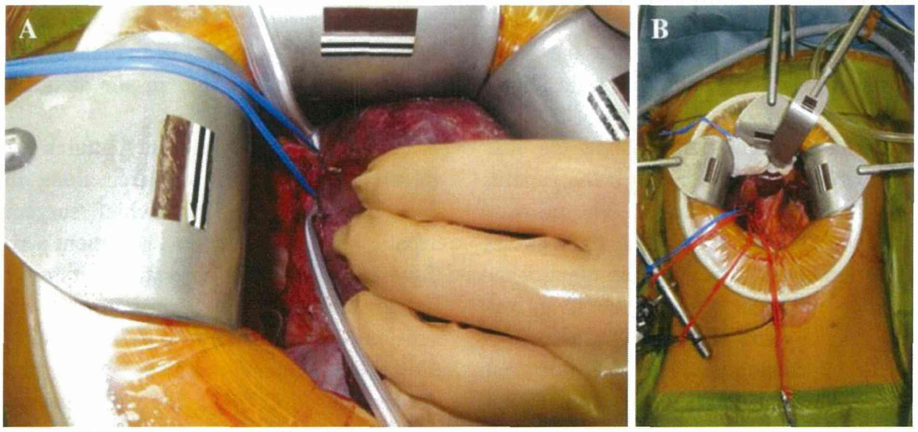
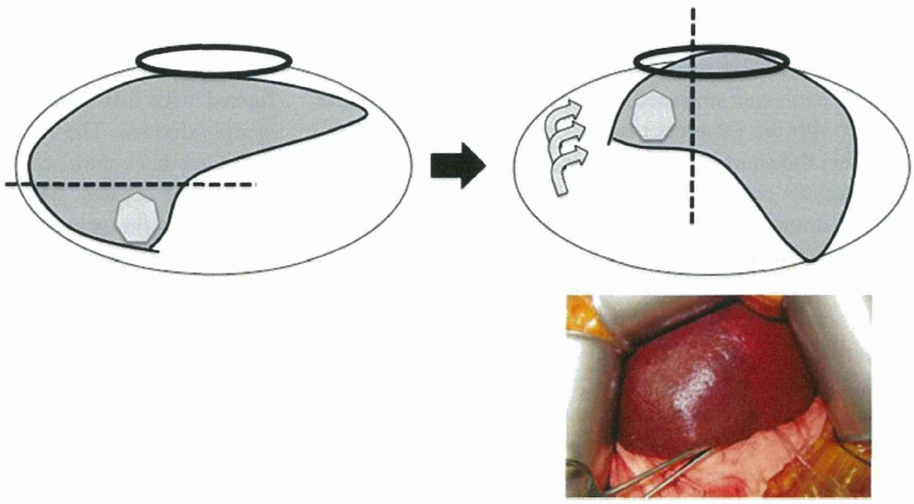


Fig. 2 **A** When mobilizing the right lobe of the liver, the surgeon can manage short hepatic veins, the right hepatic vein, and the inferior vena cava through the upper midline incision with adequate exposure. The *blue vessel loop* is encircling the right hepatic vein, and a Penrose drain also was passed around the right hepatic vein for the later hanging maneuver during parenchymal resection. **B** Hilar dissection under direct vision from the 12-cm upper midline incision. An Omni-tract surgical retractor is useful to maintain a good surgical field (Color figure online)

Fig. 3 With sufficient mobilization, the planned resection line can be exposed under an upper midline incision. The *dotted line* shows the planned resection line for a posterior sectionectomy. The photograph shows the demarcation line with control of the inflow to the posterior sector



were grade I. The median hospital stay was 13 days (range 8–123) days.

Comparing the findings for the hybrid technique and the open procedure for living donor left hemihepatectomy ($n = 24$ per group) and right hemihepatectomy ($n = 19$), no significant differences were seen in the duration of the operation [hybrid group: median 440 min (range 282–581) min; open hepatectomy: median 400 min (range 305–636) min]. In donor left hemihepatectomy, the intraoperative blood loss was significantly lower in the hybrid method group [median 510 g (range 50–1,950) vs. 637.5 g (range 250–3,150)]. No significant difference was seen in the intraoperative blood loss between open and hybrid donor right hemihepatectomy [median 625 g (range 320–1,800) vs. 710 g (range 234–2,550); Fig 4].

As a result, a hybrid method was successfully employed even in the cases that needed combined hepatectomy with hemihepatectomy and minor liver resection, or multiple minor liver resections for bilobular lesions, or a right posterior sectionectomy.

Case studies

Case 1

A 56-year-old male with hepatic carcinoid had multiple lesions in the right lobe and a lesion close to the middle hepatic vein. In addition, another tumor was present in the left-lateral section. The patient underwent right hemihepatectomy with local resection of the left-lateral section by a hybrid method. Radiofrequency ablation was performed for the lesion close to the middle hepatic vein with intraoperative ultrasound guidance (Fig. 5).

