

# The Use of Dual Energy Computerized Tomography to Detect Residual Viable Hepatocellular Carcinoma after Transarterial Chemoembolization

Pharida Pengwan, M.D., Voraparee Suvannarerg, M.D., Aphinya Charoensak, M.D.

Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

## ABSTRACT

**Objective:** To determine the value of the dual energy computerized tomography (DECT) for detection of residual viable hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE).

**Methods:** Single-source (ss) DECT of liver was performed in adult patients who were diagnosed as HCC and treated with TACE at Siriraj Hospital during October 1<sup>st</sup>, 2013- December 31<sup>st</sup>, 2014. The diagnostic 5-point performance score of conventional liver CT imaging set (CCTI) and iodinated material density imaging set (IMDI) obtained simultaneously by using DECT, were evaluated by two radiologists. The follow up imaging at 6 months was regarded as gold standard. The sensitivity and specificity were calculated by assigned score 4 or 5 lesions as positive for the presence of HCC, assigned score 1 or 2 lesions as negative for viable tumor and assigned score 3 lesions as uncertain diagnosis. McNemar's test was used to compare the sensitivity and specificity between CCTI and IMDI. The reading time of both technique and radiation dose were recorded and the mean reading time were compared using a paired *t*-test.

**Results:** Out of total 21 patients with 66 lesions, 81% were male and 19% were female with mean age  $61.8 \pm 10.2$  years old. After monitoring for 6 months, 35 of the total 66 lesions were still viable HCCs and 31 lesions became non-viable HCCs. CCTI had excellent inter-observer agreement while IMDI had moderate agreement ( $K = 0.931$  and  $0.534$ , respectively). The sensitivity of CCTI and IMDI for detection of viable tumor were 88.6% and 100%, respectively (p-value cannot be computed). The specificity of CCTI and IMDI were 96.8% and 93.5%, respectively (p-value = 1.000). The mean reading time of two radiologists for CCTI was  $151.2 \pm 134.7$  seconds and  $123.2 \pm 126.8$  seconds for IMDI (p-value = 0.048). Total radiation dose of dynamic liver CT was  $1194.22 \pm 179.44$  mGy cm.

**Conclusion:** IMDI has higher sensitivity for detection of viable HCCs after TACE and consumes less reading time than CCTI.

**Keywords:** Dual energy CT; viable HCC; transarterial chemoembolization (Siriraj Med J 2019;71: 207-213)

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of liver and is the second leading cause of cancer mortality worldwide.<sup>1,2</sup> There are more than 700,000 newly diagnosed cases each year

and more than 600,000 deaths each year throughout the world in which the major risk factors are hepatitis C virus and hepatitis B virus infection.<sup>3</sup> The treatment of HCC depends on patient status, Child pugh score, number of tumors and tumor staging.

Corresponding author: Aphinya Charoensak

E-mail: caphinya@gmail.com

Received 24 June 2017 Revised 23 July 2017 Accepted 8 December 2017

ORCID ID: <http://orcid.org/0000-0001-5179-9279>

<http://dx.doi.org/10.33192/Smj.2019.32>

Transarterial chemoembolization (TACE) is an effective palliative treatment for unresectable tumor which interrupts arterial blood supply by chemoembolic agent and results in ischemic tumor necrosis. Dynamic computed tomography (CT) or Magnetic Resonance Imaging (MRI) of the liver are commonly used for assessing tumor response after TACE. However, due to limitation of MRI availability in Thailand, most patients are followed up with CT modality.

