What is the “washout” of hepatocellular carcinoma as observed on the equilibrium phase CT?: consideration based on the concept of extracellular volume fraction

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Abstract
Purpose To verify the hypothesis that extracellular volume fraction (ECV) and precontrast CT density are the main determinants of washout of hepatocellular carcinoma (HCC) at the equilibrium phase CT.

Materials and methods Between 2018 and 2020, patients with surgically resected HCC were recruited who had undergone preoperative 4-phase CT. Those larger than 6 cm were excluded to minimize the possibility of intratumoral hemorrhage or degeneration. Two radiologists reviewed the whole images in consensus and divided cases into washout positive and negative groups. Washout positive group at the equilibrium phase was defined as “HCC showing relatively low density as compared to the surrounding background liver (BGL), irrespective of the presence of early enhancement or fibrous capsule”. Several clinico-pathological and radiological features, including ECV and precontrast CT density, were correlated to the presence of washout, using uni- and multi-variable analyses.

Results 27 HCC in 24 patients met the inclusion criteria. 22 (82%) and five HCC belonged to washout positive and negative groups, respectively. Univariable analysis revealed ECV of HCC and BGL, ECV difference between HCC and BGL, and presence of fibrous capsule on the equilibrium phase CT were the significant factors. Multivariable analysis showed ECV of HCC and BGL, and precontrast CT density of BGL, were the independently significant factors related to washout, suggesting washout is more likely observed with lower HCC ECV, higher BGL ECV, and higher BGL precontrast CT density.

Conclusion Major determinants of washout of HCC may be ECV of HCC and BGL, and precontrast CT density of BGL.

Keywords Hepatocellular carcinoma · Washout · Equilibrium phase CT · Extracellular volume fraction

Introduction
Major CT features of hepatocellular carcinoma (HCC) include arterial phase hyperenhancement (APHE) and washout (WO) at the portal venous and/or delayed phase,
which have been well established and well described, and defined in Liver Reporting and Imaging Diagnosis System (LI-RADS) 2018 [1]. As for the former, extensive investigations have been elaborated so far, revealing that APHE is a consequence of increased tumor neovascularity during multistep hepatocarcinogenesis [2], however, little studies have been done for the latter. One study has reported that WO at the portal venous phase may be related to the thickness of tumor trabecula, sinusoidal space, and histological grade of HCC [3], but the mechanism of WO at the delayed or equilibrium phase has barely been investigated.

Recently, extracellular volume fraction (ECV) of the liver has drawn attention as a biomarker of liver fibrosis, which can be easily calculated from non-contrast and equilibrium phase CT data [4–8]. ECV is a sum of intravascular and extravascular extracellular spaces, and is simply expressed as (100 − hematocrit) * Δ liver/Δ blood pool (%), where Δ represents the difference in the CT values between at the precontrast and equilibrium phase, because the concentration of iodine is considered the same for both intra- and extra-vascular spaces at the equilibrium phase [4–8]. We have recently reported the usefulness of ECV map, which is generated by subtracting precontrast images from equilibrium phase images utilizing non-linear non-rigid anatomical correction algorithm specifically adjusted to upper abdominal organs [8, 9], and promising results have been obtained for the estimation of degree of liver fibrosis [8]. Thanks to the highly accurate subtraction algorithm, the anatomical misregistration is minimized in this ECV map, and therefore precise ECV can be obtained for any small area of any part of the upper abdomen.

Theoretically, WO represents the relative lowness of the sum of precontrast CT density and iodine accumulation at the equilibrium phase of HCC as compared to that of background liver (BGL) (Fig. 1). Because ECV is a standardized index for iodine accumulation in tissues, we hypothesized that precontrast densities and ECV of HCC and BGL (pre-density$_{HCC}$, pre-density$_{BGL}$, ECV$_{HCC}$, and ECV$_{BGL}$), or their differences (Δpre-density and ΔECV) may be major determinants for the WO status of HCC, and conducted this retrospective study using ECV map to clarify the mechanism of WO of HCC at the equilibrium phase CT.

