Efficacy of laparoscopic repeat hepatectomy for recurrent liver cancer

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Abstract

Background: Patients with recurrent hepatocellular carcinoma or metastatic liver cancer from colorectal cancer after surgical resection have been treated with conventional open surgery traditionally. However, recent technical advances have made laparoscopic repeat hepatectomy (LapRH) feasible and the procedure offers advantages over open laparotomy. We herein describe the results of LRH at our institution with retrospectively compare short-term outcomes after LapRH versus initial laparoscopic partial liver resection (LapPLR).

Methods: From April 2010 to December 2017, 24 patients (16 men, 8 women; median age, 69 years) underwent LRH for cancer recurrence or metastasis after initial partial hepatectomy at our institution. LapRH involved partial hepatectomy in 21 patients and lateral segmentectomy in 3 patients. Short-term outcomes (operative time, intraoperative blood loss, and postoperative hospital stay) were compared between these 24 patients and 117 patients who underwent initial LapPLR during the same time period.

Results: There were no significant differences between the LapPLR and LapRH groups of baseline characteristics including patient age or underlying disease. None of the LapRH procedures required conversion to open surgery. There were no statistically significant differences between the groups in median operation time (268 min for LapPLR, 294 min for LapRH; p = 0.55), blood loss (224.0 mL for LapPLR, 77.5 mL for LapRH; p = 0.76), or length of hospital stay (11.0 days for LapPLR, 10.2 days for LapRH; p = 0.83).

Conclusions: Our results indicate that LapRH for recurrent liver cancer provides feasible outcomes comparable to those of initial hepatectomy. Further studies, however, are needed to confirm our results.

Key words: reoperation, hepatectomy, laparoscopy, adhesions
Introduction

Laparoscopic procedures have been widely applied in various fields of surgery, and the number of favorable reports on laparoscopic liver resection (LapLR) have been increased. Many groups have demonstrated the safety, feasibility, and oncological efficiency of LapLR. Accordingly, the use of LapLR has dramatically increased and its adaptation has expanded (1–5). Likely, we have carried out over 200 LapLRs to date and have standardized the procedure.

For the patients who have a previous abdominal surgery like recurrent hepatocellular carcinoma (HCC) and metastatic live cancer from colorectal cancer (6–8), conventional open surgery for liver resection is used to be performed in patients(6–10), whereas LapLR has typically limited indication for the tumor with small size and/or with location at easily accessible(11). For LapLR, surgeons need to contend with restricted manipulation, the lack of manual sensation, and disorientation arising from the lack of an overview (12, 13). Moreover, there still exist technical difficulties with LapLR related to liver mobilization according to adherences around the liver that could be various depending on the patients.

Reports of laparoscopic repeat hepatectomy (LapRH) have been appeared recently probably because of a development of surgical instruments and consequent stability of laparoscopic procedures (14, 15). In the LapRH, however, the technical difficulty level of the operation could be higher depends on various factors. On the other hand, taking advantage of the magnifying effect of laparoscopic surgery, pinpoint surgery in a narrow space has become possible. We have been active proponents of LapRH for recurrent liver cancer cases, and also perform LapRH for patients with a history of upper abdominal surgery as well as of hepatectomy. In this paper we report, in order to consider the safety and feasibility of the LapRH approach we have been using to date and report the short-term results for the case group in which the first laparoscopic partial liver resection (LapPLR) that is a standardized recently, was performed and the group in which LapRH was performed.
Materials and methods

Patients and categorization

All of the procedure for laparoscopic hepatectomy we performed in this study was applied to Japanese insurance. In addition, we obtained written informed consent from the all of the patients.

Study population were selected among the approximately 200 laparoscopic hepatectomies performed in our department from April 2010 to December 2017, 24 of the patients underwent LapRH. All patients underwent the first hepatectomy at our hospital, and the procedure included both laparotomy and laparoscopy. Tumor location were distributed to all segments of the liver (segments 1–8).

