**Washout pattern analysis of arterial phase enhancing hepatocellular carcinoma on dynamic MR imaging with histopathological correlation: Validity of portal venous phase imaging for predicting histological grade**

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Purpose

1. The image findings of classic HCC is well known as early enhancement in the arterial phase with negative enhancement (washout) in the delayed phase. The mechanism and significance of washout have rarely been discussed.

2. Histopathologically, HCC has the tumor plate and the tumor sinusoid as the normal liver tissue has the hepatic plate and the hepatic sinusoid.

3. We hypothesize that the size of the tumor sinusoid may be correlated with the washout pattern. The purpose is to elucidate the correlation between the washout pattern of arterial phase enhancing HCC (aHCC) on dynamic MR imaging and histological findings, with an emphasis on the size of the tumor sinusoid.

Methods and Materials

Institutional review board approval was obtained, and the requirements for informed consent were waived for this retrospective study.

Materials:

Case selection flowchart is figure 1. 9 well-differentiated HCCs with a mean size of 1.3 cm (range, 0.5 to 2.2), 30 moderately differentiated HCCs with a mean size of 2.1 cm (range, 0.5 to 4.7), and 7 poorly differentiated HCCs with a mean size of 5.4 cm (range, 2.1 to 9.3) were selected. The patients included 31 men and 10 women who ranged in age from 50 to 82 years (mean age, 66.7 years). Liver dysfunction was pre-operatively graded based on the Child-Pugh classification, and 36, 3, and 2 patients were categorized into Grades A, B, and C, respectively. The hepatitis B surface antigen was present in 5 cases and the hepatitis C virus antibody in 26 cases. Ten cases exhibited neither the hepatitis B surface antigen nor the hepatitis C virus antibody.

Pathological methods and evaluation:

Each aHCC was evaluated for fibrous capsule formation, architectural characteristics including the degree of trabeculation and sinusoid formation, the thickness of the tumor plate and the percentage of tumor sinusoidal area (PTSA) by one pathologist who was
unaware of the imaging data. The results were compared with the official pathological report, and another experienced pathologist decided when the findings were different.

1. Degree of trabeculation and sinusoid formation

Each aHCC was classified into several subtypes in accordance with the classification of the Japanese Liver Cancer Study Group: (a) pure trabecular type, (b) trabecular type with small acinar structure, (c) trabecular type with large acinar structure, (d) trabecular type with pseudoglandular structure, (e) pseudoglandular type, (f) compact type, and (g) scirrhous type. There was no fibrolamellar type of HCC in our study population, although it is added to the above classification as a special histological type. On the basis of this classification, we defined trabecular and nontrabecular groups as HCCs having a trabecular structure even in part and those with no trabecular structure, respectively. In addition, the trabecular group was categorized into three subgroups: 1, a pure trabecular subgroup, corresponding to (a); 2, a trabecular and acinar subgroup, corresponding to (b) and (c); and 3, a trabecular and others subgroup, corresponding to (d) and HCCs consisting of trabecular structures among (e), (f), and (g) (Figure 2).

2. Thickness of tumor plate and PTSA

The thickness of the tumor plate was categorized as thin, moderate, or thick when the tumor plate consisted of one to three, four to six, or seven or more rows of tumor cells, respectively. On the other hand, the size of a tumor sinusoid is difficult to measure directly under light microscopy, for three reasons. First, tumor sinusoids are incommensurably small because cellular density is very high in most HCCs. Second, it is difficult to decide where to measure because tumor sinusoid size varies even in the same HCC. Third, there is no method to measure such a short distance under light microscopy. We therefore substituted the size of the tumor sinusoid with both the size of the tumor plate and the PTSA. The PTSA was calculated by the stereological point counting method, which was a convenient way to assess area ratios (Figure 3) (reference 9). Two representative fields of view on hematoxylin and eosin staining (magnification x 200) were selected. A point grid lattice was superimposed, and the hits on the tumor sinusoid were counted. Each point grid consisted of 100 crosses, 50 µm apart. This method is reported to be more precise than optical semi-quantitative evaluation.

3. Fibrous capsule

The presence of fibrous capsule was examined.