Subjects and methods

Patients

Between January 2018 and December 2020, there were 32 consecutive surgically resected HCC patients, all of whom had undergone 4-phase preoperative CT. Among these, HCC with the largest diameter less than 6 cm were selected to minimize the chance of intratumoral degeneration or necrosis, for adequate ECV measurement. Obtaining informed consent for this study was waived by our institutional review board due to its retrospective nature.

CT protocol

Two types of CT equipment were used. One was an area-detector CT (Aquilion ONE ViSION Edition, Canon Medical Systems), and scanning parameters were as follows:

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**Fig. 1** Schematic presentation of various patterns of washout status in correlation with precontrast density of and iodine accumulation in hepatocellular carcinoma (HCC) and background liver (BGL). HU Hounsfield unit, LC liver cirrhosis. The height of the bars indicates the density of HCC and BGL at the equilibrium phase. Precontrast density would be low when fatty change is present either for BGL or HCC. When BGL is cirrhotic (LC), stromal iodine accumulation would be high in BGL. When fibrotic component or sinusoidal dilatation is present, stromal iodine accumulation would be high in HCC. We hypothesized washout status would be determined by relative relationship of the precontrast density and degree of iodine accumulation between HCC and BGL at the equilibrium phase.
0.5 mm × 80 row, 120 kVp, three-dimensional auto-exposure control (Volume EC: SD12@5 mm), 0.5 s/rotation, 0.813 beam pitch, 512 × 512 matrix, 300–350-mm field-of-view, and 1- or 2-mm reconstruction. Noise reduction was achieved by a hybrid iterative reconstruction (Adaptive Iterative Dose Reduction or AIDR 3D Weak). Second CT was Aquilion 64 (Canon Medical Systems), and parameters were as follows: 0.5 mm × 64 row, 120 kVp, three-dimensional auto-exposure control (Volume EC: SD12@5 mm), 0.5 s/rotation, 0.828 beam pitch, 512 × 512 matrix, 300–350-mm field-of-view, and 2-mm reconstruction (filtered back projection).

After obtaining precontrast images, 600 mgI/kg iodine contrast medium (Iopamiron 370, Bayer Health Care) was injected for 30 s at a variable injection rate, and arterial dominant phase images were obtained using bolus tracking method, followed by portal dominant phase at 60 s, and equilibrium phase images at 240 s after the commencement of contrast medium injection.

Assessment

One of the authors (KS) generated ECV map on the dedicated workstation according to the previously reported method [8, 9], and placed as large a circular or free-hand region-of-interest (ROI) as possible for HCC and adjacent BGL, referring to original four-phase CT images. For HCC, areas of apparent fibrous capsule and necrosis was avoided; for BGL, apparent vessels were avoid for ROI placement. The second author (ST) independently measured ECV on the ECV map, and thus the inter-rater agreements were assessed. These two authors independently measured CT values (density) of HCC and BGL on the precontrast CT as well.

These two authors also reviewed all CT images including the precontrast and equilibrium phases for all HCCs on picture archiving and communication system (RapidEyeCore, Canon Medical Systems, Tokyo) with a window level/width of 55/350, and independently assessed the presence or absence of fat, fibrous capsule (FC), HCC density as compared to BGL (low/slightly low/iso), and WO. Fat was defined as areas lower than 0 Hounsfield unit (HU) on precontrast CT; FC was defined peripheral high density rim on the equilibrium phase images. For the assessment of WO, readers were asked to interpret equilibrium phase images alone, and WO positivity was defined as relatively low density of HCC as compared to the surrounding liver tissue, irrespective of the presence of early enhancement or FC. The first author (KS) reviewed the electric charts of the patients, and relevant clinical data, including etiology of the chronic liver disease and Child–Pugh scores, were recorded. The same author reviewed pathological reports and several pathological findings related to HCC were recorded as well.

The presence or absence of WO was correlated to clinicopathological factors and CT findings including precontrast densities and ECV, to elucidate significant factors related to the presence of WO. Sub-analysis was further performed to analyze the obtained results for clarification.