The procedure of the LapRH was partial resection of the liver or lateral segmentectomy of the liver. For LRH indication, the number of tumors was within the Makuuchi criterion (16), and the site of the tumor was within or adjacent to the same area. Patients were divided into 117 cases in which laparoscopic partial liver resection (LPLR) was performed for the first time, and 24 cases of LapRH. For these groups of patients, clinical indicators of perioperative course were retrospectively examined from medical records, including operative time, intraoperative blood loss, conversion to laparotomy, morbidity, and postoperative hospital stay.

Upper abdominal surgery was defined as the presence of a distinct scar above the umbilicus derived from an operative procedure involving the subphrenic and subcostal area around the liver.

This study was approved by the ethics committee of Nippon Medical School (No.28-02-725).

Surgical technique

LapRH procedure

The patient is in a position with lower limbs open, except for the location of the tumor (right dorsal liver).

For the first port, we incise 3 cm of the navel umbilicus with an open method in every case and employ a Lap Protector™ and EZ Access® (Hakko, Nagano, Japan) on the navel. By making a 3-cm incision of umbilicus, possible adhesion of the previous surgery around the umbilicus can be safely exfoliated under direct vision. Therefore we could put same first port for all cases, even in the case with a history of upper abdominal laparotomy or with an operation scar on the umbilicus (17),
We insert a 12-mm port for the camera and two 5-mm ports for EZ Access (Fig. 1a) on the Lap Protector on the navel. After pneumoperitoneum (10 mmHg, occasionally increased up to 12 mmHg) is established through a 12-mm port, a flexible laparoscope is introduced, and the abdominal cavity is observed. In LapRH, the additional port arrangement and the number of ports are different depending on the situation, such as adhesions in the abdominal cavity. After adequate observation of the abdominal cavity, adhesion detachment was performed as necessary for additional port insertion. In addition to EZ Access on navel, we typically add 2 to 3 ports to the upper abdomen. The position of the additional ports cannot be standardized because it depends on the types and distribution of the adhesions. To maintain a cosmetic aspect, we often insert additional ports alongside the previous surgical wounds (Fig. 1b). In LapRH, upper abdominal surgery and hepatectomy could cause to have strong adhesions around the hepatic duodenal ligament, in which case we avoid Pringle maneuver ischemia (18, 19) in secondary operation. We conduct a 3D computed tomography (CT) simulation prior to surgery, which provides crucial knowledge of the positional relationship between the liver and surrounding organs (Fig. 2). Additionally preoperative simulation enable us to secure a minimum working space necessary for hepatectomy. Actual intraoperative surgical view at the initial insertion of the camera is demonstrated in Fig 3. Intraoperative ultrasonography is routinely performed to assess the tumor conditions and determine the transection line. After checking the tumor, we perform hepatectomy. For hepatic resection, the ultrasonic coagulation system (LCS) and incision device at the superficial hepatic parenchyma, and the Cavitron Ultrasonic Surgical Aspirator (CUSA) (Valley lab, Medtronic, Minneapolis, MN, USA) in the deeper portion of the hepatic parenchyma, are used for main vascular treatment, and the VIO soft coagulation system is used for hemostasis. After completing resection of the liver, the specimen is put into a protective plastic bag and extracted through the incision created by the umbilicus. In cases with an uncertain tumor location or uncontrollable bleeding, we convert to hand-assisted laparoscopic surgery or conventional open surgery.
Results

LRH was performed in 24 patients (16 males and 8 females) with a median age of 69 years. Diseases causing the treatment comprised 12 cases of HCC, 11 cases of metastatic liver cancer, and 1 case of intrahepatic cholangiocarcinoma.