**Radiological methods:**

MR imaging was performed on a 1.5-T unit with a standard four-element phased-array coil. In addition to conventional scans, dynamic MR was performed using a
three-dimensional volumetric interpolated breath-hold examination (3D-VIBE) with the following parameters: repetition time/echo time = 4.3/1.96 milliseconds, 20° flip angle, slab thickness = 4 mm (2 mm with interpolation), partition = 1, and 1 excitation, field of view = 320 x 240 mm, and matrix size = 256 x 192. These parameters were fixed for each dynamic phase. The type of data acquisition was the sequential ordering of k space. Gadopentetate dimeglumine (Gd-DTPA) was used for contrast medium. Gd-DTPA (0.2 mmol/kg) was basically given to all patients as described by Shinozaki et al. A total of 20 mL Gd-DTPA, which consisted of 1 ml Gd-DTPA for test injection study and up to 19 ml Gd-DTPA for dynamic study, was given to 38 of 41 (92.7%) of the patients, for whom the calculated dose exceeded 20 mL, because the maximum dose of Gd-DTPA covered by public insurance in Japan is 20 mL. The average dose of Gd-DTPA actually given to the patients was 17 ml (0.17 mmol/kg). Following test injection method, dynamic MR scanning was performed before and at T (arterial phase), T + 30 (portal phase), 90, and 240 seconds after the beginning of the bolus administration of Gd-DTPA.

**Radiological evaluation:**

All MR images were retrospectively reviewed in a consensus fashion by two abdominal radiologists. Washout pattern was evaluated both qualitatively and quantitatively. Qualitatively, **signal intensity in the portal phase (SIPP)** was evaluated according to the diagram (Figure 4). Quantitatively, **the signal intensity ratio of each lesion in the portal phase (SIRPP)** was evaluated. It was defined as the proportion of tumor signal intensity to that of the surrounding liver tissue in the portal phase.

**Statistical analysis:**

A $p$ value of less than 0.05 was considered statistically significant.

1. For all aHCCs

The correlation between qualitative and quantitative results for washout patterns was evaluated using correlation ratio. The relationships between washout pattern on the one hand and, on the other, histological grade, degree of trabeculation and sinusoid formation, fibrous capsule, Child-Pugh classification, and pre-contrast signal intensity were analyzed using the Jonckheere-Terpstra test.

2. For aHCCs in the trabecular group

The relationships between washout pattern and histological grade, fibrous capsule, thickness of tumor plate, Child-Pugh classification, and pre-contrast signal intensity, as well as the relationship between thickness of the tumor plate and histological grade, were also analyzed using the Jonckheere-Terpstra test. The correlations between washout
pattern and the thickness of the tumor plate on the one hand and the PTSA on the other were analyzed using the Kruscal-Wallis test.

3. Four aHCCs in the nontrabecular group

One-by-one analysis for signal intensity in the portal phase and the PTSA was done.

Images for this section:

**Fig. 1:** Case selection flowchart.
**Degree of trabeculation and sinusoid formation**

<table>
<thead>
<tr>
<th>Pure trabecular subgroup</th>
<th>Trabecular and acinar subgroup</th>
<th>Trabecular and others subgroup</th>
<th>Pseudoglandular type</th>
<th>Compact type</th>
<th>Schirrous type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabecular group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nontrabecular group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 2:** Degree of trabeculation and sinusoid formation.
Fig. 3: Stereological point counting method (reference 9) is a convenient way to assess area ratios. Two representative fields of view on hematoxylin and eosin staining (magnification x 200) are selected. A point grid lattice is superimposed, and the hits on the tumor sinusoid are counted. Arrows means tumor sinusoid.
Fig. 4: Washout pattern diagram. aHCC; arterial phase enhancing HCC, SIPP; signal intensity in the portal phase.
Results

Degree of trabeculation and sinusoid formation

46 aHCCs were divided into 42 trabecular group aHCCs, including 21 aHCCs in the pure-trabecular subgroup, 10 aHCCs in the trabecular-and-acinar subgroup, and 11 aHCCs in the other-trabecular subgroup, and 4 nontrabecular group aHCCs, including 2 compact, one pseudoglandular, and one scirrhous type of aHCC.

Statistical analyses:

For all aHCCs

1. Correlation between qualitatively (SIPP) and quantitatively (SIRPP) evaluated washout pattern and histological grade

Based on SIPP, 9, 14 and 23 aHCCs showed early, moderate, and late washout pattern, respectively. The average SIRPP of aHCCs demonstrating early, moderate, and late washout pattern were 0.80 ± 0.08, 1.05 ± 0.06, and 1.23 ± 0.11, respectively. There was a significant correlation between histological grade and SIPP or SIRPP (p = 0.0091 or p = 0.017). aHCCs showed earlier washout pattern as the histological grade worsened (Figure5). The correlation ratio between SIPP and SIRPP was 0.91, which suggests strong correlation (Figure6).

