
Takafumi Sato¹, Junichi Arita², Yosuke Inoue¹, Rintaro Koga¹, Yu Takahashi¹, Akio Saiura¹,*

¹ Department of Gastroenterological Surgery, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan;
² Hepato-Biliary-Pancreatic Division, Department of Surgery, The University of Tokyo, Tokyo, Japan.

Summary
Preoperative evaluation of liver functional reserve is important in hepatobiliary surgery. Although the indocyanine green retention rate at 15 minutes (ICG-R15) is the gold standard for this purpose, a new method without technical complexity would be preferable. We assessed the usefulness of the previously established index of convexity (IOC). In total, 159 consecutive patients who underwent both technetium-99m-galactosyl human serum albumin (⁹⁹mTc-GSA) scintigraphy and the ICG-R15 were included. Correlation coefficients between indices from ⁹⁹mTc-GSA scintigraphy and blood examinations including ICG-R15 were evaluated, and a conversion formula from the IOC to the ICG-R15 was established. The IOC showed a significantly stronger correlation with the ICG-R15 (r = −0.532, p < 0.001) than the index of blood clearance (HH15) and the receptor index (LHL15). A formula for estimating ICG-R15 from IOC was “ICG-R15 = −31.0 × IOC + 30.1”. In conclusion, the IOC is a better index for evaluating preoperative liver functional reserve than the conventional indices. A formula for estimating ICG-R15 from the IOC will be useful.

Keywords: Preoperative assessment, liver function, hepatectomy, GSA scintigraphy

1. Introduction
Preoperative evaluation of liver functional reserve is important to predict severe complication after hepatectomy, which has been more enhanced because the indication for hepatic resection has been expanded along with the development of surgical techniques and perioperative management protocols (1-5). Among many indicators of liver functional reserve (3,4,6-13), the indocyanine green retention rate at 15 minutes (ICG-R15) is the gold standard technique (1,14,15). However, the patients should be rested for 2 to 3 hours in a horizontal position and the pretest fasting is necessary before ICG-R15 test, which usually necessitates hospitalization of the patients. Moreover, the technique of ICG-R15 test is somewhat complex because three times of blood sampling after injecting ICG should be performed accurately with time-lag less than a few seconds. Additionally, the results can be inconclusive in patients with obstructive jaundice or congenital ICG excretory defects (16). Another auxiliary or even alternative examination for estimating the liver functional reserve is desired.

Technetium-99m diethylenetriamine-penta-acetic acid-galactosyl human serum albumin (⁹⁹mTc-GSA) scintigraphy is one of the prevalent examinations performed for evaluation of liver functional reserve (17-25). Conventional indices of ⁹⁹mTc-GSA scintigraphy, namely the blood clearance index (HH15) and the receptor index (LHL15), use accumulation counts of only two time points. The index of convexity (IOC) was proposed by Miki et al. (26) as a novel alternative to...
HH15 and LHL15. The IOC is calculated from hepatic accumulation counts on GSA scintigraphy at three fixed time points, surrogating the convexity of the hepatic accumulation curve of GSA scintigraphy. This index was created based on data obtained in patients, most of whom (68.5%) had hepatocellular carcinoma. However, more and more patients with liver metastases from colorectal carcinoma undergone hepatic resection thanks to advent of preoperative chemotherapy. In this study, we assessed the usefulness of the IOC utilizing a patient cohort including many patients with colorectal liver metastases. In addition, we propose a new conversion formula from the IOC to the ICG-R15.

2. Materials and Methods

2.1. Patients and data collection

A total of 159 consecutive patients underwent both $^{99m}$Tc-GSA scintigraphy and ICG-R15 test within one month before hepatic resection from June 2011 to October 2012 at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. Two patients who were diagnosed with constitutional ICG excretory defect were excluded from the study. The $^{99m}$Tc-GSA scintigraphy was incorporated into the routine preoperative examination in our hospital from 2011 after private communication with the creator of this index; the index was published in the literature in 2013 (26). The IOC, ICG-R15, and other clinical data were collected from a retrospective review of the clinical records. The indices calculated from $^{99m}$Tc-GSA scintigraphy were HH15, LHL15, and IOC. The serum levels of total bilirubin (T-Bil), direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), choline esterase, albumin (Alb), transthyretin (TTR), total cholesterol (T-Cho), prothrombin time-international normalized ratio (PT-INR), and platelet count (Plt) were determined after admission. Histopathological examination of the noncancerous part of the resected liver was performed to estimate liver impairment.