The types of previous hepatectomy and surgical procedures, and extent of adhesions for each patient, are shown in Table 1. Most cases have one abdominal surgery for hepatectomy, whereas out of the 24 patients, two patients underwent liver resection and distal gastrectomy, and one patient underwent liver resection and pancreatectomy (Table 1). Regarding first operation that was done prior to LapRH, 24 patients underwent hepatectomy: 19 cases of partial hepatic resection, 1 case of lateral segmentectomy, 1 case of right hepatectomy, 1 case of extended left hepatectomy, 1 case of anterior segmentectomy, and 1 case of posterior segmentectomy. Analysis of these patients revealed that there were no differences with respect to age, sex, disease, tumor characteristics, or type of hepatectomy. For the LapRH procedure, partial resection of the liver was performed in 21 cases and lateral segmentectomy in 3 cases. The essence of the laparoscopic surgical approach was complete laparoscopic operation in 21 cases, single port in 2 cases, and hand-assisted in 1 case (Table 2). There was no conversion to laparotomy because of an intraoperative accident, and all cases of LapRH were implemented as planned.

In this study we compared surgical time, bleeding volume, and postoperative hospital stay in 117 cases of first LapPLR and 24 cases of LapRH performed over the same time span (2010–2017). The male-to-female ratio of patients who underwent LapPLR was 69:48. The underlying disease for LapPLR was 52 cases of HCC and 65 cases of metastatic liver cancer. There was no significant difference between the groups of LapRH and LapPLR with regard to sex ratio and disease. Short-term results between the two groups are shown in Table 3. Median operation time was 268 min for LapPLR and 294 min for LapRH (p = 0.55). In addition, the median bleeding volume was 224 mL in LapPLR and 77.5 mL in LapRH (p = 0.76). There was no significant difference in mean length of hospital stay after surgery (LapPLR, 11 days and LapRH, 10.2 days; p = 0.83). Taken together, although there were no significant differences between the two groups over the short term, LapRH patients tended to do better (Table 3). Regarding post-operative comorbidity, there is only one patient who had bile leakage for which surgical drainage was necessary for management in the LapPLR group. To be surprised, none of the patients had surgical management for the
post-operative complication in the LapRH group, indicating minimally invasive of the procedure.

Discussion

Recently, the safety and usefulness of repeat hepatectomy for recurrent liver cancer and metastatic liver cancer has been proved and its demand is increasing. One of the problems at reoperation is adhesion within the abdominal cavity, whereby the surgical contents may differ depending on the extent of adhesion. Patients with a history of upper abdominal surgery and liver resection often have intra-abdominal adhesions. Postoperative adhesions are known to increase the operative time of subsequent surgeries, owing to the need for adhesiolysis and the risk of bowel and surrounding organ injury (20).

Fibrotic adhesions can hinder visualization, often crucial in LLR procedures. In addition, bleeding may occur during adhesion exfoliation. Therefore, depending on the condition of the abdominal cavity, the possibility of converting from laparoscopy to laparotomy may increase for patients with postoperative adhesions (21). It is necessary to carefully consider how laparoscopic surgery can be adapted for patients who have a history of abdominal surgery.

Technical and instrumental improvements have allowed the adoption of laparoscopic procedures for patients with a surgical history. However, the LLR procedure is more complicated. In particular, anatomical hepatectomy or hepatectomy in the subdiaphragmatic region, or cases in which the inferior vena cava has been operated on even once, have to be approached carefully and are often not applicable to LapRH. Tumors that recur in the lower area on the ventral side of the liver can be indicated for LapRH. In this regard it is important to determine the indications, which we were able to achieve through preoperative 3D-CT simulation in all 24 cases scheduled for laparoscopic surgery.

In LapRH we first approach from the umbilicus. The presence or absence of adhesion under the umbilicus is important, and in all cases, we were able to open the navel via laparotomy. Via a 3-cm incision of the umbilicus, information on the circumference of the umbilicus under direct vision can be obtained, and if
there is adhesion, peeling treatment within the range where the EZ Access is attached can be performed. Although there is a reported example whereby a fast port was inserted into a patient whose adhesion was predicted by an optical method (22), our method provides a relatively good field of view and encounters little difficulty upon inserting a laparoscope, in contrast to abdominal cavity insufflation. Alternatively, it has been reported that it is possible to investigate adhesions in the peritoneal cavity by body surface ultrasonography before surgery (23, 24). We also conduct ultrasound examinations before surgery to discern adhesions around the umbilicus; therefore, care is taken when incising 3 cm of the navel. In our procedure we do not insert the port at first but do consider that performing laparotomy while checking under direct vision and attaching a Lap Protector is safe in adhesion cases.