Dual-energy imaging is a new development in CT which improves lesion detection and characterization. Using two different simultaneous energy settings in dual-energy CT (DECT), allows the differentiation of materials on the basis of their energy-related attenuation characteristics (material density). A single x-ray tube is used in single-source DECT (ssDECT) with the fast kVp switching between 80 kVp and 140 kVp to generate computed monochromatic images, which have less beam hardening, pseudo enhancement and provide a higher contrast-to-noise ratio than polychromatic images obtained by conventional CT.<sup>4</sup> The obtained data from DECT can be reconstructed to virtual unenhanced images as well as iodinated contrast material density images. Radiation dose savings are possible if virtual unenhanced images replace true unenhanced images.<sup>5</sup>

Detection of viable tumor around the ethiodized oil-laden lesions after TACE is usually difficult. Prior study found that the color-coded iodine CT imaging (CICT) generated by dual-detector DECT, is comparable to conventional liver CT protocol for detecting viable HCCs and can reduce mean radiation dose by 18.3% when omitting the unenhanced phase CT.<sup>6</sup>

The purpose of the present study is to determine the value of DECT to detect viable HCC after TACE by comparing two imaging sets of conventional liver CT (CCTI) and iodinated material density imaging (IMDI), obtained simultaneously by using DECT.

## MATERIALS AND METHODS

### Patient population

This study was a preliminary and prospective study that was approved by Siriraj Institutional Review Board (Si 546/2013). A total of 68 adult patients (age >18 years old) who had been diagnosed as HCC and treated with TACE in Siriraj Hospital during 1 October 2013 to 31 December 2014 were recruited and written informed consent was obtained. The patients with infiltrative or hypovascular HCC, those who were treated with combination therapy, no availability of follow up imaging, or loss to follow up were excluded from the study. Finally,

21 patients were included. Demographic and clinical data of patients were recorded including age, sex, AFP level, date and number of TACE treatments.

### DECT scanning and post-processing

All included patients were followed up with liver CT imaging by using ssDECT scanner (Discovery CT750HD; GE Healthcare Technologies, Milwaukee, WI, USA) after TACE treatment about 4-6 weeks. DECT scan was performed only in arterial phase by using Gemstone Spectral Imaging (GSI) abdomen protocol number 3 with following scan protocol: detector coverage 40 mm., helical thickness 5.0 mm., pitch and speed 1.375:1 mm/rotation, rotation time 0.5 second, display FOV 35 cm., CTDI Vol 18.33 mGy. Reconstruction option (GSI ASiR 20%) and standard reconstruction type with slice thickness 1.25 mm. and interval 1.25 mm. were used.

Pre-contrast phase and portovenous phase were performed by using single energy CT of 120 kVp with following scan protocol: detector coverage 40 mm., pitch and speed 1.375:1 mm/rotation, rotation time 0.5 second, auto mA (min 200 mA, max 500 mA), noise index 20, and reconstruction 1.25 mm.

For iodine contrast medium administration, we used Iopamiro (370 mg Iodine/ml) with Medrad-XDS Stellant CT injection system (Bayer Healthcare LLC, Whippany, New Jersey, USA). Dose of contrast medium was 2 ml/kg. Flow rate and delayed scanning time for arterial phase was adjusted by patient body weight in order to obtain late arterial phase. Flow rate 3 cc/min and delayed time of 40 sec for patient body weight < 50 kg, flow rate 3.5 cc/min and delayed time of 38 sec for patient body weight 50-70 kg and flow rate 4 cc/min and delayed time of 35 sec for patient body weight >70 kg. Portovenous phase was obtained at a fixed delayed time at 80 seconds after contrast medium injection.

The computed monochromatic images at 70 keV were generated for arterial phase of CCTI at post-processing workstation. Then, the iodinated material density images were created by processing of the 70 keV computed monochromatic image using mono material density compare technique of GE workstation.

### Data collection and interpretation

Two CT imaging sets were independently reviewed by two radiologists who had experience of 13 years for reader 1 and 5 years for reader 2. CCTI set included pre-contrast phase, arterial phase computed monochromatic image at 70 keV and portovenous phase. For IMDI set, post-processing iodinated material density images were

used for arterial phase. Two radiologists reviewed each imaging set at time interval about 8 weeks to exclude recognition bias.

The number of tumor, tumor size, and reading time of two radiologists for each imaging set, radiation dose and type of follow-up imaging were recorded. Five-point performance score was used to evaluate post TACE response.

Score 1: Dense iodized oil uptake with or without a thin marginal rim enhancement.

Score 2: Suggestive of a non-viable tumor with a mildly thickened, smooth marginal rim enhancement, but without nodular enhancement.

