Sex Dimorphism in the Outcome of Preoperative Right Portal Vein Embolization

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Hypothesis: Although studies indicate that patient sex modulates the process of hepatic regeneration, it remains unknown whether sex has a role in the outcome of preoperative right portal vein embolization (PVE). We analyzed the effects of patient sex on the outcome of right PVE followed by major hepatectomy.

Design: Retrospective study.

Setting: Academic research.

Patients: Eighty-eight patients (42 men and 46 women) who underwent preoperative right PVE for bile duct carcinoma were analyzed retrospectively.

Main Outcome Measures: The percentage liver volume change, the plasma indocyanine green clearance rate, and the rate of postoperative hepatic failure were compared between men and women.

Results: The mean (SD) volume of the nonembolized lobe after PVE in women (323 [61] mL/m²) was statistically significantly greater than that in men (287 [61] mL/m²) (P = .008). The mean (SD) ratio of the nonembolized lobe to the total liver volume was also statistically significantly greater in women (45.8% [5.8%]) than in men (42.0% [5.9%]) (P = .003). The mean (SD) indocyanine green clearance rate of the future liver remnant was 0.075 [0.014] in women and 0.056 [0.011] in men (P = .001). The incidence of postoperative hepatic failure was higher in men (12 of 42 [28.6%]) than in women (8 of 46 [17.4%]) (P = .16).

Conclusion: These results indicate that sex dimorphism can be present in the outcome of preoperative right PVE.

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Animal models have demonstrated that normal physiology and pathophysiology of the liver are different for males and females of the same species.1-8 Investigations have shown sex-dimorphic responses in various hepatic stress models, including ischemia-reperfusion,1 liver cirrhosis,2 alcoholic liver disease,3 and hemorrhagic shock and resuscitation.4,5 Female sex also has been shown to be associated with the pathogenesis of hepatic disorders in humans, such as adenoma,9 hepatoma,1 and focal nodular hyperplasia.8 The results of these studies indicate that there are different pathways in the hepatic pathophysiology between males and females.

Preoperative portal vein embolization (PVE) has been performed widely before extended hepatectomy for hepatoma,9 metastatic colorectal cancer,10 and bile duct carcinoma.11 After PVE, the nonembolized lobe enlarges because of hepatocyte hypertrophy and replication,12 which increases the safety of major hepatectomy. Post-PVE patients fared better than non-PVE patients for postoperative peak bilirubin concentrations, occurrence of liver failure, and prolonged hospital stay.13,14 Several pathologic conditions are known to affect the capacity of hepatic regeneration after PVE or partial hepatectomy. These include diabetes mellitus,15,16 malnutrition,17 aging,18 infection,19 chronic alcohol consumption,20 and biliary obstruction.21 Patient sex is another important factor that may have an effect on the process of hepatic regeneration. A clinical study by Imamura et al16 showed that male sex was a negative factor relative to the hepatic regeneration rate following PVE. This seems to be consistent with a study by Shan et al22 reporting that female sex is associated with better hepatic regeneration.
regeneration, although the model they used was a hepatectomy model and not a PVE model. However, no clinical study (to our knowledge) has, to date, specifically analyzed sex dimorphism in the outcome of hepatic regeneration after PVE. Therefore, the objective of this study was to determine whether there is a difference between male and female patients in the outcome of right PVE followed by major hepatectomy.

A previous PVE study included multiple types of disease such as hepatocellular carcinoma, colorectal liver metastasis, and bile duct carcinoma. Patients having hepatocellular carcinoma frequently exhibit cirrhosis, which may impair hepatic regeneration. The surgical procedure for colorectal liver metastasis is variable depending on the status of tumor spread. In contrast to these studies, we herein included only bile duct carcinomas that required right-sided hepatectomy. Liver function and the surgery performed were similar among all patients included in this study. The outcomes evaluated were clinical characteristics, volumetric computed tomography (CT) findings, the plasma indocyanine green (ICG) clearance rate, and the rate of postoperative hepatic failure.

**METHODS**

Preoperative right PVE and subsequent right hepatectomy were performed in 109 patients (55 men and 54 women) from May 1, 1991, to December 31, 2004, at Nagoya University Hospital, Nagoya, Japan. Of these, 21 patients (13 men and 8 women) were excluded from the study because of delayed postembolization CT longer than 21 days (11 cases), recanalization of the embolized portal vein after PVE (6 cases), or the absence of precise measurement data (4 cases). Therefore, 88 patients (42 men and 46 women) were included in the study.