We believe that laparoscopic hepatectomy is possible regardless of the extent of adhesion if we can install EZ Access and insert a laparoscope under pneumoperitoneum (Fig. 3a). Laparoscopic surgery is more useful than conventional laparotomy for adhesion treatment in the abdominal cavity, especially the abdominal wall and omentum or intestinal adhesions. There are also reports about the usefulness of laparoscopic adhesion-detaching surgery (Fig. 3b) (25–27). We believe that it is better to use gravity, pneumoperitoneum pressure, and the magnifying effect from the organ side instead of proceeding from the abdominal wall of the adhered side, because the pneumoperitoneum in the abdominal cavity and the “zoom” effect of the laparoscope make the boundary between the intestinal tract and the other organs easier to discern.

For cases with a history of abdominal surgery, we perform resection of the liver parenchyma after conventional abdominal surgery, with detachment of adhesions on the abdominal wall and surrounding hepatic tissues and organs. Especially in the case of repeat hepatectomy, the conventional laparotomy procedure involves unnecessary exfoliation and surgical operation to secure a suitable space for the operative field, further inviting prolonged operating time. However, in LapRH the adhesion-stripping operation can be kept to a minimum time range, although there are exceptions.

For cases of partial resection of liver segment 8 after posterior segmentectomy of the liver, hepatectomy under hand-assisted treatment instead of pure laparoscopic surgery is recommended, because the liver has been removed from the diaphragm in the previous operation and placed adjacent to the previous hepatic cross section. This sometimes forms biloma in the cross section of the liver, and in the case of a
tumor near the diaphragm or the inferior vena cava, we think it preferable in future to remove it from LapRH indications. Regarding the indications for LapRH, it is necessary to reconsider these carefully as the number of cases accumulates.

Intraoperative ultrasonography is an indispensable tool in LLR because we cannot confirm the tumor directly by laparoscopy. In repeat hepatectomy cases, intraoperative ultrasonography cannot be used successfully if the liver surface is deformed and there is liver displacement caused by adhesion, and there are frequent limitations on movement. In repeat hepatectomy, because of deformation and mutation of the liver it is no longer a conventional dissection, so it is important to recognize the space within the abdominal cavity.

By simulating the liver tumor using the preoperative volume analyzer Synapse Vincent (Fuji, Tokyo, Japan), it is possible to reach the liver parenchyma and the tumor by the shortest route, that is, by securing a space where the device can move with minimal adhesion. Unlike conventional laparotomy, it is not necessary to secure a wide surgical field. In LapRH, pinpoint operation in a narrow, limited space is possible by taking advantage of the magnifying effect. In our experience LapRH secures a working space only for hepatectomy and eliminates other adhesions. These procedures can be planned in advance by simulating the position of the tumor and the relationship between the hepatic resection area and surrounding organs.

We found that the smaller working space required by LapRH allowed for minimal adhesion dissections and a direct tumor approach. For example, in the LapRH after right lobectomy, the previous segment of liver apex and the stomach wall adhered, but because this was identified by the preoperative simulation as shown in Fig. 2, a strategy for adhesion detachment was devised. Surgical adaptations also differ depending on surrounding adherent organs. Adherence of the duodenum, jejunum, and colon wall is not a good indication for LRH because it is extremely difficult to overcome.

Conventional repeat hepatectomy requires an adhesion treatment of the site and range to secure the operative field, which is not necessary for hepatectomy because of the large laparotomy. Therefore, compared with open surgery, LapRH reduces the time spent before hepatectomy. There are many LapRH cases where adhesions around the hepatic duodenal ligament are highly advanced, and all cases of ischemia by Pringle maneuver are avoided. There are often adhesions of the upper part of the hepatic duct, duodenum, and pancreas, and supplementing a surgical procedure increases the risk of unexpected complications.
Indeed, there was no increase in the amount of bleeding during surgery without having performed ischemia by the Pringle method. There was no significant difference in the amount of intraoperative bleeding in the LapRH group in comparison with the LapPLR group performed under ischemia. One of the factors that reduced the amount of bleeding during surgery was the development of energy devices. Also, it is equally important not to damage multiple organs and expose them to bleeding during hepatectomy.