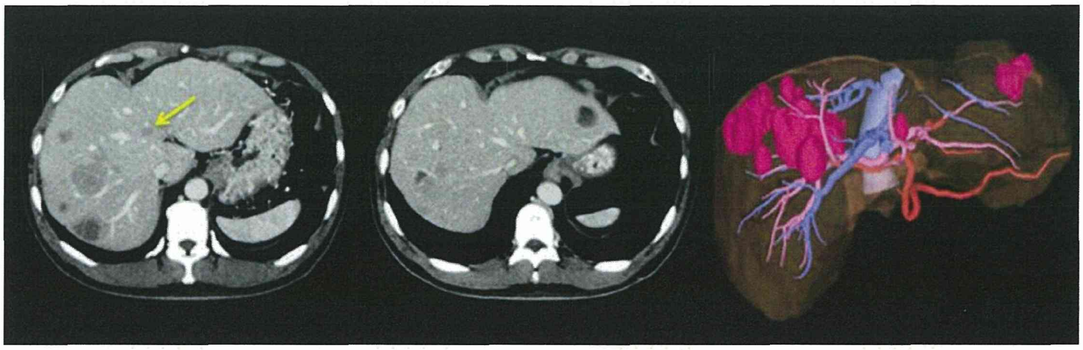


Fig. 4 CT images of multiple hepatic carcinoid tumors treated by hybrid resection, and a lesion treated by radiofrequency ablation (*arrow*). The *right panel* is a 3D reconstructed image made from CT scans obtained by a Synapse Vincent instrument (Fujifilm Medical, Tokyo, Japan)

Case 2

A 75-year-old male with multiple colorectal liver metastases. The tumors were located in segments 4, 6, and 7 (Fig. 6A). Because his hepatic functional reserve was disturbed as a result of the adverse effects of chemotherapy, a right hemihepatectomy was not possible. The patient underwent multiple local resections by a hybrid method through a 10-cm upper midline incision (Fig. 6B).

Case 3

A 74-year-old female with solitary hepatocellular carcinoma in segment 7 underwent an extended posterior sectionectomy by a hybrid method (Fig. 7).

Discussion

We herein reported the largest case series of hepatectomies performed by hybrid methods. To date, two other large case series employing hybrid methods have been reported [1, 5]. Our data further support the safety, feasibility, and efficacy of the hybrid approach for anatomical liver resection.

Although the term "hybrid method" is becoming common, there are some differences among institutions in terms of the following procedures: the location of the incision, the trocar locations, the extent of hand-assist procedures, etc. At our institution, we have adopted an upper midline incision for both the hand access and the open procedure. The hybrid method with an upper midline incision can be performed irrespective of the type of resection. Even posterior sectionectomies (S6 + 7) were consistently performed through the upper midline incision after hand-assisted right lobe mobilization. The benefits of anatomical resection for HCC have been reported [6, 7]. Hepatic parenchymal resection under direct vision in hybrid method can achieve meticulous and accurate resection with exposing vessels as well as conventional open procedure.

In addition to the effective application of the hybrid method for anatomical liver resections, we consider that a multiple partial hepatectomy is a good indication for the hybrid technique. Bilobular multiple liver tumors can be consistently managed through the short upper midline incision after the sufficient mobilization of the liver.

The upper midline incision contributes to the effective hand assist compared with access through a subcostal incision as a result of the wider working space. In terms of ergonomics, a hand-assist through the upper-midline incision may be more natural, because the rotation of the liver and the hand movement of the first assistant go in the same direction. Furthermore, the midline incision offers easy access to bilobular lesions. By using a GelPort hand device in place of trocar insertion, less port surgery can be achieved.

Hand-assisted procedures performed during the management of the area around the IVC and hepatic veins guarantees that there can be rapid emergency management of incidental massive bleeding. We consider that dividing the short hepatic veins and the subsequent encircling of the right hepatic vein or the common trunk of the middle hepatic vein and left hepatic vein can be more securely performed under direct vision compared to by a laparoscopic procedure. Once the right lobe is mobilized, the liver can be rotated to the left of the midline and retracted; therefore, the surgeon can easily approach the IVC and the right hepatic vein even through a minilaparotomy with a short upper midline incision. Because the IVC and hepatic hilum are basically located in the middle of the abdomen, the surgeon can approach these areas without stress through the midline under the exposure provided by the wound retractor and surgical retractor. The safety guaranteed by the hand-assist procedure seems to be superior to the magnification effect obtained during laparoscopy.