Statistical analysis

As for quantitative variables (ECV and density measurement), inter- and intra-rater agreement between the two radiologists was assessed by intraclass correlation coefficients, and the averaged value between the two radiologists were adopted for statistical assessment. As for qualitative variables (CT features), kappa values were calculated for agreement assessment between the two radiologists, and disagreement was resolved by consensus. Unvariable analysis was performed with t test or Fisher’s exact probability test for parametric variables, and with chi-square test, Mann–Whitney test, or Wilcoxon’s rank test, for non-parametric variables. Before performing multivariable analysis, multicollinearity was considered to be present when correlation coefficient was greater than 0.4 among the variables, and either one of them was discarded. Then, multivariable analysis was performed for factors related to our hypothesis (ECVHCC, ECVBGL, ΔECV, pre-densityHCC, pre-densityBGL, and Δpre-density) and significant ones at univariate analysis using nominal logistic regression method. p values less than 0.05 was considered as statistically significant. All statistical analyses were performed using JMPⓇ 14.3.0 (SAS corporation).

Results

There were 27 HCC in 24 patients which met the inclusion criteria. WO was present in 22 HCC and 5 HCC showed no WO. 5 HCC without WO exhibited isodensity as compared to the surrounding liver. As for the assessment of WO status, there was no disagreement between the two radiologists (κ value 1.0).

As for variables, four clinical, eight pathological, and nine radiological (CT) factors were assessed (Table 1). The kappa values between the two radiologists for qualitative variable assessments ranged from 0.83 to 0.92, suggesting excellent agreement. Intra-class correlation coefficients for quantitative variable assessments ranged from 0.81 to 0.95, also suggesting excellent agreement. Among these variables, correlation coefficients between ECVHCC and ΔECV (ECV_BGL–ECV_HCC), and between ECV_BGL and ΔECV, were −0.82 and 0.53, respectively (Table 2), and therefore ECVHCC and ECV_BGL were adopted as variables representing these three factors, considering the positive multicollinearity. Similarly, correlation coefficients
between precontrast density of HCC (pre-density_{HCC}) and Δpre-density (pre-density_{BGL} – pre-density_{HCC}), and between pre-density_{BGL} and pre-density_{HCC}, were −0.93 and 0.46, respectively (Table 2), and therefore pre-density_{BGL} and Δpre-density were adopted as variables representing these three factors. Univariable analysis revealed presence of FC at the equilibrium phase CT, ECVs of HCC and BGL as significant factors, and pathological presence of intratumoral fat was marginal (p = 0.05) (Table 1). These three significant and one marginal factors, and pre-density_{BGL} and Δpre-density were input to nominal logistic regression analysis, revealing ECV_{HCC}, ECV_{BGL}, and pre-density_{BGL} were independently significant factors (Table 3). Namely, the smaller ECV_{HCC} is, and the larger ECV_{BGL} and pre-density_{BGL} are, HCC are more likely to show WO on the equilibrium phase CT. Representative cases are shown in Figs. 2 and 3.