Portal vein embolization was performed using an ipsilateral approach as previously described. Briefly, a catheter sheath was inserted into the anterior branch of the right portal vein under ultrasonographic guidance, and a 6F catheter was advanced into the target portal vein. Fibrin glue (Beriplast P; Hoechst Japan, Tokyo, Japan; or Bolheal; Fujisawa Pharmaceutical, Tokyo), mixed with iodized oil (Lipiodol; Kodama Pharmaceutical, Tokyo) or 100% ethanol, and microcoils were used as embolic material.

Serial transverse CT and ICG clearance tests were performed for each patient before and after PVE. The median interval between PVE and CT was 14 days (range, 7-21 days). The volumes of the embolized and nonembolized lobes were calculated using computer analysis for CT images. Borders between embolized and nonembolized lobes were determined before surgery by manual delineation in which the hepatic vessels were used as guides. To adjust for differences in liver volume between men and women, the volumes of the embolized and nonembolized livers were divided by the body surface area (BSA). The ratios of the embolized and nonembolized liver volumes to the total liver volume were calculated before and after PVE. Maximum serum total bilirubin concentrations within 3 weeks after hepatectomy were recorded, and a value of greater than 10 mg/dL (to convert bilirubin concentration to micromoles per liter, multiply by 17.104) was considered postoperative hepatic failure.

Comparisons of data among male vs female patients were made using the Mann-Whitney test for continuous variables and Fisher exact test for categorical data. Data before and after PVE were compared using paired t tests. P < .05 was considered statistically significant.

**RESULTS**

The demographics and clinical features of 88 patients stratified by sex are summarized in Table 1. The mean age was not statistically significantly different between male and female patients. Height, body weight, and BSA were statistically significantly greater in male patients than in female patients. At our institution, PVEs were performed mostly for biliary ductal malignant neoplasms, and no hepatocellular carcinoma or colorectal metastasis cases were included in this study. There were more cases of bile duct carcinoma among men and more cases of gallbladder cancer among women. More than 90% of all patients had undergone percutaneous transhepatic biliary drainage before surgery to relieve obstructive jaundice or to treat cholangitis. Portal vein embolization was performed after these symptoms had subsided. No patient had liver cirrhosis. The proportion of patients with cholangitis and diabetes mellitus, which are known to decrease liver proliferation capacity, was not statistically significantly different between men and women. The mean (SD) interval between PVE and CT was not statistically significantly different between men (13.4 [2.4] days; range, 8-20 days) and women (13.7 [3.2] days; range, 7-21 days) (P = .58).

Because the liver volume is proportional to the BSA, the liver volumes before and after PVE were normalized to the BSA and are given in Table 2. The average volume of the embolized lobe, nonembolized lobe (ie, left lateral and left medial lobes), and total liver were not different between male and female patients before PVE. The mean volume of the nonembolized lobe after PVE in female patients was statistically significantly greater than that in male patients (P = .008). Similarly, the proportion of the nonembolized lobe, expressed as a percentage of the total liver volume, was not statistically signifi-
male patients (statistically significantly higher in female patients than in male patients). The ICG clearance rate before PVE was significantly greater in female patients (10.8%) compared with male patients (8.9% [3.8%]), although the results were not statistically significantly different (P = .02).

Table 3. Plasma Indocyanine Green Clearance Rate (ICGK) and the Future Liver Remnant (FLR) ICGK

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Male Patients</th>
<th>Female Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-PVE</td>
<td>Post-PVE</td>
<td></td>
</tr>
<tr>
<td>Embolized lobe/BSA</td>
<td></td>
<td>63.0 (7.0)</td>
<td>50.2 (5.9)</td>
<td>.22</td>
</tr>
<tr>
<td>Nonembolized lobe/BSA</td>
<td></td>
<td>31.1 (6.6)</td>
<td>42.0 (5.9)</td>
<td>.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-PVE, %</td>
<td>Post-PVE, %</td>
<td></td>
</tr>
<tr>
<td>Embolized lobe</td>
<td></td>
<td>3.0 (2.0)</td>
<td>2.0 (2.0)</td>
<td>.07</td>
</tr>
<tr>
<td>Nonembolized lobe</td>
<td></td>
<td>3.0 (2.0)</td>
<td>2.0 (2.0)</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-PVE %</td>
<td>nonembolized lobe</td>
<td>.02</td>
</tr>
<tr>
<td>Embolized lobe/FLR ICGK</td>
<td></td>
<td>8.9 (3.8)</td>
<td>10.8 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Nonembolized lobe/FLR ICGK</td>
<td></td>
<td>1.9 (3.8)</td>
<td>3.0 (4.1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PVE, portal vein embolization.