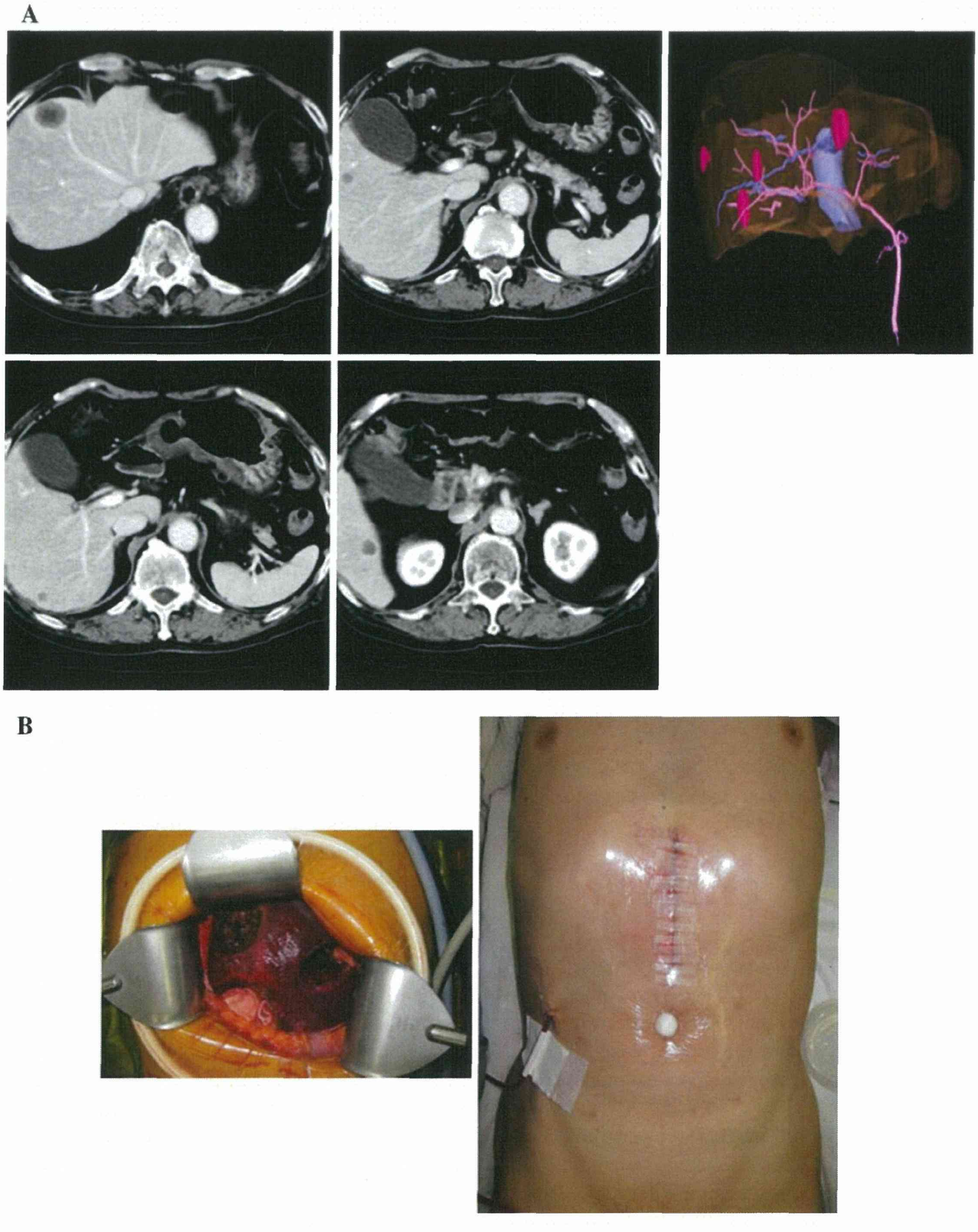


Fig. 5 **A** CT images of multiple colorectal metastases treated by a hybrid method. The *right panel* is a 3D reconstructed image made from CT scans obtained by a Synapse Vincent instrument (Fujifilm Medical, Tokyo, Japan). **B** Local resection was performed for four lesions because of insufficient liver functional reserve for major hepatectomy. A 10-cm upper midline incision was made for the hybrid method

Reducing blood loss is one of the goals of liver surgery, and several technical inventions have been introduced to achieve this, including the Pringle maneuver [8, 9] and selective vascular occlusion [10], among other techniques. Regarding surgical devices, the CUSA has contributed to the safety of hepatectomies by making it easy to identify the vessels during parenchymal transections. However, because the CUSA cannot seal tissues, meticulous ligation is required to avoid bleeding or bile leakage from the cut surface of the liver. Saline-linked electric cautery (SLC) is

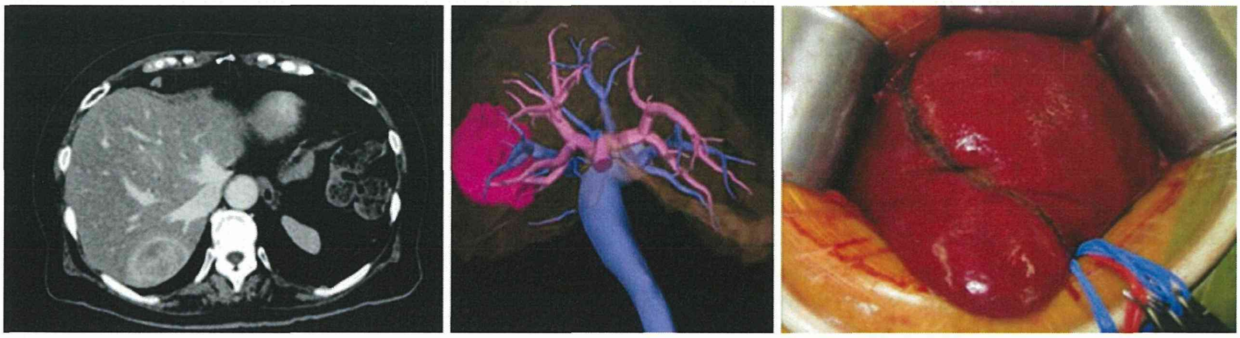


Fig. 6 Contrast-enhanced CT scan showed a mass lesion in segment 7 of the liver. The *middle panel* is a 3D reconstructed image made from CT scans obtained by a Synapse Vincent instrument (Fujifilm Medical, Tokyo, Japan). The intraoperative photograph shows the line of resection for the posterior sectionectomy

