**	**33**	**50.7%**	**97.6%**	**76.97%**

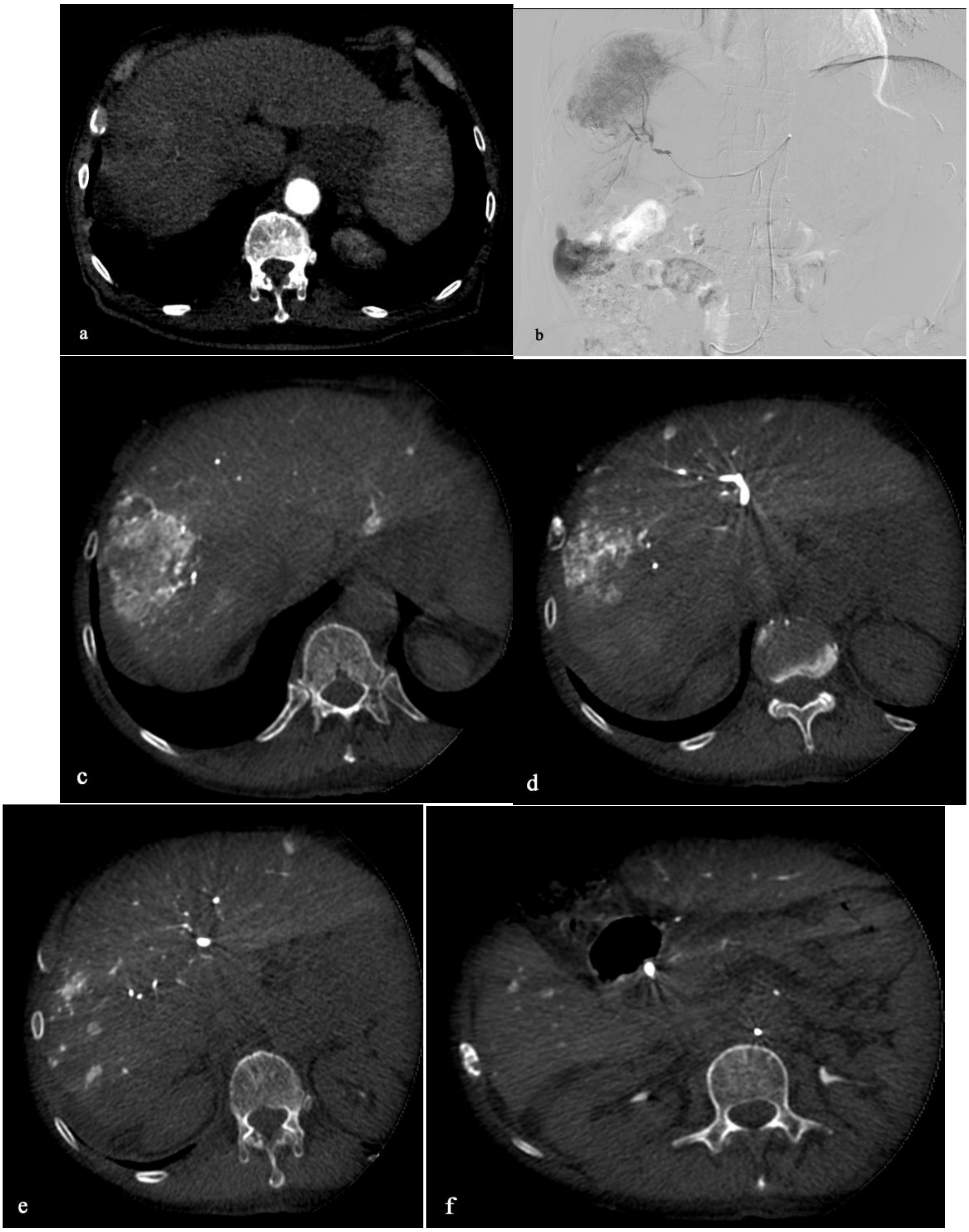

Figure (1): a) preimagingCT:faintly enhancing tumorinthe right lobe of the liver (segment VIII),b) DSA: the tumor seen in the right lobe, c:f) CBCT: the tumor in the right lobe clearly seen at segment VIII, Other additional tumors seen in segment II, III V and VI

Table 7 showed comparison between DSA and CBCT regarding tumor feeder detection. On DSA modality, we detect one feeder vessel in 47(94.0%) tumors from all tumor detected in DSA and two feeders vessels for 2 (4.0%) tumors and three feeder vessels for 1 (2.0%) tumor. On CBCT modality we detect one feeder vessel in 48(71.6%) tumors from all tumors detected in CBCT and two feeders vessels for 4 (6.0%) tumors and three feeder vessels for 15 (22.4%) tumors. The detectability of tumor-feeding branches (one and three feeders vessels detected) with CBCT was highly significantly than that with nonselective DSA (P 0.001), while in those tumors with two feeders vessels there was no statistically significantly difference between CBCT and DSA among the studied patients (*P*=0.633).

Table 7.Comparison between DSA and CBCT regarding tumor feeder detection.

Number of feeders /tumor	DSA		CBCT		Test value	P-value	Sig.
	No.	%	No.	%			
One feeder	47	94.0%	48	71.6%	9.375	0.002	**HS**
Two feeders	2	4.0%	4	6.0%	0.228	0.633	NS
Three feeders	1	2.0%	15	22.4%	10.082	0.001	**HS**

DSA could detect 54 feeding vessels for all tumors detected by DSA (total number of tumors detected by DSA was 50 tumors). CBCT could detect 101 feeding vessels for all tumors detected by CBCT (total number of tumor detected by CBCT was 67 tumors). The detectability of tumor-feeding branches with CBCT was highly significantly than that with DSA (*P*=0.004) Table 8.