We normally measure the plasma ICG clearance rate before and after PVE to evaluate the function of the future liver remnant. The ICG clearance rate before PVE was statistically significantly higher in female patients than in male patients (P = .02) (Table 3). The ICG clearance rate did not decline after PVE in male or female patients. These results indicate that our PVE procedure did not alter hepatic function in either sex. Furthermore, the ICG clearance rate of the future liver remnant, which was calculated using a formula [ICG clearance rate x (% volume of the future liver remnant/100)], was statistically significantly higher in female patients compared with male patients before and after PVE (Figure). In our department, patients with an ICG clearance rate of the future liver remnant of less than 0.05 are considered high risk for major hepatectomy, as a previous study showed that postoperative mortality rates were statistically significantly higher among patients with rates of less than 0.05 than in patients with rates of 0.05 or higher. No female patient, whereas 8 male patients (19%), had an ICG clearance rate of the future liver remnant of less than 0.05 after PVE (Figure). These results suggest that major hepatectomy may have been performed with greater functional reserve in female patients compared with male patients.

After PVE, the patients underwent right hepatectomy with caudate lobectomy, or extended right hepatectomy with caudate lobectomy and extraportal biliary duct resection. The extent of liver resection following PVE was statistically significantly different in male vs female patients (Table 4). Extended right hepatectomy was performed more often in female patients (23 patients [50%]) than in male patients (10 patients [24%]), as gallbladder cancer was more prevalent in women than in men. Therefore, our results demonstrate that more extended surgery was performed in female patients than in male patients. The number of procedures of combined pancreateoduodenectomy or portal vein resection with reconstruction was similar between male and female patients. Nevertheless, the incidence of postoperative hepatic failure, as determined by a serum total bilirubin concentration of greater than 10 mg/dL within 3 weeks after hepatectomy, was greater in male patients (12 of 42 [29%]) than in female patients (8 of 46 [17%]), although the results were not statistically significantly different (P = .16).

Preoperative PVE is widely used before major hepatectomy to induce hypertrophy of the future liver remnant and to reduce the risks of major hepatectomy. The safety and usefulness of PVE have been reported in retrospective and prospective studies. Studies have analyzed the factors that affect the outcome of PVE. Portal vein embolization has been shown to be more beneficial in patients having chronic liver disease compared with patients having normal liver function in a prospective clinical trial. Another study demonstrated that the portal pressure and the serum hyaluronic concentration, an indicator of sinusoidal endothelial function, were useful predictors of the outcome of PVE. However, few studies, such as Imamura et al., have examined the effects of patient sex on the outcome of PVE. The hepatic pathophysiology is different between men and women, especially during hepatic stresses. Moreover, the regeneration capacity of the liver has been shown to be associated with the status of sex hormone and receptor expression.

In view of this, we sought to determine if patient sex has a role in the outcome of preoperative PVE. Only cases of biliary tract malignancy were included because they usually are not accompanied by liver fibrosis and hepatitis, which might affect the regeneration capacity. To further characterize the comparison, only cases with right PVE were selected and reviewed, as the ratio of the embolized lobe to the total liver volume and...
the performed surgical procedure are different between right lobe and left lobe embolizations.

The size of the liver, as measured by CT, has been shown to correlate well with the BSA,\textsuperscript{25,33} and the livers of men are generally larger than those of women. Therefore, each datum of liver volume was divided by the BSA to facilitate comparison. Although no difference was observed before PVE, our data showed a statistically significantly greater volume of nonembolized lobe in female patients compared with male patients following PVE when the volume was adjusted by the BSA. The extent of increase in the nonembolized lobe volume by PVE was also statistically significantly higher in female patients. However, these results do not directly imply that the female liver is more potent in regeneration capacity than the male liver. The results may simply be due to the statistically significant difference in BSA between men and women. Other methods to standardize the different liver volumes between men and women should be evaluated in future studies.

The ICG clearance rate was statistically significantly higher in female patients even before PVE. After PVE, the ICG clearance rate did not deteriorate in male or female patients, and the statistically significant difference between men and women remained. To our knowledge, there is no clinical study that has specifically measured and compared the ICG clearance rates between male and female patients using this method. These observations also need further evaluation by a prospective randomized study.

The ICG clearance rate of the future liver remnant was statistically significantly higher in female patients. In a previous study\textsuperscript{27} analyzing 240 consecutive cases of PVE for biliary cancer, mortality rates were statistically significantly higher in patients whose ICG clearance rate of the future liver remnant after PVE was less than 0.05 compared with those whose index was 0.05 or higher. In the present study, the mortality rates between men (4 of 42 [10%]) and women (3 of 46 [7%]) are not statistically significantly different. The incidence of postoperative hepatic failure also was not statistically significantly different, although it was higher among male patients (12 of 42 [29%]) than among female patients (8 of 46 [17%]). Together, these data indicate that preoperative right PVE for bile duct carcinoma seems to be associated with better outcomes in female patients than in male patients. Relative to the outcome of PVE, Imamura et al\textsuperscript{16} studied 84 patients subjected to preoperative PVE and determined by multiple regression analysis that male sex was associated with reduced hypertrophy in the nonembolized lobe. However, their study did not specifically evaluate the effect of patient sex. To our knowledge, the present study is the first to specifically analyze the effect of patient sex on the outcome of preoperative right PVE.