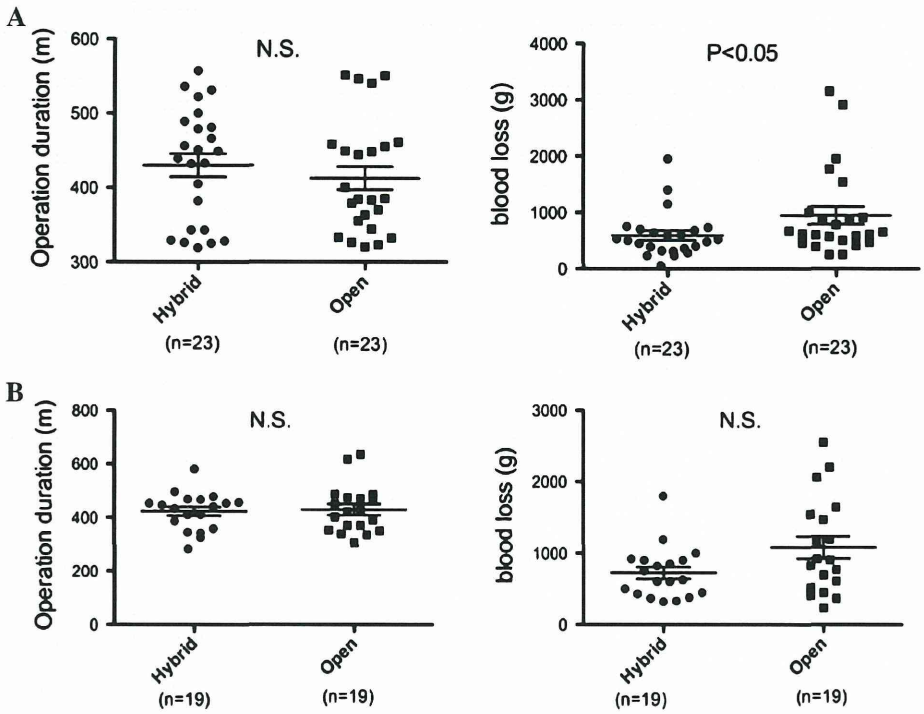


Fig. 7 Comparing the surgical outcomes of the hybrid procedure and open procedure for **A** living-donor left hemihepatectomy and **B** right-donor left hemihepatectomy

another novel device that contributes to reducing the need for ligation during liver parenchymal transections, because it can be used for tissue sealing [11]. Aloia et al. [12] introduced a two-surgeon technique for hepatectomies to resect neoplasms in adults, and demonstrated promising results. Palavecino et al. [13] demonstrated that the mean intraoperative blood loss was significantly decreased after the introduction of the two-surgeon technique compared with other techniques (stapling alone, ultrasonic dissection alone, saline-linked cautery alone, and the clamp-crush technique). We previously demonstrated that SLC could be adapted safely for living liver donor surgery without injuring either the graft or the remnant liver [14]. With the introduction of the liver hanging maneuver, which brings the transection line to just beneath the upper midline incision with pulling up of the liver [5, 15], to the hybrid method, parenchymal transection with the two-surgeon technique can be conducted as well as during open procedures. As a result, parenchymal transection can be successfully completed through the 10- to 12-cm upper midline incision without additional stress for the surgeon.

The upper midline incision that we adopted for the hybrid procedure is considered to have several advantages compared to the right subcostal incision, which was previously reported for the hybrid method. The upper midline can avoid muscle disruption and disturbing the sensory nerve dominating the abdominal wall. Jain et al. [16] reported the presence of persistent numbness of the abdominal skin between the subcostal incision and the umbilicus in patients who had undergone liver transplantation. Surprisingly, 100 % of the patients ($n = 101$) had persistent numbness up to 9 years following liver transplantation. Five percent of these patients developed thermal injuries or blunt trauma complications. According to the results of a randomized, double-blind trial concerning midline versus transverse incisions in major abdominal surgery, although no relevant differences between midline and transverse incisions were observed for pulmonary complications, the median length of hospital stay and incidence of incisional hernias after 1 year was higher, and patients showed more wound infections, in the transverse group ($P = 0.02$) [17]. Given the development of the above-mentioned postoperative complications, the upper midline incision seems to be a more reasonable approach.