Score 3: Suspicious for viable tumor seen as equivocal nodular enhancement or an irregularly thickened marginal rim enhancement.

Score 4: Suggestive of viable tumor with more prominent abnormal findings

Score 5: Definite viable tumor

The discordant performance score for each imaging set was consensus by two radiologists and undetected lesion was rated as score 0.

To compare the diagnostic performance of both imaging sets, the present study used imaging follow up with hepatic angiogram, liver MRI or liver CT until 6 months as gold standard. A viable tumor was defined as hypervascularized and neovascularized tumor staining on hepatic angiogram, or a lesion that demonstrated arterial enhancement or portovenous washout on liver CT/MRI. Non-viable tumor was defined as lesion without hypervascularized and neovascularized staining on hepatic angiogram, or dense lipiodol staining lesion without arterial enhancement or portovenous washout on liver CT/ MRI.

### Statistical analyses

Agreement between two radiologists for each imaging set were determined using weighted kappa (quadratic weight, K) which was classified as; K of 0.00-0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80 and 0.81-1.00 for poor, fair, moderate, good and excellent agreement, respectively. To calculate the sensitivity and specificity for each modality, lesions assigned to score 4 or 5 were regarded as positive for the presence of HCC and lesions assigned to score 1 or 2 were regarded as negative for viable tumor. Lesions assigned to score 3 was regarded as uncertain diagnostic lesions. McNemar's test was used to compare the sensitivity and specificity between CCTI and IMDI. A paired *t-test* was applied to compare mean reading time between CCTI and IMDI. The radiation dose was reported using descriptive statistics. All statistical data analyses were

performed using SPSS 18.0. P-value of less than 0.05 indicated a statistically significant difference.

### RESULTS

A total of 21 patients, 17 patients (81%) were male and 4 patients (19%) were female with mean age  $61.8 \pm 10.2$  years old (range 42-82 years). At the time of the TACE, the mean serum alpha-fetoprotein (AFP) level was about  $165.9 \pm 498.9$  IU/ml (Max= 2248 and Min= 2.3 IU/ml). Episodes of TACE treatment were 1<sup>st</sup> time in 7 patients (33.3%), 2<sup>nd</sup>-4<sup>th</sup> times in 12 patients (57.1%) and  $\geq 5^{\text{th}}$  times in 2 patients (9.5%). Number of lesions treated with TACE was single lesion in 8 patients (38.0%), 2-5 lesions in 11 patients (52.4%) and  $> 5$  lesions in 2 patients (9.6%). Mean duration of CT after TACE was about  $6.57 \pm 3.27$  weeks. There were 66 lesions in these 21 patients. Tumor size ranged from 0.5-16.3 cm., mean  $2.71 \pm 2.97$  SD.

At 6 months follow-up, 14 patients underwent conventional liver CT, 3 patients underwent hepatic angiogram with TACE, 3 patients underwent both of conventional liver CT and hepatic angiogram with TACE and only one patient underwent liver MRI with Primovist. There were 35 viable HCCs lesions and 31 non-viable HCCs lesions.

Table 1 showed diagnostic 5-point performance score of overall ethiodized oil-laden lesions and viable HCCs. The lesion detection rate of overall ethiodized oil-laden lesions and viable HCCs were excellent (97.1% - 100%) by both imaging sets. The inter-observer agreement between both radiologists for overall ethiodized oil-laden lesions were excellent. However, the inter-observer agreement for viable HCC lesions by CCTI was excellent (K = 0.931), but the inter-observer agreement by IMDI was moderate (K = 0.534).

Table 2 showed diagnostic 5-point performance score of overall ethiodized oil-laden lesions of both imaging sets after consensus by two radiologists. The iodinated material density image detected more viable tumor (score 4 and 5, n=35 vs. n=31) but less uncertain diagnosis (score 3, n=2 vs. n=4) and non-viable tumor (score 1 and score 2, n= 29 vs. n= 30) than conventional CT image.