Table 1 Clinico-pathological and radiological factors vs washout status

| Clinical factors | Washout + (n = 22) | Washout − (n = 5) | p value | ICC/κ value |
|------------------|--------------------|-------------------|---------|-------------|
| Age | 73.9 ± 9.0 (n = 20) | 71.3 ± 9.8 (n = 4) | NS (0.73) |
| Sex (m/f) | 17/3 (n = 20) | 2/2 (n = 4) | NS (0.17) |
| Chronic liver disease (B/C/NBNC) | 3/13/6 | 2/1/1 | NS (0.06) |
| Child–Pugh score (5/6) | 22/0 | 5/0 | NS (1.00) |
| Pathological factors | | | | |
| Tumor size (mm) | 29.4 ± 13.2 | 23.8 ± 9.6 | NS (0.64) |
| Macroscopic type (NiM/SN/MN) | 2/17/3 | 1/3/1 | NS (0.72) |
| Histological grades (e/w/m/p) | 2/8/9/3 | 1/3/1/0 | NS (0.70) |
| Growth pattern (tr/pg/c/s) | 14/1/7/0 | 4/0/1/0 | NS (0.71) |
| Scirrhous subtypea (p/n) | 20/2 | 5/0 | NS (0.42) |
| Septal formation (p/n) | 12/10 | 3/2 | NS (0.83) |
| Intratumoral steatosis (p/n) | 7/15 | 4/1 | NS (0.05) |
| Bile production (p/n) | 3/19 | 1/4 | NS (0.72) |
| Fibrous capsule (p/n) | 6/16 | 1/4 | NS (0.73) |
| BGL presence of cirrhosis (p/n) | 5/17 | 0/5 | NS (0.24) |
| Radiological factors | | | | |
| Precontrast density of HCC (low/ slightly low/iso) | 9/6/6 | 2/2/1 | NS (0.90) | 0.83 |
| FC on equilibrium phase CT (p/n) | 15/7 | 1/4 | 0.04 | 0.85 |
| Intratumoral steatosis (p/n) | 4/18 | 1/4 | NS (0.93) | 0.92 |
| ECV of HCC | 27.4 ± 6.5 | 37.6 ± 5.3 | <0.01 | 0.83 |
| ECV of BGL | 29.6 ± 5.1 | 24.3 ± 2.5 | 0.01 | 0.81 |
| ΔECV(BGL–HCC) | 27.2 ± 6.4 | 37.3 ± 5.9 | 0.01 |
| Precontrast HU of HCC | 43.0 ± 17.9 | 39.6 ± 9.0 | NS (0.12) | 0.95 |
| Precontrast HU of BGL | 58.4 ± 5.7 | 56.6 ± 9.2 | NS (0.46) | 0.85 |
| Precontrast ΔHU (BGL – HCC) | 15.3 ± 16.0 | 17.0 ± 10.3 | NS (0.37) |

ICC intraclass correlation coefficient, m/f male/female, B/C hepatitis B/C infection, NBNC non-B non-C, NiM small nodule with indistinct margin, SN simple nodular, MN confluent multinodular, e early HCC, w/m/p well, moderately, and poorly differentiated, tr trabecular, pg pseudoglandular, c compact, s scirrhus, p/n positive/negative, BGL background liver, HCC hepatocellular carcinoma, FC fibrous capsule, ECV extracellular volume fraction, HU Hounsfield unit

*aBecause there was no scirrhus dominant case, HCC with scirrhus component, if any, were included

Table 2 Multicollinearity assessment

| Factor Vs factor | r² | r | p-value |
|------------------|----|---|--------|
| ECV of HCC ECV of BGL | 0.002 | 0.045 | 0.82 |
| ΔECV | 0.67 | −0.82 | <0.0001 |
| ECV of BGL ΔECV | 0.29 | 0.53 | 0.0041 |
| Pre-density of HCC Pre-density of BGL | 0.21 | 0.46 | 0.016 |
| ΔPre-density | 0.86 | −0.93 | <0.0001 |
| Pre-density of BGL ΔPre-density | 0.0088 | −0.094 | 0.64 |

r correlation coefficient, ECV extracellular volume fraction, pre-density Hounsfield unit on precontrast CT, HCC hepatocellular carcinoma, BGL background liver
As a sub-analysis, we plotted all cases on the graph with $x$ and $y$ axes representing $\Delta$density and $\Delta$ECV, respectively (Fig. 4). First, a regression line was drawn for the five HCCs which showed no WO, in other words, exhibiting iso-density as the BGL at the equilibrium phase CT. This line therefore indicates where the effect of CT density elevation difference due to iodine accumulation ($\Delta$ECV) is just cancelled or balanced by the difference in precontrast densities between HCC and BGL ($\Delta$pre-density). The area above this line (right upper hand) represents where equilibrium phase density of HCC is lower than that of BGL, namely WO is positive, either by lower $\Delta$ECV or by higher $\Delta$pre-density.