2.2. $^{99m}$Tc-GSA scintigraphy

After intravenous injection of 3 mg of $^{99m}$Tc-GSA (1 ml, 185 MBq; Nihon Medi-Physics Co., Ltd., Nishinomiya, Japan), dynamic images were recorded with the patient in the supine position using a gamma camera (Infinia 3; GE Healthcare, Chicago, IL, USA) under a large field of view. Digital images were acquired at the rate of 30 seconds per frame until 30 minutes after the injection. The regions of interests (ROIs) were determined by specialized medical engineers. The radiation counts obtained from the ROIs for the whole liver and heart were recorded at each time point. The data were processed on a workstation (GENIE Xeleris, version 3.1; GE Healthcare).

2.3. IOC

The IOC was calculated as $[L(15) \times 2 - L(3) - L(27)] / [(L(27) - L(3))$, the HH15 was calculated as $H(15) / H(3)$, and the LHL15 was calculated as $L(15) / [L(15) + H(15)]$, where $L(t)$ and $H(t)$ indicate the radiation counts at $t$ minutes after $^{99m}$Tc-GSA injection within the whole liver and whole heart, respectively. This index is a surrogate for the numerical index of the convexity of the curve of liver radiation counts until 27 minutes after injection (26). The IOC was devised using line ratio: the ratio of each distance between the midpoint of $L(3)$ and $L(27)$ to $L(15)$ (Figure 1A) and the midpoint of $L(3)$ and $L(27)$ to $L(27)$ (Figure 1B).

2.4. Statistical analysis

The correlation between the indices from $^{99m}$Tc-GSA scintigraphy and all other indices were analyzed using Spearman’s rank correlation coefficient test as a nonparametric test. A linear model was calculated by simple and multiple regression analyses with a stepwise method using significant $p$ values. Subanalyses comparing liver functional indices were performed after the division of the patients into the following groups: first and repeat hepatectomy groups, non-chemotherapy and chemotherapy groups, and non-cirrhosis and cirrhosis groups. The correlations among the indices were also analyzed using Spearman’s rank correlation coefficient test. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Statistical significance was established at $p < 0.05$

3. Results

3.1. Patient characteristics

Table 1 shows the background of the patients.
Preoperative chemotherapy was performed in 32% and a repeat hepatectomy (i.e., second time or more) was performed in 19% of all patients. 55% of all patients had liver metastasis, 33% had hepatocellular carcinoma, and 11% had cholangiocarcinoma. Among 87 patients with liver metastasis, colorectal carcinoma was the origin of the liver metastasis in 73 patients (84%). Of these 73 patients, preoperative chemotherapy was administered to 51 patients: 5-fluorouracil, leucovorin, plus oxaliplatin (FOLFOX) in 23 patients, capecitabine plus oxaliplatin (CapeOX) in 11, capecitabine in 6, 5-fluorouracil, leucovorin, plus irinotecan (FOLFIRI) in four, and other regimens in seven. Molecular target drugs were used in 31 patients: anti-vascular endothelial growth factor antibody (bevacizumab) in 18 and anti-epidermal growth factor receptor antibody (cetuximab or panitumumab) in 11.

Postoperative histopathological examination of the noncancerous part of the resected liver revealed normal liver in 119 patients, fatty liver in 4, chronic hepatitis in 10, and liver cirrhosis in 26. The cirrhosis group included patients with liver cirrhosis and chronic viral hepatitis, and the non-cirrhosis group included the remaining patients with normal and fatty liver (Table 1).