2. Correlation between SIPP and degree of tarbeculation and sinusoid formation

There was also a significant correlation between SIPP and degree of trabeculation and sinusoid formation (p = 0.023). aHCCs showed earlier washout as the histological architecture got closer to the pure trabecular type (Figure7).

There was no statistically significant correlation between washout pattern with Child-Pugh classification, the presence of fibrous capsule and pre-contrast signal intensity (data not shown).

For aHCCs in the trabecular group

There was a significant correlation between histological grade and SIPP or SIRPP again (p = 0.0047 or p = 0.029) (Figure8). Furthermore, a significant correlation between the thickness of the tumor plate and SIPP or SIRPP was found (p = 0.0174 or p = 0.0169).
aHCCs showed earlier washout as the thickness of the tumor plate increased. There was also a significant correlation between histological grade and the thickness of the tumor plate ($p=0.0004$) (Figure 10). aHCCs with thicker tumor plates showed worse histological grades.

Refer to typical examples of aHCCs showing late and early washout patterns (Figure 11 and 12).

No significant correlation was obtained between the PTSA and washout pattern or tumor plate thickness (data not shown). There was no significant correlation between SIPP and pre-contrast signal intensity (one high, six iso-, and 39 low intensity aHCCs, respectively). No significant correlation between SIPP and Child-Pugh classification, and fibrous capsule was obtained (data not shown).

For aHCCs in the nontrabecular group

Two moderately differentiated aHCCs (one scirrhous and one pseudoglandular) showed late washout patterns, while two poorly differentiated compact aHCCs showed early washout patterns (Figure 13).
Correlation between quantitatively (SIPP) and qualitatively (SIRPP) evaluated washout pattern and histological grade for all aHCCs. (n = 46)

<table>
<thead>
<tr>
<th>Histological grade</th>
<th>SIPP</th>
<th>SIRPP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Iso-</td>
</tr>
<tr>
<td>Well</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Moderately</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>poorly</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

There was a significant correlation between histological grade and both of SIPP (p < 0.01) and SIRPP (p < 0.05). 

**aHCC showed earlier washout as the histological grade advanced.** Data in SIPP are numbers of aHCC nodules. Data in SIRPP are average +/- standard deviation.

**Fig. 1:** Correlation between qualitatively (SIPP) and quantitatively (SIRPP) evaluated washout pattern and histological grade for all aHCCs. (n = 46)
**Fig. 2:** Correlation between SIPP and SIRPP.

<table>
<thead>
<tr>
<th>Degree of trabeculation and sinusoid formation</th>
<th>SIPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure trabecular subgroup</td>
<td>2</td>
</tr>
<tr>
<td>Trabecular-and-acinar subgroup</td>
<td>2</td>
</tr>
<tr>
<td>Trabecular-and-others subgroup</td>
<td>3</td>
</tr>
<tr>
<td>Non-trabecular group</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Iso-</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure trabecular subgroup</td>
<td>2</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Trabecular-and-acinar subgroup</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Trabecular-and-others subgroup</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Non-trabecular group</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

There was a significant correlation between SIPP and degree of trabeculation and sinusoid formation ($p < 0.05$). aHCCs showed earlier washout as the histological architecture got closer to the pure trabecular subgroup. Data are numbers of aHCC nodules.

**Fig. 3:** Correlation between SIPP and degree of trabeculation and sinusoid formation for all aHCCs. (n = 46)
Correlation of SIPP and SIRPP with histological grade for aHCCs in the trabecular group. (n = 42)

<table>
<thead>
<tr>
<th>Histological grade</th>
<th>SIPP</th>
<th>SIRPP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Iso-</td>
</tr>
<tr>
<td>Well-</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Moderately</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>poorly</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

There was a significant correlation between histological grade and both of SIPP (p < 0.01) and SIRPP (p < 0.05). aHCCs showed earlier washout as the histological grade advanced again. Data in SIPP are numbers of aHCC nodules. Data in SIRPP are average +/- standard deviation.