### Table 3  Nominal logistic regression analysis

| Factor                      | $p$-value | Unit odds ratio (95% CI)$^a$ | Range odds ratio (95% CI)$^a$ |
|-----------------------------|-----------|------------------------------|-----------------------------|
| ECV$_{HCC}$                 | 0.00016   | 1.30 (1.05–1.62)             | 2174.0 (3.72–1,269,606)     |
| ECV$_{BGL}$                 | 0.00027   | 0.76 (0.55–1.06)             | 0.0043 (5.87 $e^{-6}$–3.12) |
| Pre-density$_{BGL}$         | 0.0024    | 0.94 (0.80–1.11)             | 0.22 (0.0039–12.66)         |
| FC on CT                    | 1.00      |                              |                             |
| $\Delta$Pre-density         | 1.00      |                              |                             |
| Intratumoral steatosis      | 1.00      |                              |                             |

$CI$ confidence interval, $ECV$ extracellular volume fraction, $HCC$ hepatocellular carcinoma, $BGL$ background liver, $pre-density$ Hounsfield unit on precontrast CT, $FC$ on CT fibrous capsule on equilibrium phase CT, $\Delta$density the difference in density between HCC and BGL, $intratumoral$ steatosis pathological fatty change of HCC

$^a$Unit and range odds ratios were calculated by univariable logistic regression analysis, because multivariable model did not converge, probably due to small number of washout negative cases.

![Fig. 2](image_url) 63 year-old man with chronic hepatitis C infection. Pathologically, a well differentiated hepatocellular carcinoma, mainly consisting of trabecular component, associated with fibrous capsule, was diagnosed. No septal formation or fatty change was evident.  

- **a** Pre-contrast CT. The tumor exhibits almost iso- to minimally low density (arrow). Measured density were 55 and 59 Hounsfield units for the tumor and the background liver, respectively. 
- **b** Arterial phase CT. The tumor shows homogeneous enhancement (arrow).
- **c** Equilibrium phase CT. The tumor exhibits apparent “washout” (arrow).
- **d** Extracellular volume fraction (ECV) map reveal apparently lower value of the tumor, as compared to the background liver. Measured ECV were 20.2 and 26.1% for the tumor and the background liver, respectively.

In this case, although the precontrast density of the tumor or the liver were almost identical, it was considered apparently lower ECV of the tumor contributed to the positive washout.
On the other hand, the area below this line (left lower hand) represents where equilibrium phase density of HCC is higher than that of BGL, namely, WO is negative, showing delayed or prolonged enhancement, although there was no such case in our present cohort. As shown in Fig. 4, all HCC with positive WO were virtually above that line.

Discussion

As we hypothesized, multivariable analysis showed ECV\textsubscript{HCC}, ECV\textsubscript{BGL}, and precontrast density of BGL, were independently significant factors related to WO status of HCC. In other words, the smaller ECV\textsubscript{HCC} is, and the larger ECV\textsubscript{BGL} and pre-density\textsubscript{BGL} are, the more likely WO is observed on equilibrium phase CT. The reason why pre-density\textsubscript{BGL} was not significant on univariable analysis may be small number of subjects. The negative influence of steatosis in BGL on the WO status, namely, that WO of HCC may be obscured by the presence of BGL steatosis, has recently been reported by several investigators [10, 11] and is concordant to our results.

One may argue that because both washout status (objective variable) and ECV (explanatory variable) are determined by the precontrast and equilibrium phase densities, our results may be self-evident. It is true, that both variables are related to the same CT densities, but actually are determined by completely different ways; the former (washout status) is determined by whether the sum of precontrast density and degree of iodine accumulation is less than that of BGL (Fig. 1), whereas the latter (ECV) is determined by the formula as shown in the Introduction section, being an index of iodine accumulation standardized by several physiologic factors including renal function, body mass index, degree of anemia, and also by dosage of contrast agent. In other words, ECV and washout are related to each other in some extent, but are two different variables, because there