Previous studies\textsuperscript{20,30,34,35} also proposed that patient sex, through differences in the sex hormone milieu, may modulate hepatic regeneration. It is also well known that women in the proestrus stage of the estrus cycle tolerate the deleterious effects of trauma, hemorrhage, and ischemia-reperfusion on cardiovascular and immunological functions far better than men.\textsuperscript{4,5,36-39} Studies\textsuperscript{20,33} have

Table 4. Surgery Performed

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male Patients (n=42)</td>
<td>Female Patients (n=46)</td>
</tr>
<tr>
<td>Resected segment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hepatectomy</td>
<td>32 (76)</td>
<td>21 (46)</td>
</tr>
<tr>
<td>Extended right hepatectomy</td>
<td>10 (24)</td>
<td>23 (50)</td>
</tr>
<tr>
<td>Right trisectionectomy</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Pancreatoduodenectomy</td>
<td>9 (21)</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Portal vein resection</td>
<td>14 (33)</td>
<td>13 (28)</td>
</tr>
</tbody>
</table>

Figure. Future liver remnant indocyanine green clearance rate (FLR ICGK) stratified by patient sex. \( *P < .05 \) vs pre–portal vein embolization (PVE) by paired \( t \) test. \( \dagger P < .05 \) vs male patients by paired \( t \) test.
also shown that estrogen receptor expression in the rat liver increased after 70% partial hepatectomy; serum estrogen concentrations also were elevated following major hepatectomy, whereas testosterone levels decreased in animals and in humans under those conditions. These results indicate that female sex hormones promote, whereas male hormones suppress, hepatocyte proliferation. However, the mean age of the patients included in the present study was 63 years or older; therefore, they may not have had high-circulating sex hormone levels. However, the sex steroid levels were not measured, and it remains unknown if high estrogen levels were responsible for the observed results. In addition, the interval between the time of PVE and subsequent volumetric CT was variable (range, 7-21 days), although the mean time was not different between men and women. The precise reason why a sex-dimorphic outcome following PVE occurs is unclear. Nevertheless, it seems that women, even in the postmenopausal stage, have better hepatic regeneration capacity than men of comparable age. A well-controlled prospective randomized study is required to elucidate whether patient sex or the level of sex hormones modulates the rate of hepatic regeneration after PVE. Sex differences in the surgical outcome of major hepatectomy after PVE should also be analyzed by a prospective study to validate the results observed herein.

In summary, this study demonstrated a sex-dimorphic outcome following right PVE before major hepatectomy. Greater volume and function of the future liver remnant after PVE were obtained in female patients compared with male patients, suggesting that female patients may fare better in the outcome of preoperative right PVE in biliary malignancies.

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Yokoyama and colleagues report a possible correlation between sex dimorphism and clinical outcome after PVE in 88 patients, including 42 men and 46 women, each of whom had a carcinoma arising from the gallbladder or the intrahepatic or extrahepatic biliary tract. All 88 patients underwent planned resection of the right lobe of the liver. The authors observed that PVE was associated with higher percentage changes in the liver volume and in the ICG clearance among women than among men, even after adjusting for differences in body size. A similar sex difference was observed in patients who did not undergo preoperative PVE. In addition, the risk of postoperative liver failure after PVE was lower in women than in men. Based on the latter data, which coincidentally were not statistically significant, the authors postulated that the observed findings resulted from the effect of differences in sex hormones and receptors on liver regeneration.

The conclusions of this study are not substantiated by the available data. The authors did not measure the level of sex hormones or receptors. In addition, the mean age of men and women was 63 years or older. That most women were likely to be postmenopausal raises questions about the levels of sex hormones and the validity of the authors’ conclusions. Other factors may have contributed to the observed sex differences in clinical outcome. It is also unclear why or how differences in patient sex would affect ICG clearance rates before or after liver resection.

The authors report an interesting observation, but the lack of quantitative data raises questions about the validity of their conclusions. Future prospective studies that measure levels of inflammatory cytokines, growth hormones, sex hormones, and other gut- or pancreas-derived factors known to affect liver regeneration are necessary to validate this study. Expanded studies will also be necessary to determine whether the conclusions of this study are limited to patients with biliary tract malignant neoplasms or can be generalized to patients with other hepatic malignant neoplasms or benign conditions of the liver such as hepatitis or cirrhosis.

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