We believe preoperative simulation to be useful and important in delineating the relationship between liver surface and surrounding organs for intraoperative LapRH, in addition to the relationship between regular tumor and intrahepatic vessels. In our experience of LapRH, good results were obtained by meticulous dexterity and preparation.

Although not significant, the number of hospital days after LapRH surgery was lower compared with the length of stay after the initial surgical case, owing to the minimally invasive nature of LapRH. In addition to fewer postoperative days until discharge, the patients who underwent LapRH experienced satisfactory bed rest and left the hospital in good spirits.

With more widespread use of LapRH predicted, it seems that most cases of repeat hepatectomy will be performed with partial hepatectomy without requiring anatomical hepatectomy. As a feature of LapRH, hepatectomy can be performed with an effective operative field that cannot be achieved with a conventional laparotomy field, taking advantage of adhesion. For example, surgery using the state in which the liver has been lifted can be carried out by adhesion of the peritoneum and the liver surface directly under the previous surgical handiwork. This is often convenient for LLR. Unlike multiple organs, the liver is peculiar to parenchymal organs, and because of its weight the condition whereby the liver is lifted by adhesion may be convenient.

In the case where the principal locus of the tumor existed on the dorsal side of the extrahepatic area and the ventral side of the liver adhered to the abdominal wall, it was possible to excise it very efficiently from the dorsal side without lifting the liver. In conventional LLR it is difficult to sever the tumor unless the liver is lifted with forceps. Based on our experience so far, LapRH is an excellent technique for tumors close to the liver surface on the ventral side. However, it is necessary to carefully examine the situation with respect to the site to which the surgical approach has been applied, the diaphragm, and the area adjacent to the inferior vena cava.
LapRH is superior in terms of stress relief and bodily regulation, and it is possible to perform the procedure in the minimum space necessary for hepatectomy, as can be seen from our results. The use of LapRH as a treatment for recurrent liver cancer will increase in the future. We also need to increase the number of cases to gain experience, formalize the procedure, and advance its development.

Unexpectedly, the results (Table3) indicate that the LapRH group had no statistic inferior to the LapPLR group regarding operation time and bleeding. It is probably because that the improvement of the surgical skill, team works, or development of instruments. It is necessary, however, to research with more large number of forward study in the future because this study has a small number of population in the LapRH group.

Conclusion

The magnified visual effect of laparoscopy makes hepatectomy possible in a more limited space. This is largely due to technical improvements of laparoscopic hepatectomy and the development of energy devices. LapRH is useful for treating recurrent HCC, as it shows good results in intraoperative bleeding volume and hospital length of stay after surgery in comparison with laparotomy reversal resection (14,15). In the future LapRH promises to become the preferred surgical choice for the treatment of recurrent liver cancer.

Conflict of Interest: The authors declare that they have no conflict of interest.
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FIGURE LEGENDS

Fig. 1. (a) LapRH after right hepatectomy, Lap Protector™ was attached to the navel. We used a 12-mm port and, 5-mm ports for EZ Access. (b) LapRH after excision of the anterior segment of the liver. We created a 5-mm incision wound consistent with the previous surgical handiwork.

Fig. 2. In the case of recurrence after liver left lobectomy, the relationship between the residual liver and the surrounding organs such as the stomach and duodenum are delineated by 3D-CT simulation. This image shows the area between the dissected liver section and tumor and the stomach and surrounding organs. The recurrent tumor is in the vicinity of the previously dissected hepatic section.