Some authors have reported previously the feasibility of major hepatectomy using a midline incision, including living donor hepatectomy [18, 19]. Lee et al. concluded that the procedure after an upper midline incision was more difficult in male donors with large fatty livers and deep truncal cavities. Without randomized, controlled trials, we presently cannot show objective data comparing our procedure and midline hepatectomy without laparoscopy. However, laparoscopic mobilization of the liver under pneumoperitoneum has been reported to be a safe and effective procedure with a good multidirectional surgical view and a wide working space [1, 20]. Hence, this virtue of laparoscopic procedure would allow for mobilization of the liver even in patients with deep truncal cavities, irrespective of the length of the midline incision. The influence of each patient's constitution on our technique seems to be smaller than that on midline major hepatectomy without a laparoscopic procedure. In this study, 17 patients (17 %) had a BMI >25, which is the cutoff value between normal and overweight. Among these patients, four had a BMI >30, which is considered obese. We therefore considered that our procedure can be applied in almost all patients, except those with morbid obesity accompanied by an extremely thick abdominal wall.

Furthermore, quick celiotomy and closure of the abdomen also were benefits of the upper midline incision [21]. The additional duration of the preparation for laparoscopic procedure was offset by the rapid opening and closing of the abdominal incision.

Although the long-term outcomes should be carefully evaluated, given the aforementioned advantages, in addition to the safety and feasibility, we consider that our technique should become more widely accepted as a standard hybrid method. Moreover, this method does not require expert laparoscopic surgical skills.

Disclosures Drs. Akihiko Soyama, Mitsuhisa Takatsuki, Tomohiko Adachi, Amane Kitasato, Yasuhiro Torashima, Koji Natsuda, Takayuki Tanaka, Izumi Yamaguchi, Shiro Tanaka, Ayaka Kinoshita, Tamotsu Kuroki, and Susumu Eguchi have no conflict of interest or financial ties to disclose.

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BRIEF ARTICLE

Chronological changes in the liver after temporary partial portal venous occlusion

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Abstract

AIM: To investigate time-dependent changes caused by temporal portal vein obstruction and subsequent reperfusion in the lobe with or without an occluded portal vein.

METHODS: The portal vein (PV) of the anterior lobe of the liver of a male Wistar rat (8 wk-old) was obstructed (70%) for 12, 24, 36 and 48 h, respectively, and models were sacrificed at 48 h after reperfusion (each group: n = 10). The histological changes and the status of liver regeneration were compared between a liver biopsy performed on each lobe after temporary obstruction of the portal vein in the same rat liver, and the liver extracted at the time of sacrifice (48 h after reperfusion).

RESULTS: With regard to the obstructed lobe, the liver weight/body weight ratio significantly decreased according to obstruction time. On the other hand, in the non-obstructed lobe, there were no significant differences within each group. The duration of PV occlusion did not seem to be strong enough to introduce liver weight increase. Stimulation of liver regeneration was brought about in the non-occluded lobe by 12-h occlusion, and was sustained even at 48 h after reperfusion. The obstructed lobe atrophied with the passage of time in the obstructed state. However, the proliferating-cell nuclear antigen labeling index also increased at 48 h after reperfusion, and a repair mechanism was observed.

CONCLUSION: Temporary blood flow obstruction of the portal vein may become a significant trigger for liver regeneration, even with an obstruction of 12 h.

Key words: Temporary; Portal vein; Occlusion; Regeneration; Liver

Core tip: This paper describes the chronological effects of temporary portal venous branch ligation on liver regeneration in rats. These results imply that, in the future, it might be possible to control liver regeneration. In the clinical setting, we have just completely occluded the portal venous branch irreversibly.

Hamasaki K, Eguchi S, Soyama A, Hidaka M, Takatsuki M, Fujita F, Kanetaka K, Minami S, Kuroki T. Chronological changes in the liver after temporary partial portal venous occlusion. *World J Gastroenterol* 2013; 19(34): 5700-5705 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i34/5700.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i34.5700

INTRODUCTION

Permanent obstruction of the portal vein, as clinically applied in portal branch ligation (PBL) or percutaneous transhepatic portal venous embolization, evokes liver regeneration[1-4]. This technique enables relatively major hepatic resection for malignancy in an occluded liver lobe[5-9]. In addition, PBL has been used to induce a regenerative stimulus for transplanted hepatocytes or pancreatic islet cells for cell therapy[10,11].

Although short term temporary occlusion can induce some degree of liver regeneration, an investigation of liver regeneration caused by temporary portal vein obstruction, as well as time-dependent changes resulting from reperfusion, has not yet been performed[12]. Therefore, the current study aimed to examine time-dependent changes in a lobe with a portal vein occlusion of an unobstructed portal vein caused by temporary portal vein obstruction and reperfusion as the central focus.

MATERIALS AND METHODS

Animals

Male Wistar rats (200-240 g, Japan SLC Inc., Shizuoka, Japan) were used for the experiments. All animals were maintained at 24 ℃ with a 12-h light-dark cycle and given free access to tap water and standard laboratory chow. The animals were treated in accordance with the guidelines stated in the University of Nagasaki Research Animal Resources during all experimental procedures.

Experimental design

The portal vein of the anterior lobe (medial and left lobes) of the liver of a male Wistar rat (8 wk old) was occluded (70%) for 12, 24, 36 and 48 h, respectively (Figure 1). Rats to be sacrificed were prepared at 48 h after each reperfusion (models for each group: n = 10, Figure 2). The histological changes over time and the status of liver regeneration were compared between liver biopsies performed from each lobe after temporary obstruction of the portal vein in the same rat liver, and the liver extracted at the time of sacrifice (48 h after reperfusion).