Table 8.Detectability of Tumor-feeding vessels per modality.

	DSA	CBCT	Test value	P-value	Sig.
Total No. of feeder vessels detected /modality	54	101	10.683	0.004	HS

DISCUSSION

Cone Beam CT is a relatively novel way of producing CT-like images using a flat-detector angiographic system that might be useful for difficult interventional procedures during TACE to treat HCC(11).

C-arm CT generates substantially more information than DSA because it delineates the exact location of a target tumor in images in multiple planes and its relationship to surrounding soft-tissue structures.

The benefit of using cone beam CT during TACE has already been demonstrated by several studies. First, Liapi et al.(12)reported the usefulness of cone beam CT during TACE in 2 patients with HCC carcinoma having complex vascular anatomy. They argued that in such cases, cone beam CT imaging [1] decreased contrast medium dose as well as radiation exposure for patients and physicians by decreasing multiple DSA images and [2] allowed treatment of hepatic tumors with complex vascular anatomy that otherwise would have been difficult to treat. Kakeda et al.(11)demonstrated that cone beam CT imaging provided clinically acceptable image quality in the assessment of 52 HCCs and that in 81% of the cases it provided additional information for treatment compared with DSA imaging. Similarly, Miyayama et al. (10)demonstrated that cone beam CT imaging was useful in detecting and treating small HCC lesions that could not be demonstrated on angiography.

DSA is capable of unsurpassed temporal resolution and in-plane spatial resolution but is limited by the lack of soft tissue contrast and also by its projectional, non-3D images (13). CBCT has a smaller focal spot and larger matrix than multidetector CT (MDCT), which results in higher spatial resolution(14).

Furthermore, hepatic arteries could be better depicted on CBCT images, because CBCT hepatic arteriography had the advantage of direct injection of contrast media from target vessels compared to MDCT scanning with peripheral injection. This is an important advantage when performing chemoembolization for HCC with CBCT hepatic arteriography because it enables the demonstration of subtle feeding arteries and provide a three dimensional roadmap for microcatheter navigation to the target vessel or superselectivechemoembolization(15).

The results of our study support earlier findings on CT hepatic arteriography(16) and C-arm CT applied to hepatic interventions(17). C-arm CT provided essential information not available with DSA in 58.3% of our chemoembolization patients, similar to that reported by Miyayama et al, (18).

In the present study we used CBCT protocol (Artis zee floor mounted system with Dyna CT; Siemens, Forchheim, Germany), 321 projection images with 10.4-s acquisition with 207° rotation of a 30 × 38 cm FPD of the angiographic C-arm around the patient. Optimal thick cross-sectional images are obtained for observation of CBCT images on a workstation (Siemens Medical Systems). The matrix size is 512 × 512, and the field of view (FOV) is 25 cm. Maximum intensity projection (MIP) images from CBCT can also be used to observe the vascular anatomy.

The advantages of CBCT come with their own caveats: potentially increased radiation dose, contrast medium volume, and procedural time and the need for patient cooperation for a longer breath-hold. The radiation dose delivered during a single CBCT acquisition is greater than that delivered during a single DSA acquisition. However, unlike DSA, the skin dose of CBCT is distributed over 200° because of the rotational nature of the acquisition. More over, a single CBCT has the possibility of yielding the same information as multiple DSA acquisitions in technically challenging cases. CBCT, when performed in addition to standard DSA, adds to the total volume of contrast medium administered. However, as is true with radiation dose arguments, a single CBCT may offer equivalent or even more information than multiple DSA acquisitions. In addition, the contrast medium used for CBCT is diluted to 50% concentration to decrease streak artifact(13).

Technical aspects of transcatheter arterial chemoembolization may also impact survival. Yamakado et al. (19)analyzed the survival rates of patients with HCC (less than 7 cm, fewer than five lesions) treated by chemoembolization. They reported that the survival rates of the selective chemoembolization group (ie, chemoembolization at segmental artery or more distal level) were significantly higher than those of the non selective chemoembolization group (ie, chemoembolization at lobar or proper hepatic artery; (P =.0034). Iwamoto et al.(20)reported that patients treated with cone-beam CT–assisted chemoembolization had significantly higher overall (P =.005) and local progression-free (P =.003) survival rates than those who received chemoembolization with DSA alone.

Ultraselectivetranscatheter arterial chemoembolization has a strong therapeutic effect on small HCC lesions. With advancement of imaging modalities, such as multi– detector-row helical CT scanners and MR imaging systems, smaller HCC lesions can be discovered. However, in such tumors, identification of the tumor-feeding branch on DSA, as well as tumor staining, is more difficult because the tumors are usually less hypervascular(10).

In conclusion, CBCT has satisfactory ability to detect 58.3 % additional tumors in comparison to pre imaging (CT/MRI) while DSA could detect 38.8% additional tumors in comparison to pre imaging (CT/MRI). CBCT could identify single feeding vessel in 71.6% of tumors detected by CBCT, two feeders vessels for 6.0% tumors and three feeder vessels for 22.4% tumors in comparison to DSA which could identify single feeding vessel in 94.0%of tumors detected by DSA, two feeders vessels for 4.0%tumors and three feeder vessels for 22.4% tumors .The detectability of tumor-feeding branches with CBCT was highly significantly than that with DSA (P=0.004)

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