ICG Clearance Test and 99mTc-GSA SPECT/CT Fusion Images

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Keywords

Liver function · Indocyanine green · GSA SPECT

Summary

Preoperative estimation of future remnant liver function is critical for major hepatic surgery to avoid postoperative morbidity and mortality. Among several liver function tests, the indocyanine green (ICG) clearance test is still the most popular dynamic method. The usefulness of ICG clearance test parameters, such as $ICGR_{15}$, K_{ICG} , or PDR_{ICG} , has been reported by many investigators. The transcutaneous non-invasive pulse dye densitometry system has made the ICG clearance test more convenient and attractive, even in Western countries. The concept of future remnant K_{ICG} (rem K_{ICG}), which combines the functional aspect and the volumetric factor of the future remnant liver, seems ideal for determining the maximum extent of major hepatic resection that will not cause postoperative liver failure. For damaged livers with functional heterogeneity among the hepatic segments, fusion images combining technetium-99m-diethylenetriaminepentaacetic acid-galactosyl human serum albumin single photon emission computed tomography (99mTc-GSA SPECT) and X-ray CT are helpful to precisely estimate the functional reserve of the future remnant liver. Another technique for image-based liver function estimation, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid(Gd-EOB)-enhanced magnetic resonance imaging, may be an ideal candidate for the preoperative determination of future remnant liver function. Using these methods effectively, morbidity and mortality after major hepatic resection could be reduced.

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Introduction

The preoperative estimation of future remnant liver function is essential for extensive liver resection to avoid postoperative morbidity and mortality. Estimation of remaining liver volume is the first step in creating a surgical plan. The hepatic circulation-based 3-dimensional (3D) hepatectomy simulation system, which was first reported in 2005, has largely contributed to the accurate assessment of the remaining liver volume [1]. This kind of computer-assisted volumetry allows the precise calculation of either the ratio of remnant liver volume to total liver volume (RLV/TLV) or the ratio of remnant liver volume to body weight (RLV/BW). Using these ratios, several investigators have reported safe thresholds to prevent postoperative liver failure in non-cirrhotic patients [2–4]. However, a more cautious assessment of the functional aspects of remnant liver is required in patients with underlying liver disease such as cirrhosis, or in patients with impaired liver function due to chemotherapy for liver metastasis from colorectal cancer [5, 6]. In addition, portal vein embolization (PVE) or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) have been employed for extensive liver resection to avoid postoperative complications by inducing hypertrophy of the future remnant liver. In these methods, especially in ALPPS, a discrepancy between the volumetric increase and the functional improvement in the future remnant liver has been reported [7–9].

For the assessment of preoperative liver function, static and dynamic tests are available. The Child-Turcotte-Pugh (CTP) [10, 11] and model for end-stage liver disease (MELD) [12, 13] scoring systems are well-known methods for the static assessment of liver function and are useful for predicting postoperative morbidity and mortality [14–17]. However, static laboratory tests are sometimes insensitive at predicting postoperative liver functional reserve. Thus, dynamic liver function tests have been used in deciding about the operability of patients with underlying liver disease. The preoperative estimation of future remnant liver function is especially critical in patients with functional heterogeneity among the

Table 1. Indocyanine green (ICG) clearance test parameters in the assessment of hepatic function

	Description	Calculation	Unit
ICGR15	ICG retention ratio after 15 min	$(C_{\text{ICG}(15)} / C_{\text{ICG}(0)}) \times 100$	%
K_{ICG}	rate constant (k) of ICG indicator-dilution curve	$C_{\text{ICG}(t)} = C_{\text{ICG}(0)} \times e^{-kt}$	min^{-1}
PDR_{ICG}	plasma disappearance rate of ICG	$K_{\text{ICG}} \times 100$	$\% \text{ min}^{-1}$
$C_{\text{ICG}(t)}$ = ICG concentration at time point t [34]; k = fractional ICG concentration change per minute; e = Euler's number.			

hepatic segments. Thus, for the evaluation of the effectiveness of PVE or ALPPS, dynamic liver function tests which can estimate spatial functional distribution in the liver are required. Among several dynamic tests, the indocyanine green (ICG) clearance test and fusion images of technetium-99m-diethylenetriaminepentaacetic acid-galactosyl human serum albumin single photon emission computed tomography (99mTc-GSA SPECT)/X-ray computed tomography (CT) are discussed in this review.