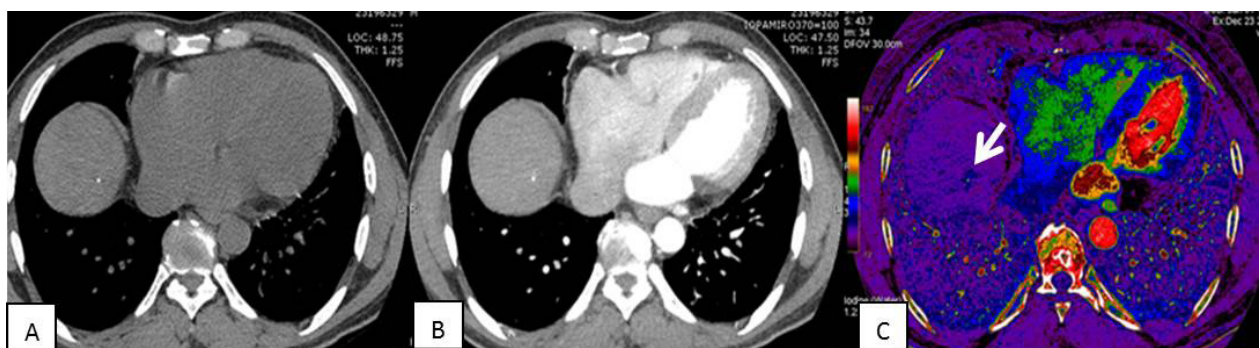
Of the total 35 viable HCC lesions, IMDI correctly defined as viable tumor in all lesions (score 4 and 5, n = 9 and 26; sensitivity = 100%) whereas CCTI defined as viable tumor in 31/35 lesions (score 4 and 5, n = 6 and 25; sensitivity = 88.6%). There was one missed viable tumor (Fig 1) and three uncertain diagnostic lesions (score 3) by CCTI (Fig 2). McNemar p-value cannot be computed to compare the sensitivity between IMDI and CCTI due

**TABLE 1.** Diagnostic 5-point performance score of overall ethiodized oil-laden lesions and viable HCCs.

Type of lesion	Imaging set		Score						Lesion detection rate	Weighted K value
			0	1	2	3	4	5		
Overall ethiodized oil-laden lesions (n=66)	CCTI	Reader 1	1	20	11	5	3	26	98.5%	0.968
		Reader 2	1	21	6	7	7	24	98.5%	
	IMDI	Reader 1	0	23	6	7	2	28	100%	0.942
		Reader 2	0	28	0	1	13	24	100%	
Viable HCCs (n=35)	CCTI	Reader 1	1	0	1	4	3	26	97.1%	0.931
		Reader 2	1	0	0	3	7	24	97.1%	
	IMDI	Reader 1	0	0	0	5	2	28	100%	0.534
		Reader 2	0	0	0	0	12	23	100%	

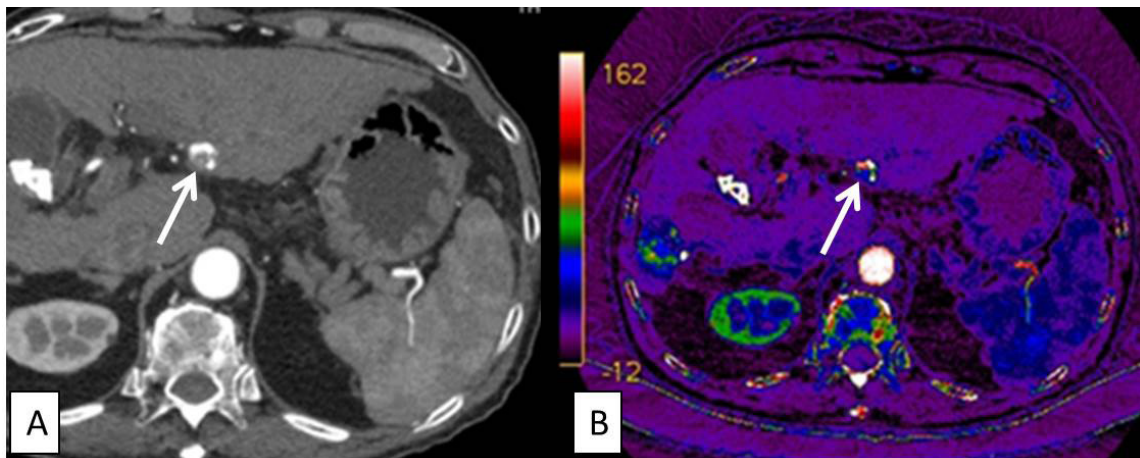
**TABLE 2.** Diagnostic 5-point performance score of overall ethiodized oil-laden lesions (n= 66) of both imaging sets after consensus by two radiologists.