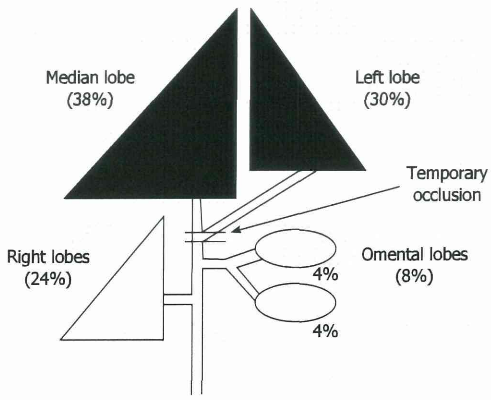

Figure 1 Schematic drawing of the rat model. The portal vein of the anterior lobe (black area) of the liver was occluded (68%) for various durations, while the arteries remained open.

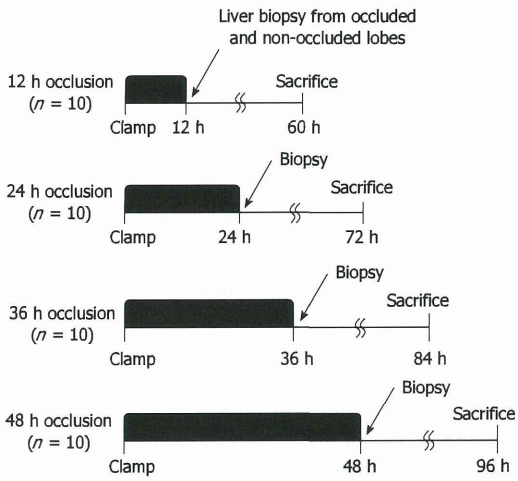

Figure 2 Experimental protocol. The portal vein of the anterior lobe (median and left liver lobes) of the liver of a male Wistar rat was occluded (70%) for 12, 24, 36 and 48 h. Rats to be sacrificed were prepared at 48 h after each reperfusion (models for each group: n = 10).

Liver to body weight ratio

The body weights and liver weights were recorded following the sacrifice of the rats to compare the rate of liver regeneration. The liver weight was expressed as a percentage of the body weight (%) and used as an index.

Histology and immunohistochemistry

Formalin-fixed paraffin embedded (4 μm) sections were used for hematoxylin-eosin (HE) staining. Proliferating-cell nuclear antigen (PCNA) immunostaining was performed to examine hepatocyte proliferation using a mouse monoclonal antibody against PCNA (clone-PC 10; Dako, Kyoto, Japan)[13]. Briefly, liver tissue specimens were fixed in 10% buffered formalin, embedded in paraffin and then cut into 5 μm sections. The deparaffinized sections were heated in a microwave three times in phosphate-buffered saline (PBS) for 5 min each and were then washed three times with PBS for 5 min each. After blocking endogenous peroxidase activity, the specimens were washed three times with PBS for 5 min each. The sections were incubated with an antibody against PCNA overnight at 4 ℃. After washing several times with PBS, biotin-labeled secondary antibody was added for 1 h at room temperature. After washing several times with PBS, the tissue peroxidase activity was visualized using diaminobenzidine.

The PCNA labeling index (PCNA LI) was then determined as the number of PCNA-positive cells among 1000 counted cells.

Statistical analysis

All of the data were expressed as the mean ± SD. The Mann-Whitney U-test was used for data analysis. A level of P < 0.05 was considered statistically significant.

RESULTS

With regard to the obstructed lobe, the liver weight/body

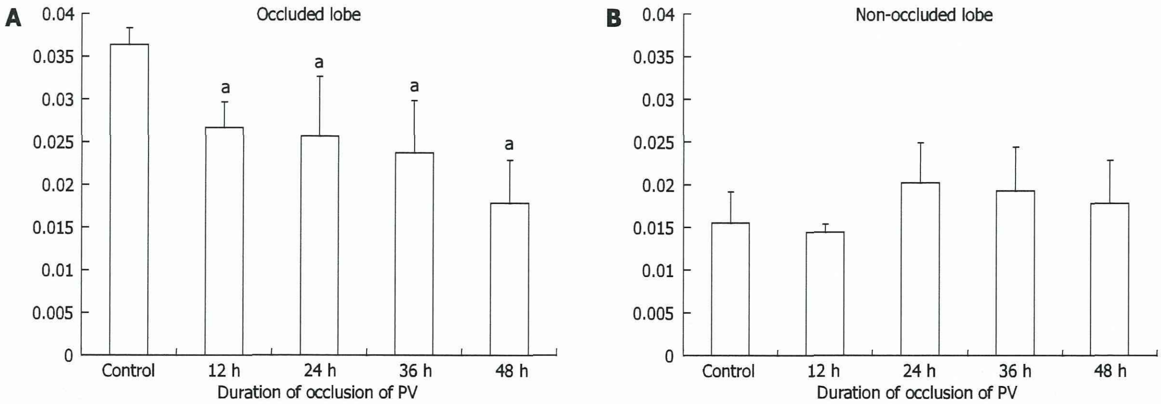

Figure 3 Liver weight/body weight. A: The liver weight/body weight ratio was decreased by temporary occlusion of the occluded anterior lobes; B: There were no significant differences within each group in non-occluded lobe. $^aP < 0.05$ *vs* control group.