ICG Clearance Test

The ICG clearance test has been the most popular dynamic liver function test, especially in Eastern countries. ICG is a non-toxic, inert, anionic water-soluble tricarboxyanide dye, first introduced by Fox and Brooker for the assessment of cardiac output [18]. Soon after, the usefulness of this dye for assessing liver function and hepatic blood flow was reported by several investigators [19, 20]. ICG administered intravenously is almost exclusively extracted by the liver, and its elimination is dependent on hepatocyte function, liver blood flow, and bile secretion. Thus, the ICG clearance test is considered to accurately correlate with hepatic function and has been widely used in clinical settings in Eastern countries for a long time.

The standard method for quantifying hepatic ICG clearance is ex-vivo photometric analysis of consecutive blood samples obtained within a 15-min frame after intravenous bolus injection [19, 20]. The absolute clearance of ICG or the fractional change per minute can be calculated from a concentration-time curve obtained. This method is accurate and reproducible, but has not been widely adopted in Western countries because of its invasiveness and complexity. Transcutaneous non-invasive pulse dye densitometry (PDD), which was first invented by Aoyagi who is also known for the invention of pulse oximetry [21, 22], is now commercially available in both Western and Eastern countries. Two PDD systems for the ICG clearance test are available: the LiMON device (Pulsion Medical System, Munich, Germany) and the DDG-3000 analyzer (Nihon-Kohden, Tokyo, Japan). Both devices calculate ICG retention 15 (ICGR15; the ICG retention ratio after 15 min) and the rate constant (k) of the indicator-dilution curve using backward dynamic extrapolation (K_{ICG}). The k value is then multiplied by 100 to obtain the plasma disappearance rate of ICG (PDR_{ICG}). Acceptable accuracy of the PDD system has been reported after comparing data derived from invasive and non-invasive methods [23–27]. These non-invasive PDD systems have made

the ICG clearance test more attractive even in Western countries, and many investigators have recently reported its usefulness as a non-invasive dynamic liver function test [28–31].

ICGR 15

ICGR15 is the ratio between the ICG concentration 15 min after injection and the initial concentration; $\text{ICGR15} (\%) = C_{\text{ICG}(15)} / C_{\text{ICG}(0)} \times 100$ (table 1). ICGR15 has been widely used as an alternative to K_{ICG} or PDR_{ICG} because of its relative convenience. K_{ICG} or PDR_{ICG} require serial blood sampling and ex-vivo photometric analysis using a standard invasive method, while ICGR15 can be calculated from one-point sampling at 15 min. Clinical data concerning preoperative ICGR15 and postoperative liver failure have been accumulated from the early 1980s [32–38], and a decision tree for the hepatectomy procedure, which includes ICGR15 as a parameter in addition to the presence or absence of ascites and the serum total bilirubin level, has been proposed [39]. Very low mortality has been reported using the decision tree for the hepatectomy procedure [40], and the use of ICGR15 was recommended for the preoperative assessment of liver function in the evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan [41].

PDR_{ICG} or K_{ICG}

The plasma disappearance rate of ICG (PDR_{ICG} ; % per minute) is the percentage change over the time of the reduction in ICG blood concentration starting from a concentration of 100%. The rate constant (k) of the ICG indicator-dilution curve (K_{ICG}) can be calculated using backward dynamic extrapolation of the elimination phase $C_{\text{ICG}}(t) = C_0 \times e^{-kt}$. The k value is then multiplied by 100 to obtain the PDR_{ICG} as a percentage per minute (table 1). K_{ICG} or PDR_{ICG} have been thought to reflect the pharmacokinetics of ICG more accurately than ICGR15 because the former require multiple sampling time points. However, K_{ICG} or PDR_{ICG} had not been widely used worldwide, except in Japan, because of the complexity of the method. After the non-invasive PDD systems became commercially available, many investigators reported the usefulness of these parameters to assess perioperative liver function [30] and even more so to predict the prognosis of critically ill patients [42–45].

