



Title	Postoperative assessment of donor's hepatic asialoglycoprotein receptor function using Tc-99m GSA scintigraphy in living donor liver transplantation [an abstract of dissertation and a summary of dissertation review]
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Citation	北海道大学. 博士(医学) 甲第11666号
Issue Date	2015-03-25
Doc URL	http://hdl.handle.net/2115/59102
Rights(URL)	http://creativecommons.org/licenses/by-nc-sa/2.1/jp/
Type	theses (doctoral - abstract and summary of review)
Note	配架番号 : 2148
Additional Information	There are other files related to this item in HUSCAP. Check the above URL.
File Information	Kentaro_Kobayashi_abstract.pdf (論文内容の要旨)



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学位論文内容の要旨

博士の専攻分野の名称 博士 (医 学) 氏名 小林 健太郎

学 位 論 文 題 名

Postoperative assessment of donor's hepatic asialoglycoprotein receptor function using Tc-99m GSA scintigraphy in living donor liver transplantation
(Tc-99m GSA シンチグラフィを用いた生体肝移植ドナーにおける術後のアシアロ糖タンパク受容体機能評価に関する研究)

【Background】

Living donor liver transplantation is an established surgical approach to treat patients with severe hepatic disorders. Despite technical advances and accumulated experience with liver resection, living liver donation is associated with size-dependent complications. Scintigraphy using technetium-99m-diethylenetriaminepentaacetic acid-galactosyl-human serum albumin (Tc-99m GSA) is a widely used for in-vivo imaging to quantify liver function.

The purpose of Chapter 1 was to determine if the current partial hepatectomy procedures are completed under the safety margin of the resectable size, by measuring asialoglycoprotein receptor (ASGPR) function of donor's remnant liver. In chapter 2, I will show the chronological data of liver volume and GSA scintigraphy, and propose a hypothesis regarding liver regeneration potential.

Chapter1

【Methods】

Seventy-four living donors (35 ± 11 yrs old, ranging from 18 to 62) underwent Tc-99m GSA scintigraphy at 1 postoperative week (1POW). There were 3 types of hepatectomy: left lobe hepatectomy (n=46), lateral lobe hepatectomy (n=11), and right lobe hepatectomy (n=17). We evaluated the scintigraphic results using established parameters of GSA clearance from the blood pool (HH15). Based on the literature, we consider $HH15 < 0.55$ to indicate normal ASGPR function, and $0.55 \leq HH15 < 0.65$ to mild impairment. We analyzed the sizes of the resected livers calculated using computed tomography in relation to ASGPR function and the regeneration volume of the donors' residual liver.

【Results】

The average resected size was 337 ± 170 mL, corresponding to $28 \pm 12\%$ of the original donor's whole liver volume. No donors showed $0.65 \leq HH15$, suggesting moderate or severely impaired ASGPR function. However, larger resection size (35–53%) was positively associated with higher HH15 values ($R=0.53$, $p<0.001$). In the range of HH15 (0.35–0.64) among present donors, higher HH15 values did not affect the regeneration volume ($R=0.03$, $p=NS$).

【Discussions】

Although the present results confirmed the safety of the partial hepatectomy of less than 54% of donors' original liver volume, it demonstrated mildly impaired ASGPR function in donors who underwent larger resection ($\geq 35\%$ of the original liver volume). This may indicate the need for careful postoperative attention to prevent significant life-threatening complications.

【Conclusion of chapter 1】

Liver dysfunction defined by GSA clearance was observed in 7/19 (37%) of larger resection group ($\geq 35\%$) and in only 2/55 (4%) of smaller resection group. Thus, we suggest that 35% may be the cut-off of safe hepatectomy.

Chapter 2

【Methods】

Forty-five donors (left lobe hepatectomy; n=28, lateral lobe hepatectomy; n=8, right lobe hepatectomy; n=9) underwent GSA scintigraphy four times after hepatectomy, including 1, 2, 4, and 12 POW. From ^{99m}Tc -GSA scintigraphy, Receptor density index (RDI) was calculated by liver uptake at 15 minutes (LU15) divided by remnant liver volume. The abdominal CT images were used to measure the liver volume.

【Results】

At 1-POW, RDI was significantly higher in right lobectomy group (0.00058 ± 0.00014 ml⁻¹) than in left lobectomy group (0.00027 ± 0.00007 ml⁻¹, $P < 0.0001$) and lateral lobectomy group (0.00033 ± 0.00009 ml⁻¹, $P < 0.0001$), indicating that right lobectomy group had the highest liver function per unit volume among three groups at 1-POW. Right lobectomy group then started to decrease in RDI until 2-POW and remained stable after 2-POW. Similar but less-steep trends were observed in the other groups (left lobectomy and lateral lobectomy groups). Correlation analysis was done between each time-point RDI vs. regenerated fraction. RDI at 1-POW was found to be most strongly associated with regenerated fraction ($R = 0.71$, $P < 0.0001$).

【Discussions】

We found that donors who underwent larger resection had a larger RDI. In addition, a larger RDI was associated with larger regenerated fraction of the liver. Since RDI is considered to represent ASGPR function per unit volume, these results suggested that the ASGPR function per unit volume is upregulated after hepatectomy. Also, the liver that has greater potential of proliferation has more active ASGRP receptor function per unit volume.

Because the current investigation was just a correlation analysis, the causal relationship is still unknown. In the orchestrated process of liver regeneration, little is known about the role of ASGRP. Many molecules, including interleukin (IL)-1, -6, tumor necrosis factor (TNF)- α , and hepatocyte growth factor (HGF), and many cells, including Kupffer cells, hepatic stellate cells and hepatic endothelial cells (HEC), are known to be involved in liver regeneration process.

It is known that HGF increases hepatic ^{99m}Tc -GSA uptake in a rodent model and that IL-1 and 6 promote ASGPR synthesis. Thus, it is reasonable that liver regeneration can be visualized indirectly and non-invasively by measuring ASGPR function using ^{99m}Tc -GSA scintigraphy.

We demonstrated that RDI is the parameter that can predict liver regeneration potential after hepatectomy of healthy donors. In clinical settings, however, it would be more useful if RDI can provide the information for patients.

【Conclusions of chapter 2】

Donors who underwent larger resection had a larger RDI, which was associated with larger regenerated fraction of the liver. Estimating ASGPR function using ^{99m}Tc -GSA and RDI may predict the liver regeneration potential.