**Fig. 4:** Correlation of SIPP and SIRPP with histological grade for aHCCs in the trabecular group. (n = 42)
Correlation of SIPP and SIRPP with thickness of tumor plate for aHCCs in the trabecular group. (n = 42)

<table>
<thead>
<tr>
<th>Thickness of tumor plate (row number of tumor cells)</th>
<th>SIPP</th>
<th>SIRPP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Iso-</td>
</tr>
<tr>
<td>Thin (one to three)</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Moderate (four to six)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Thick (seven or more)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

There was a significant correlation between tumor plate thickness and both of SIPP (p<0.05) and SIRPP (p<0.05). aHCC showed earlier washout as a thickness of the tumor plate increased. Data in SIPP are numbers of aHCC nodules. Data in SIRPP are average +/- standard deviation.

Fig. 5: Correlation of SIPP and SIRPP with thickness of tumor plate for aHCCs in the trabecular group. (n = 42)
**Correlation between tumor plate thickness and histological grade for aHCCs in the trabecular group. (n = 42)**

<table>
<thead>
<tr>
<th>Thickness of tumor plate (row number of tumor cells)</th>
<th>Histological grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well-</td>
</tr>
<tr>
<td>Thin (one to three)</td>
<td>8</td>
</tr>
<tr>
<td>Moderate (four to six)</td>
<td>1</td>
</tr>
<tr>
<td>Thick (seven or more)</td>
<td>0</td>
</tr>
</tbody>
</table>

There was a significant correlation between histological grade and tumor plate thickness (p<0.001). **The plate thickness increased as the histological grade advanced.** Data are numbers of aHCC nodules.

**Fig. 6:** Correlation between tumor plate thickness and histological grade for aHCCs in the trabecular group. (n = 42)
Dynamic MR imaging showed a high-intensity mass (arrow) in the arterial phase (upper left). The signal intensity in the portal phase remained high (arrow) (upper right). Surgical and histopathological survey revealed pure trabecular subgroup HCC with a thin tumor plate and a 13% tumor sinusoidal area (hematoxylin and eosin staining, x 50) (bottom). Small arrows (→) showed tumor sinusoids.

w/d: well-differentiated, PTSA: percentage of tumor sinusoidal area

Fig. 7: Typical case presentation 1.
Case 2 (79M, p/d HCC, pure trabecular subgroup, thick tumor plate, PTSA 12)

Dynamic MR imaging showed a high-intensity mass (arrow) in the arterial phase (upper left). The signal intensity in the portal phase changed to low (arrow) (upper right). Surgical and histopathological surveys revealed pure trabecular subgroup HCC with thick tumor plate and a 12% tumor sinusoidal area (hematoxylin and eosin staining, ×50) (bottom). Small arrows (→) showed tumor sinusoids.

p/d: poorly differentiated, PTSA: percentage of tumor sinusoidal area

Fig. 8: Typical case presentation 2.
- **Washout pattern and PTSA for aHCCs in the nontrabecular group.** (n = 4)

<table>
<thead>
<tr>
<th>Histological architecture (n, histological grade)</th>
<th>SIPP</th>
<th>PTSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scirrhous (1, modelately)</td>
<td>High</td>
<td>3.5</td>
</tr>
<tr>
<td>Pseudoglandular (1, modelately)</td>
<td>High</td>
<td>11.5</td>
</tr>
<tr>
<td>Compact (2, poorly)</td>
<td>Iso- &amp; Low</td>
<td>5.0 &amp; 3.0</td>
</tr>
</tbody>
</table>

Two moderately differentiated HCCs (one scirrhous type and one pseudoglandular type) showed late washout patterns, while two poorly differentiated HCCs (two compact type) showed early washout patterns.

**Fig. 9:** Washout pattern and PTSA for aHCCs in the nontrabecular group. (n = 4)
Conclusion

1. Washout patterns of aHCCs were correlated with histological grade.

2. Washout patterns of aHCCs in the trabecular group were correlated with tumor plate thickness (Figure 14).

Images for this section:

- Main factor suggested to affect washout pattern of aHCC in the trabecular group
  - In our results, there were close correlations between histological grade, tumor plate thickness, and aHCC washout pattern. The PTSA was consistent regardless of the washout pattern or tumor plate thickness. In consequence, aHCC with a thicker tumor plate is thought to have a wider tumor sinusoid. On the other hand, aHCCs with thinner tumor plates and better histological grades should have larger numbers of thinner tumor sinusoids. The theory of flow dynamics called the Hagen-Poiseuille equation supports our results clearly (reference 10). The volumetric flow rate is in inverse proportion to the biquadrate of the radius.

![Diagram showing washout patterns and tumor structures](image)

**Fig. 1:** Main factor suggested to affect washout pattern of aHCC in the trabecular group.
References


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