Rem K_{ICG}

The preoperative estimation of liver function employing ICGR15, PDR_{ICG} , or K_{ICG} is important for obvious reasons. How-

ever, how well the future remnant liver will actually function after hepatic resection is a much more interesting issue for liver surgeons. Namely, it is critical to assess the maximum extent of major hepatic resection that will not cause postoperative liver failure. The concept of future remnant K_{ICG} (rem K_{ICG}), which is calculated from the preoperative K_{ICG} and the proportion of the future remnant liver volume to the whole functional liver parenchymal volume (rem K_{ICG} = preoperative K_{ICG} $\times$ proportion of the future liver remnant), was first proposed by Takasaki et al. [32]. This concept of combining the functional aspect and the volumetric factor of the liver seems ideal for predicting postoperative liver function after extended liver resection, despite its complexity. Takasaki et al. [32] proposed that rem K_{ICG} > 0.062 is a safety threshold for postoperative mortality [32]. Other investigators also reported that postoperative morbidity was low in patients with rem K_{ICG} > 0.06 after a major hepatectomy [46], or that rem K_{ICG} $\geq$ 0.05 was a threshold for survival in patients with bile duct cancer who underwent preoperative PVE [47]. More recently, on the basis of statistical analysis, a rem K_{ICG} of 0.05 has been again reported as a useful cut-off value for predicting mortality and morbidity in patients with biliary cancer [48, 49]. On the other hand, morbidity was 100% in a rem K_{ICG} range of < 0.03 [46], indicating that in patients with rem K_{ICG} below 0.03 liver resection is contraindicated.

After the non-invasive PDD systems became available and a real-time and rapid ICG clearance test was possible, intraoperative estimation of remnant liver function by trial clamping of selective arterial and portovenous inflow was reported [29, 50, 51]. In addition, early prediction of postoperative liver dysfunction using real-time PDR_{ICG} has also been proposed after major liver resection [30, 52] or liver transplantation [53–55]. Recent advances in the 3D CT volumetric system in combination with non-invasive PDD systems have made accurate calculation of rem K_{ICG} easier. Thus, the non-invasive ICG clearance test has become a more attractive and convenient modality.

Limitations of the ICG Clearance Test

The ICG clearance test is a reliable dynamic liver function test but has some limitations. First, ICG elimination should be interpreted with caution in patients with cholestasis. Bilirubin and ICG competitively bind to the same organic anion transporting polypeptides such as 1B3 (OATP 1B3) [56], possibly leading to a reduced uptake of ICG in patients with obstructive jaundice. This condition could also be observed in the early postoperative period after liver transplantation in patients with pretransplant hyperbilirubinemia. The usefulness of the LiMAx test, another dynamic liver function test, is also reported in Western countries [8, 57, 58]. The LiMAx test evaluates whole liver function, detecting the $^{13}\text{CO}_2/^{12}\text{CO}_2$ ratio in expired air, which depends on the rate of metabolism of ^{13}C -methacetin by P450 1A2 (CYP1A2) in hepatocytes [57]. While LiMAx, as a whole liver function test, is similar to the ICG clearance test, it can be used independent of cholestasis. However, the LiMAx test requires specialized equipment to detect ^{13}C , and is expensive. Therefore, it should be cautiously observed whether the LiMAx test really possesses significant advantage over

the ICG clearance test. Portal flow is also an important factor affecting ICG clearance. In patients with giant splenorenal shunt, specifically decreased ICG clearance values are often observed compared to other liver functional parameters. In patients with constitutional ICG excretory defect [59], the ICG clearance test is also not efficient.

GSA-SPECT Fusion Image

The ICG clearance test is still a gold standard dynamic method to assess liver function as mentioned above. Rem K_{ICG} , which combines the volumetric factor of the remnant liver and ICG pharmacokinetics, is an ideal concept in a situation where the functional distribution is supposed to be homogeneous throughout the liver. However, functional heterogeneity among the hepatic segments often exists in a damaged liver, cirrhotic liver, liver after PVE, or liver with portal tumor thrombus. Such situations require other dynamic liver function tests that can estimate spatial functional distribution in the liver.

The asialoglycoprotein receptor (ASGPR) is located on the sinusoidal surface of hepatocytes and is involved in the clearance of glycoproteins containing terminal galactose residues from the circulation [60]. Vera et al. [61–63] first reported ASGPR-mediated binding of ^{99m}Tc -galactosyl-neoglycoalbumin (^{99m}Tc -NGA) in vitro and in vivo. In addition, a decrease in hepatic ASGPR expression has been reported in patients with liver damage [64]. Thus, analysis of ASGPR expression has been widely performed using ^{99m}Tc -GSA, an analog of asialoglycoproteins, to estimate liver function in damaged livers [65–69]. For example, a receptor index parameter (LHL15), obtained from the liver and heart time-activity data as the ratio of radioactivity of the liver over that of the liver plus heart at 15 min after intravenous injection of Tc-GSA correlated well with classical indicators for hepatic functional capacity such as the serum albumin level, serum bilirubin level, prothrombin time, ICGR15, or CTP criteria score [65, 70].