3.2. Correlation between the GSA scintigraphy indices and other indices

Scatter diagrams of the ICG-R15 and each index obtained from 99mTc-GSA scintigraphy, namely, IOC, HH15, and LHL15, in all patients group are shown in Figure 2. Scatter diagrams of subgroups are shown in Figure 3. Table 2 shows the correlation coefficients between the indices obtained from 99mTc-GSA scintigraphy and other indices. The IOC showed the strongest correlation ($r = -0.532, p < 0.01$) to ICG-R15 compared with HH15 ($r = 0.336, p < 0.01$) and LHL15 ($r = -0.348, p < 0.01$). This trend was seen in all subgroups except the cirrhosis group. The IOC showed the strongest correlation to most of other indices (total bilirubin, direct bilirubin, choline esterase, albumin, transthyretin, and Plt). Non-chemotherapy group and cirrhosis group showed stronger correlation coefficients between IOC and ICG-R15 ($r = -0.605, p < 0.001$; $r = -0.600, p < 0.001$). In the chemotherapy group and repeat hepatectomy group, only the IOC showed a significant correlation with the ICG-R15. ICG-R15 and Plt showed stronger correlation coefficients ($r = 0.532, p < 0.01$; $r = 0.496, p < 0.01$) to the IOC followed by TTR ($r = 0.420, p < 0.01$).

3.3. Linear regression equation and conversion formula

Based on a simple linear regression analysis, a conversion formula estimating ICG-R15 value from the IOC value was generated: "ICG-R15 = −30.4 × IOC + 29.8" ($r = -0.605, p < 0.001$; $r = -0.600, p < 0.001$). In the chemotherapy group and repeat hepatectomy group, only the IOC showed a significant correlation with the ICG-R15. ICG-R15 and Plt showed stronger correlation coefficients ($r = 0.532, p < 0.01$; $r = 0.496, p < 0.01$) to the IOC followed by TTR ($r = 0.420, p < 0.01$).

4. Discussion

In this study, the IOC showed a significant correlation with the ICG-R15, which is the current gold standard test for estimating liver functional reserve. The IOC is a surrogate for the curve convexity of continual hepatic radiation counts during 30 minutes following
the injection (26), of which the calculation is so complicated. This novel index uses only three hepatic radiation counts at 3, 15, and 27 minutes after injection, respectively. A larger IOC value indicates that $^{99m}$Tc-GSA accumulates in the liver more rapidly and the curve of the radiation counts reaches to a plateau faster, meaning higher hepatic capacity of uptake.

The correlation coefficients between ICG-R15 and the IOC were significantly stronger than the conventional indices of HH15 and LHL15. The calculation of the IOC incorporates three radiation counts at different time points, while that of HH15 incorporates two counts. The IOC utilizes more information obtained from the scintigraphy than HH15, thus may be superior to HH15. The calculation of LHL15 incorporates a hepatic radiation count and a heart radiation count only at single time point of 15 minutes, respectively, so that IOC may be superior to LHL15 from the similar viewpoint. Furthermore, both HH15 and LHL15 use radiation counts from the heart, of which the ROI usually includes not only the heart but also the liver because the two organs are tightly adjacent. This inaccuracy of measuring

---

**Figure 2. Scatter diagrams of the ICG-R15 and the indices of $^{99m}$Tc-GSA scintigraphy.** ICG-R15: indocyanine green retention rate at 15 min, GSA: galactosyl human serum albumin.

**Figure 3. Scatter diagrams of the ICG-R15 and IOC for each subgroup.** ICG-R15: indocyanine green retention rate at 15 min, IOC: index of convexity, First: first hepatectomy, Repeat: repeat hepatectomy, Chemo: preoperative chemotherapy, Normal: normal liver in noncancerous area of the liver, Cirrhosis: liver cirrhosis in noncancerous area of the liver.
of the radiation count may cause the difference. Another possible reason for the difference would be difference of the mechanisim. The IOC focuses on the change of the rate of material uptake, while the HH15 indicates clearance rate of the material from the blood pool, and the LHL15 indicates the proportion of hepatic uptake to all injected material at one time point.