CCTI score	IMDI score						Total
	0	1	2	3	4	5	
0	0	0	0	0	1	0	1
1	0	22	0	0	0	0	22
2	0	3	4	1	0	0	8
3	0	0	0	1	3	0	4
4	0	0	0	0	3	3	6
5	0	0	0	0	2	23	25
Total	0	25	4	2	9	26	66



**Fig 1.** Demonstrated missed viable tumor by CCTI but could be detected by IMDI.

- A. Unenhanced CT image showed a tiny ethiodized oil-laden lesion near liver dome.
- B. Arterial phase computed tomographic monochromatic image at 70 keV showed no definite arterial enhancement (score 0)
- C. Arterial phase iodinated material density image showed nodular arterial enhancement (arrow) surrounding ethiodized oil-laden lesion (score 4).



**Fig 2.** Demonstrated uncertain diagnostic lesion by CCTI but defined as viable tumor by IMDI.

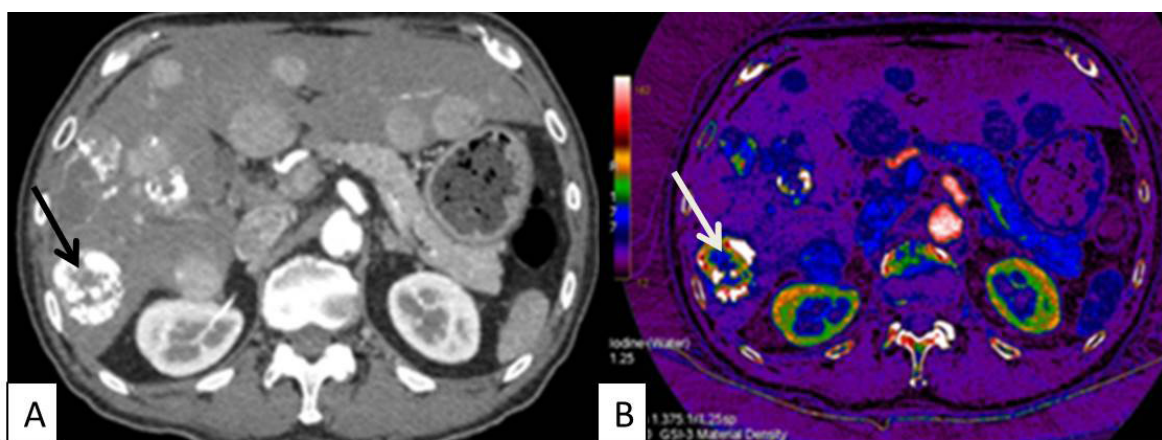
- A. Arterial phase computed monochromatic image at 70 keV showed a partial ethiodized oil-laden lesion with equivocal nodular enhancement (arrow); score 3.
- B. Arterial phase iodinated material density image showed nodular arterial enhancement (arrow); score 4. Another viable HCC was also seen at hepatic segment VI (score 5).

to 100% sensitivity of IMDI. Among 31 non-viable HCC lesions, IMDI was defined as non-viable tumor in 29/31 lesions (score 1 and 2,  $n=25$  and 4; specificity=93.5%) and uncertain diagnosis (score 3) in 2/31 lesions. CCTI defined as non-viable tumor in 30/31 lesions (score 1 and 2,  $n=22$  and 8; specificity=96.8%). The remaining one case was defined as uncertain diagnosis (score 3). **Fig 3** showed a non-viable HCC lesion which was defined as uncertain diagnosis (score 3) by both imaging sets. There was no statistically significant difference of the

specificity between IMDI and CCTI (McNemar  $p$ -value = 1.000).