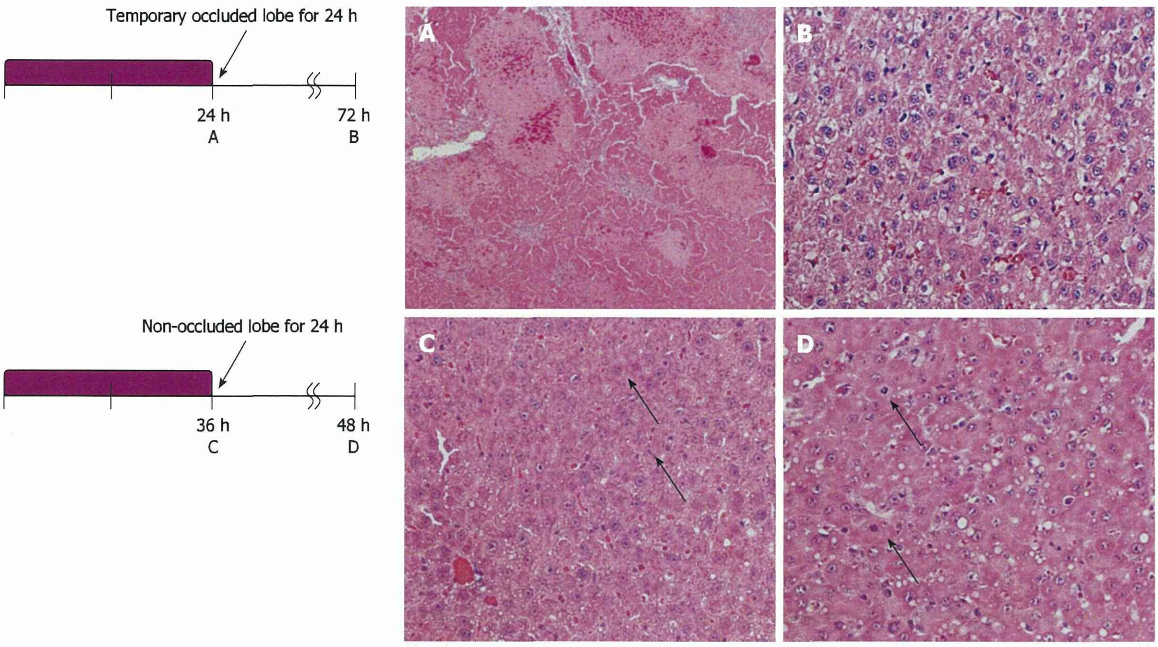

Figure 4 Changes in hepatic histology. Histology in temporary occluded lobes. A: 24 h occlusion, × 100; B: 36 h occlusion, × 400; C: In non-occluded lobes 24 h occlusion, × 100; D: 48 h occlusion, × 400 is shown by HE staining. In the occluded liver lobe, before reperfusion, coagulative necrosis may be observed around the central vein in proportion to the occlusion time. However, the above-mentioned necrotic area decreased at 48 h after portal vein reperfusion. In the non-occluded liver lobe, hepatocytes became hypertrophic, and some mitoses could be observed (arrows).

weight ratio significantly decreased with increasing obstruction time (Figure 3). On the other hand, in the non-obstructed lobe, there were no significant differences within each group. The duration of PV occlusion did not seem to be strong enough to induce an increased in liver weight.

Liver histology was investigated under HE staining (Figure 4). In the occluded liver lobe, before reperfusion, coagulative necrosis was observed around the central vein in proportion to the occlusion time. However, after 48 h of reperfusion, the above-mentioned necrotic area decreased. On the other hand, in the non-occluded liver lobe, hepatocytes became hypertrophic, and some mitoses were observed.

In the non-obstructed lobe, there were no significant differences in the PCNA LI within each group (Figure 5). LI seemed to peak at 36 h of biopsy (non-obstructed models at 12, 24, 36 and 48 h = 24%, 32%, 36% and 31%, Figure 5C). In the non-occluded lobe at 48 h after reperfusion (models for each group = 33%, 32%, 36% and 32%), the PCNA LI was still significantly increased at all points compared with the control (Figure 5D).