Fig. 3 57-year-old man with chronic hepatitis B infection and habitual alcohol over-intake. Pathologically, a well differentiated hepatocellular carcinoma, mainly consisting of compact component, associated with fibrous capsule, was diagnosed. Within the tumor, apparent septal formation was seen, but no fatty change was evident. a Precontrast CT. The tumor exhibits almost iso- to minimally lower density than the background liver (arrow). Measured densities were 50 and 54 Hounsfield units for the tumor and the background liver (segment 4), respectively. b Arterial phase CT. The tumor shows heterogeneous enhancement (arrow). c Equilibrium phase CT. The washout of the tumor is not apparent, showing heterogeneous appearance (arrow). d Neither on extracellular volume fraction (ECV) map, the tumor is hard to be recognized. Measured ECV were 33.5 and 26.8% for the tumor and the background liver, respectively. In this case, although the precontrast density of the tumor or the liver were almost identical, it was considered higher ECV of the tumor obscured the apparent washout.
In our study, but recent investigations with larger cohort
may at least partly be attributable to the small number of subjects
was not a significant factor at multivariable analysis. The reason why intratumoral steatosis
would lower the density of HCC may reasonably
lead to WO positivity. The reason why intratumoral steatosis
was not a significant factor at multivariable analysis may at
least partly be attributable to the small number of subjects
in our study, but recent investigations with larger cohort
also reported similar results [10]. Fibrous capsule (FC) was
pathologically observed in 7 out of 27 tumors (26%), which
was not related to WO status, on the other hand, radiological
FC was recognized in 16 out of 27 tumors (59%), which was
significantly related WO positivity at univariate analysis. This
discrepancy may be explained as follows: radiological
FC as observed on the equilibrium phase CT is considered to
represent complex of true or pathological FC and surround-
ing compressed liver parenchyma with sinusoidal dilatation,
which would retain iodine contrast at the equilibrium phase
CT [12]. This compressed liver parenchyma with dilated
sinusoids alone, therefore, even without true or pathological
FC, may result in hyperdense rim, namely FC appearance,
explaining the higher incidence of radiological FC (59%)
that of pathological FC (26%). This FC appearance has
been reported to have illusional effects as if WO was present
even though the densities inside and outside of FC is identi-
cal [13]. This is in concordance with recent report [10]. Scir-
rhous type HCC is a rare subtype of HCC, accounting for 5% of
all HCC, characterized by its abundant stromal fibrosis
[14, 15]. This stromal fibrosis has been reported to cause
delayed or prolonged enhancement on CT [15], which should
be negatively related to WO status. In our series, however,
there was no typical scirrhous HCC, and only two cases had
scanty scirrhous components, both of which showed clear
WO. Another subtype of HCC which would theoretically
show delayed or prolonged enhancement, obscuring WO, is
HCC with substantial peliotic change [16, 17]. There was no
such case in our patient group either.

Recently, Mehara et al. [18] have published a meticulous
pathological report on the intratumoral fibrosis of HCC.
They revealed that there are significant amount of collagen
and elastin within HCC, which are closely related to vari-
ous histopathological and immunohistochemical features
of HCC, some of which have been shown to be associated
with biological aggressiveness of HCC and consequently,
patient prognosis [18]. As mentioned earlier, ECV is a sum
of intravascular and extravascular extracellular spaces, and
the latter is where intratumoral fibrosis of HCC is present;
because the former (intravascular or sinusoidal space) has
been reported to be almost constant regardless of the histo-
logical grades of HCC [8]. ECV could potentially be a good
biomarker to represent intratumoral fibrosis, which might
predict biological aggressiveness of HCC, and hopefully
patient prognosis as well.

There are several limitations present in our study. First,
the total number of subjects is small, particularly that of WO
negative tumors, which could have influenced the current
results as mentioned above. Second, pathological specimens
were not reviewed specifically for this study, and simply
pathological reports, made by one expert pathologist, were
referred to for pathological feature assessment. Third, we
used two different CT scanners, which could have affected

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**Fig. 4** A graph with x and y axes representing Δpre-density (precontrast density of background liver – that of tumor) and ΔECV (ECV of background liver – that of tumor), respectively, for sub-analysis. Pink dots indicate hepatocellular carcinoma (HCC) without washout, for which a regression line is shown in red. Black dots indicate HCC with washout, all of which are located above the regression line.
the results. Fourth, generation of ECV map is not available at all institutions. Finally, because of its retrospective nature, some biases could not be completely excluded.

In conclusion, WO of HCC on the equilibrium phase CT is likely to be determined by ECV of HCC and BGL, and also by precontrast density of BGL. Radiologists should be aware of this issue when interpreting CT images.

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Declarations

Conflict of interest All authors have no conflict of interest to disclose, and understand and follow the ethical responsibilities of authors (https://www.springer.com/journal/11604/submission-guidelines#Instructions%20to%20Authors_MANUSCRIPT%20PREPARATION). There is no financial fund to support this study.

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