The overall mean reading time of two radiologists for CCTI was  $151.2 \pm 134.7$  seconds and  $123.2 \pm 126.8$  seconds for IMDI ( $p$ -value = 0.048).

**Table 3** showed the mean radiation dose of dynamic liver CT. Mean total radiation dose was  $1194.22 \pm 179.44$  mGycm. Mean value of the CTDI Vol were  $12.17 \pm 2.09$  mGy, 13.33 mGy, and  $12.17 \pm 2.06$  mGy for unenhanced, arterial and portovenous phases, respectively.



**Fig 3.** Demonstrated a non-viable HCC lesion which was defined as uncertain diagnosis (score 3) by both imaging sets.

- A. Arterial phase computed monochromatic image at 70 keV showed a partial ethiodized oil-laden lesion with equivocal nodular enhancement (arrow) at central part of lesion.
  - B. Arterial phase iodinated material density image also showed equivocal nodular enhancement (arrow) at central part of lesion.
- After 6 months follow-up, this lesion was confirmed a non-viable tumor. All of other remaining lesions seen on both images were correctly defined as viable tumors (score 5).

**TABLE 3.** Mean radiation dose of dynamic liver CT.

Phase	CTDI Vol (mGy)	Mean $\pm$ SD	DLP (mGy cm)
Unenhanced	12.17 $\pm$ 2.09		384.21 $\pm$ 79.49
Arterial	13.33		423.39 $\pm$ 33.76
Portovenous	12.17 $\pm$ 2.06		386.63 $\pm$ 77.46
Total DLP			1194.22 $\pm$ 179.44

## DISCUSSION

Due to lack of MRI availability, conventional CT of liver is usually used to assess therapeutic response of HCC after TACE. However, it has only 43% accuracy, 36% sensitivity and 57% specificity for evaluation of tumor viability after TACE.<sup>7</sup> DECT has potential benefit to detect hypervascular hepatic lesions including HCC. Based on the fact that contrast material has higher attenuation at lower peak voltage<sup>8</sup>, computed monochromatic images obtained from ssDECT at lower keV levels can provide greater conspicuity of hypervascular hepatic lesions with less noise than polychromatic images from conventional CT.<sup>4</sup> However, evaluation of viable HCC after TACE is usually difficult because ethiodized oil in the chemotherapeutic agent used in TACE contains iodine which can mimic focal hepatic enhancement on iodinated material density image.<sup>4</sup> Therefore, unenhanced images must be obtained and interpreted in conjunction with enhanced images.<sup>9,10</sup>

The present study showed that IMDI had only moderate inter-observer agreement. This could be from both readers had little experience in IMDI. It would be better if the third radiologist with high experience was assigned to judge a discordant performance score. The reading time of IMDI was reduced by 28 seconds when compare with CCTI (p-value = 0.048). IMDI had sensitivity of 100% and specificity of 93.5% for detection of viable HCC after TACE while the sensitivity and the specificity of CCTI were 88.6% and 96.8%, respectively. Calculation of the sensitivity and the specificity was done by assigning the score 3 lesions as uncertain diagnosis. If the authors assigned the score 1 or 2 lesions as negative for viable tumor and lesions with score 3, 4, or 5 as positive for the presence of HCC, the sensitivity and the specificity of CCTI will be 97.1% and 96.8%, respectively while the sensitivity and the specificity of MDICI will remain unchanged. CCTI in the present study had much higher

sensitivity and specificity than prior study<sup>7</sup> because it used computed monochromatic image at 70 keV during arterial phase instead of polychromatic images from conventional CT. The possible explanation of very high sensitivity and specificity in the present study could be that almost all of viable lesions (34/35 lesions) had area of ethiodized oil staining < 90%. This resulted in untroubled differentiation between viable tumor and ethiodized oil.