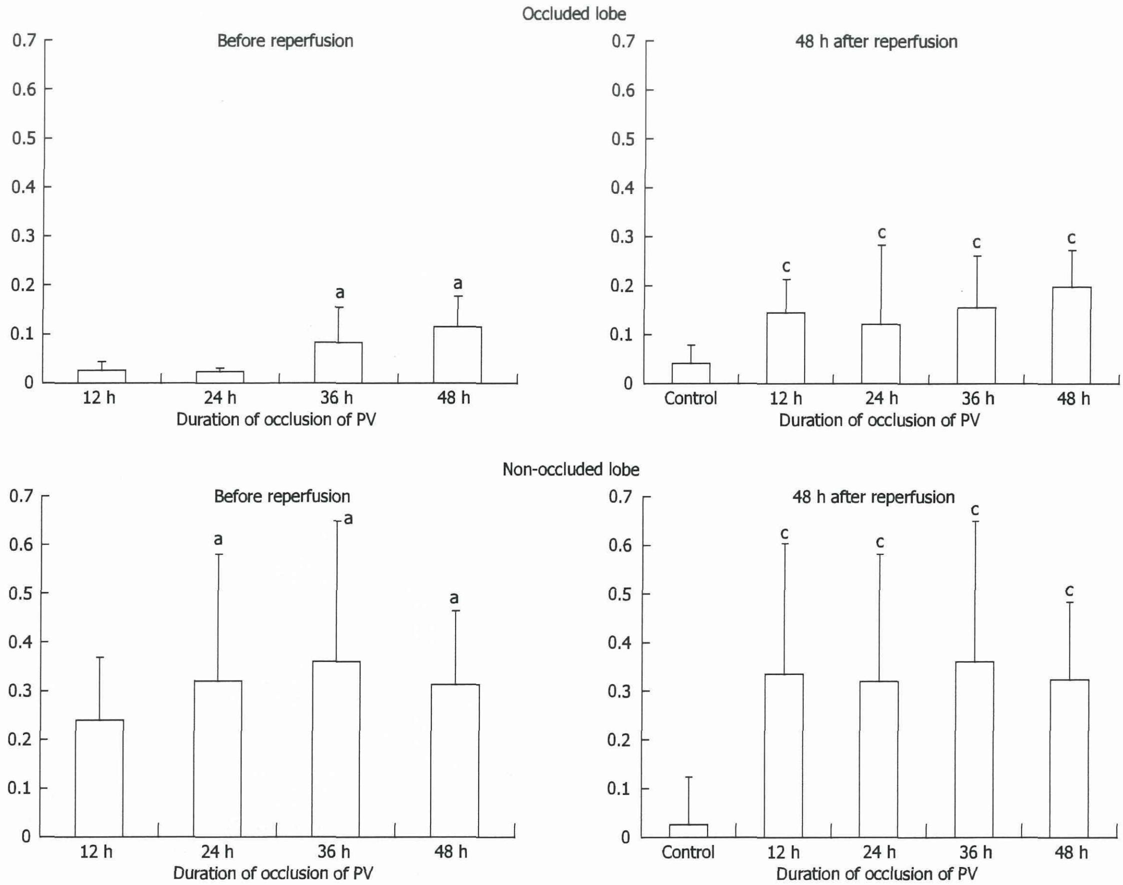

Figure 5 Proliferating-cell nuclear antigen labeling index. Proliferating-cell nuclear antigen (PCNA) labeling index in each lobe at the time before reperfusion and 48 h after reperfusion. $^aP < 0.05$ *vs* 12 h group; $^cP < 0.05$ *vs* 24 h group. PV: Portal vein.

On the other hand, hardly any positive cells were observed in a biopsy of the obstructed lobe (obstructed models at 12, 24, 36 and 48 h = 2%, 2%, 8% and 10%). However, at 48 h after reperfusion, an increase in LI was observed (models for each group = 14%, 12%, 15% and 19%).

DISCUSSION

Portal venous branch ligation or embolization (PBL or PBE) can induce atrophy of the ligated lobe, while inducing hypertrophy of a non-ligated lobe, which enables extended hepatectomy for a malignant tumor in a ligated lobe[14-16]. In addition, PBL has been used as a regenerative stimulator to induce transplanted cell proliferation in animal models for hepatocyte-based cell therapy[17-23]. The length of time of occlusion needed to induce remnant liver regeneration, *i.e.*, temporary portal venous occlusion, remains unknown. In the present study. the stimulation of liver regeneration brought about in the non-occluded liver lobe was sustained, even after 48 h from reperfusion. Thus, temporary blood flow obstruction of the portal vein may be a significant trigger of liver regeneration, with an obstruction of at least 12 h. However, the duration of PV occlusion in this study did not seem to be long enough to induce an increase in liver weight.

Interestingly, there was no significant difference in PCNA LI in the non-occluded lobe according to the duration of portal vein occlusion up to 48 h. Therefore, in the clinical setting, the same extent of liver hypertrophy may be induced with temporary balloon occlusion in as short as 12 h, to minimize an invasive procedure, although there might be difference among species.

As a cell therapy, many investigator have used liver for the engraftment of many cell types[10-12,14-16]. In fact, transplanted cells (hepatocytes, pancreatic islet cells or genetically engineered cells) could be induced to proliferate using temporary portal venous occlusion. Although there must be some differences between humans and rodents in terms of liver regenerative activity, our results provide a new insight into temporary stimulation of liver regeneration for subsequent treatment procedures[24-26].

On the other hand, the PCNA labeling index of the obstructed lobe was also increased 48 h after portal venous reperfusion. This could be a repair mechanism for portal vein ischemia in the occluded lobe, although PCNA LI was lower compared to that in the non-occluded lobe that undergoes liver regeneration[14]. Although it