Moreover, ^{99m}Tc -GSA SPECT, which enables the evaluation of regional GSA accumulation in the liver, was developed to precisely investigate the regional distribution of hepatic function [71–73]. There are several ^{99m}Tc -GSA SPECT parameters such as the liver uptake ratio (LUR) [74, 75], liver uptake density [74, 76], liver uptake value corrected for body surface area (LUV) [77], or uptake index [78, 79]; all these parameters basically depend on the regional strength of radioactivity in the liver. The parameter LUR correlates well with the extent of ASGPR expression immunohistochemically evaluated, and a parallel decrease in LUR and ASGPR protein expression was observed in the fibrotic liver [80]. It is noteworthy that functional heterogeneity among hepatic segments has been reported in damaged liver by employing ^{99m}Tc -GSA SPECT [72, 81, 82], suggesting its usefulness for the precise prediction of postoperative hepatic functional reserve in the damaged liver.

Recent advances in X-ray CT systems, including 3D CT simulation [1], have made precise preoperative surgical planning for liver

resection easier. Therefore, fusion images combining ^{99m}Tc -GSA SPECT and X-ray CT could be critically helpful for preoperative surgical decision making [80, 83–86]. Accordingly, future remnant liver function has been estimated on the fusion images, calculating the strength of radioactivity in the future remnant hepatic area (fig. 1), and expressed as remnant LUR [80], remnant LUV [87], R0-remnant [83], or functional hepatic resection rate (FURR) [86]. Even though these methods have not been widely accepted in clinical practice worldwide because of their complexity, they are especially useful in patients with regional heterogeneity of liver function, that is, patients who undergo preoperative PVE for insufficient remnant liver volume [7, 74, 88] or who receive bile duct drainage for obstructive jaundice due to bile duct cancer [89]. In these contexts, ^{99m}Tc -GSA SPECT/X-ray CT fusion images are supposed to be useful for the evaluation of the effectiveness of ALPPS in terms of hepatocyte proliferation and function in the future remnant liver.

In European countries, hepatobiliary scintigraphy (HBS) using ^{99m}Tc -mebrofenin is often employed to estimate spatial functional distribution in the liver [90–94]. Upon intravenous administration, ^{99m}Tc -mebrofenin is extracted exclusively by the hepatocytes, and excreted in the bile via the ATP-dependent export pump. The transporter of ^{99m}Tc -mebrofenin and ICG partially overlaps [56]. Thus, ^{99m}Tc -mebrofenin HBS relies on pharmacokinetics similar to those of the ICG clearance test, and is mechanistically completely different from ^{99m}Tc -GSA SPECT. From the view point of the increase in the number of hepatocytes, ^{99m}Tc -GSA SPECT may possibly be more suitable for evaluating functional improvement in the future remnant liver after PVE or ALPPS.

Fusion images combining ^{99m}Tc -GSA SPECT and X-ray CT are a theoretically rational method, and its clinical usefulness has been reported as mentioned above. However, this method has not been in widespread use in Western countries because of its complexity and equipment requirements. Another technique for image-based liver function estimation, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI), could be an ideal candidate for the preoperative determination of liver function [95]. Gd-EOB-enhanced MRI can display regional liver function with good spatial resolution, which is critically useful for preoperative surgical decisions. For the evaluation of its usefulness as a liver functional test, the best conditional setting and the interpretation of the acquired data are currently under investigation [76].

Fig. 1. Fusion images combining X-ray computed tomography (CT) and technetium- 99m -diethylenetriaminepentaacetic acid-galactosyl human serum albumin single photon emission computed tomography (^{99m}Tc -GSA SPECT). The strength of radioactivity in the future remnant liver can be accurately estimated on the fusion images (lower) combining X-ray CT (upper left) and ^{99m}Tc -GSA SPECT (upper right).

Conclusion

The ICG clearance test remains the most popular dynamic liver function test and has become a more convenient method after non-invasive PDD systems were made available. According to safety criteria employing ICGR_{15} , PDR_{ICG} , or K_{ICG} , morbidity and mortality after major hepatic resection can be reduced. For patients with functional heterogeneity among the liver segments, fusion images combining ^{99m}Tc -GSA SPECT and X-ray CT are useful to precisely predict future remnant liver function. Gd-EOB-enhanced MRI could also become an ideal candidate for imaging-based liver function tests.

Disclosure Statement

The author declares that he has nothing to disclose representing a potential conflict of interest with respect to this manuscript.

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