In the present study, the most common cause for hepatectomy was liver metastasis (54%), and preoperative chemotherapy was performed in as many as 59% of these patients. The IOC was initially devised as 59% of these patients. The IOC was initially devised to consider the each cause and medical history, and perhaps other hand, chemotherapy group showed the lowest correlation coefficient between IOC and ICG-R15 in cirrhosis group was stronger than most other subgroups, which is consistent with the previous report. On the other hand, chemotherapy group showed the lowest correlation value. This trend may be because various regimens of chemotherapy were performed according to the each cause and medical history, and perhaps because small sample size. Further analysis utilizing a large number of patients undergoing chemotherapy is not significant.

---

**Table 2. Correlation coefficients between the indices obtained from GSA scintigraphy and blood tests**

<table>
<thead>
<tr>
<th>Items</th>
<th>All Patients (n = 159)</th>
<th>Non-chemotherapy, First heptatectomy, and Non-cirrhosis Group (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOC</td>
<td>ICG-R15</td>
<td>ICG-R15</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>HH15 p</td>
</tr>
<tr>
<td>ICG-R15</td>
<td>0.352</td>
<td>0.336</td>
</tr>
<tr>
<td>T-Bil</td>
<td>0.349</td>
<td>0.321</td>
</tr>
<tr>
<td>D-Bil</td>
<td>0.372</td>
<td>0.350</td>
</tr>
<tr>
<td>Cho-E</td>
<td>0.343</td>
<td>0.321</td>
</tr>
<tr>
<td>Alb</td>
<td>0.323</td>
<td>0.300</td>
</tr>
<tr>
<td>TTR</td>
<td>0.242</td>
<td>0.210</td>
</tr>
<tr>
<td>Plt</td>
<td>0.242</td>
<td>0.210</td>
</tr>
</tbody>
</table>

**Figure 4. Simplified diagram of conversion formula from IOC to ICG-R15 in the first heptatectomy group.** IOC: index of convexity, ICG-R15: indocyanine green retention rate at 15 min.
necessary.

The correlation coefficients were worse in the repeat hepatectomy group than in the first hepatectomy group. A possible cause for this is the deformity of the liver shape after the preceding hepatectomy; setting of ROI during 99mTc-GSA scintigraphy may be difficult in some cases. The ROI setting should be confirmed if the IOC value showed discrepancy with expected one in the patients who had undergone hepatectomy.

In the chemotherapy group, the correlation coefficients were unsatisfactory. Sinusoidal obstructive syndrome (SOS) and chemotherapy-associated steatohepatitis (CASH) are well-known side effects of chemotherapy affecting liver functional reserve (27-29). SOS is characterized by obstruction of a central vein within a sinusoid, and CASH is caused by a metabolic disorder. The IOC indicates the rate of the material uptake and its alteration, while the ICG-R15 indicates the clearance of the material from the blood pool, deeply influenced by the velocity of portal venous flow. This difference of mechanisms may be the key for explaining this discrepancy and, perhaps, either of the two examinations may be superior to the other in patients undergoing chemotherapy. This should be further confirmed utilizing data including postoperative complication.

We created a conversion formula for estimating the ICG-R15, which so far is the gold standard for estimating liver functional reserve. Because the liver functional reserve is so complicated that no one can precisely define this term, the liver surgeons should decide surgical indication and plan for hepatic resection referring to not only ICG-R15 but also other indices. A conversion formula from the IOC value to the ICG-R15 value may be useful in comparison to ICG-R15 value. Moreover, in patients with congenital ICG excretory defect or those with portosystemic shunt, this formula may be more enhanced in estimating the liver functional reserve.

In conclusion, the IOC is superior to the conventional index obtained from 99mTc-GSA scintigraphy in terms of evaluating liver functional reserve. A conversion formula from the IOC to ICG-R15 is proposed for further utility in preoperative patient management.

Acknowledgements

We are grateful to Dr. Kenji Miki from the Department of Gastrointestinal Surgery of JR Tokyo General Hospital for his presentation of the research data and explanation of the concept and calculation method of the index of convexity before publication of his report.

References

15. Takamoto T, Hashimoto T, Sano K, Maruyama Y,


(Received January 19, 2017; Revised March 17, 2017; Accepted April 2, 2017)