Radiation dose is a concerned issue of DECT. Radiation dose minimizing is possible if obviating unenhanced CT acquisition.<sup>4,5</sup> However, unenhanced CT is essential for assessing therapeutic response of HCC after TACE. The present study shown that mean value of the CTDI Vol of arterial phase obtained from ssDECT (13.33 mGy) was slightly higher than the CTDI Vol of unenhanced and portovenous phases performed by single energy CT (12.17  $\pm$  2.09 mGy and 12.17  $\pm$  2.06 mGy). Prior study tried to develop a method to discriminate viable HCC from ethiodized oil by limiting the window setting of the color-coded iodine map of DECT without unenhanced images.<sup>6</sup> Result showed that the color-coded iodine CT is comparable to conventional CT for detection of viable HCC after TACE, while it allows a reduction in radiation dose. However, the range of Hounsfield unit (HU) in viable HCC is partially overlapped with normal hepatic parenchyma. A further study is needed.

The present study had some limitations. First, it was a preliminary study with a small number of population. Second, the readers had little experience in interpretation of the material density images and there was only moderate inter-observer agreement between both readers. It is required to have more experience in the interpretation skill of DECT images. Third, there was no pathological confirm of viable HCC.

## CONCLUSION

IMDI has higher sensitivity for detection of viable HCCs after TACE with less consumed reading time than CCTI. DECT including unenhanced and enhanced acquisitions has high sensitivity and specificity to detect viable HCC after TACE with slightly higher radiation dose than conventional liver CT. Further research is needed to develop a method for radiation dose reduction.

## ACKNOWLEDGMENTS

The authors (VS, AC) were supported by Chalermphrakiat Grant, Faculty of Medicine Siriraj Hospital, Mahidol University. The authors wish to thank Dr. Chulaluk Komoltri for the statistical analysis.

## REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-86.
2. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009;27:1485-91.
3. Shariff MI, Cox IJ, Gomaa AI, Khan SA, Gedroyc W, Taylor-Robinson SD. Hepatocellular carcinoma: current trends in worldwide epidemiology, risk factors, diagnosis and therapeutics. *Expert Rev Gastroenterol Hepatol* 2009;3:353-67.
4. Silva AC, Morse BG, Hara AK, Paden RG, Hongo N, Pavlicek W. Dual energy (Spectral) CT: applications in abdominal imaging. *Radio Graphics* 2011;31:1031-46.
5. Ho LM, Yoshizumi TT, Hurwitz LM, Nelson RC, Marin D, Toncheva G, et al. Dual energy versus single energy MDCT: measurement of radiation dose using adult abdominal imaging protocols. *Acad Radiol* 2009;16:1400-7.
6. Lee JA, Jeong WK, Kim Y, Song SY, Kim J, Heo JN, et al. Dual-energy CT to detect recurrent HCC after TACE: initial experience of color-code iodine CT image. *Eur J Radiol* 2013;82:569-76.
7. Hunt SJ, Yu W, Weintraub J, Prince MR, Kothary N. Radiologic monitoring of hepatocellular carcinoma tumor viability after transhepatic arterial chemoembolization: estimating the accuracy of contrast-enhanced cross-sectional imaging with histopathologic correlation. *J Vasc Interv Radiol* 2009;20:30-8.
8. Yeh BM, Shepherd JA, Wang ZJ, Teh HS, Hartman RP, Prevrhal S. Dual energy and low-kVp CT in the abdomen. *AJR Am J Roentgenol* 2009;193:47-54.
9. Kim HC, Kim AY, Han JK, Chung JW, Lee JY, Park JH. Hepatic arterial and portal venous phase helical CT in patients treated with transcatheter arterial chemoembolization for hepatocellular carcinoma: added value of unenhanced images. *Radiology* 2002;225:773-80.
10. Kim SH, Lee WJ, Lim HK, Lim JH. Prediction of viable tumor in hepatocellular carcinoma treated with transcatheter arterial chemoembolization: usefulness of attenuation value measurement at quadruple-phase helical computed tomography. *J Comput Assist Tomogr* 2007;31:198-203.