Fig. 3. Intraoperative surgical view. (a) If EZ Access can be attached, observation around the umbilicus by the laparoscope is possible and adhesion peeling is easy. (b) Adhesive detachment of the peritoneum, intestinal tract, mesentery, and omentum under pneumoperitoneum has a good visual field and is easy to do.
Fig 2
Fig 3a

Fig 3b
Table 1

| Surgical History                  | Procedure                      | Approach   | Adhesion |
|-----------------------------------|-------------------------------|------------|----------|
| Hepatectomy (n=21)                | S8 partial resection          | Thoracotomy| Mild     |
| S5 partial resection              | S8 partial resection          | Thoracotomy| Mild     |
| S5 partial resection              | S5 partial resection          | Laparoscopic| Mild    |
| Extended left lobectomy, Hepatic duct jejunostomy | Laparotomy         | Severe     |
| Posterior segmentectomy           | HALS                          | Severe     |
| S5 partial resection              | S4 partial resection          | Laparoscopic| Mild    |
| S5 partial resection              | S7,S8 partial resection       | Laparoscopic| Severe  |
| S3 partial resection              | S3 partial resection          | Laparoscopic| Mild    |
| S4,S5,S6,S7 partial resection     | S4 partial resection          | Laparoscopic| Mild    |
| S5 partial resection              | S4,S8 partial resection       | Laparoscopic| Mild    |
| Extended right lobectomy          | S5 partial resection          | Laparoscopic| Mild    |
| S5 partial resection              | Anterior segmentectomy, S1 partial resection | Laparotomy| Severe  |
| S8 segmentectomy, MHV combined resection | Laparotomy         | Severe     |
| S5 partial resection              | S8 partial resection          | Laparoscopic| Mild    |
| S8 partial resection              | S2, S3 partial resection      | Laparoscopic| Mild    |
| Hepatectomy+Gastrectomy (n=2)     | S3,S4,S6 partial resection: Distal gastrectomy | Laparotomy| Severe  |
| Hepatectomy+Pancreatectomy (n=1)  | S8 partial resection: Distal gastrectomy | Laparotomy| Severe  |
| Lateral segmentectomy, Distal pancreatectomy | Laparoscopic          | Severe     |

Operation procedure and approach methods that was done prior to LapRH were tabulated. And adhesion at the LapRH were also summarized. Note The degree of adhesions was classified according to Beck et al. (20) (mild = grade 1–2, severe = grade 3–4). S: segment; HALS, hand assisted laparoscopic surgery.
### Table 2

**Characteristics of the patients with LRH**

| Sex | Age | Disease | LRH procedure | No. of tumors | Size of tumor (mm) | Chronic liver disease |
|-----|-----|---------|---------------|---------------|-------------------|----------------------|
| 1   | F   | 66      | Met           | Lateral segmentectomy | 1 | 32      | –            |
| 2   | M   | 73      | HCC           | S5 partial resection   | 1 | 20      | +            |
| 3   | M   | 67      | HCC           | S3,S8 partial resection | 2 | 15, 18  | +            |
| 4   | F   | 78      | ICC           | S8 partial resection   | 1 | 25      | –            |
| 5   | M   | 69      | Met           | S4,S8 resection (HALS) | 2 | 15, 18  | –            |
| 6   | M   | 60      | HCC           | Lateral segmentectomy | 1 | 27      | +            |
| 7   | M   | 76      | HCC           | S3 partial resection   | 1 | 18      | +            |
| 8   | F   | 82      | Met           | S8 partial resection   | 1 | 22      | –            |
| 9   | F   | 53      | Met           | S8 partial resection   | 1 | 20      | –            |
| 10  | M   | 76      | HCC           | S6,S7 partial resection | 2 | 16, 18  | +            |
| 11  | M   | 73      | Met           | S3 partial resection (3rd Hx) | 1 | 25      | –            |
| 12  | M   | 56      | Met           | S1 partial resection (3rd Hx) Lateral segmentectomy, | 2 | 22, 15  | –            |
| 13  | M   | 60      | HCC           | S3 partial resection (TANKO) | 1 | 28      | +            |
| 14  | F   | 59      | Met           | S3 partial resection (TANKO) | 1 | 32      | –            |
| 15  | F   | 53      | Met           | S5 partial resection   | 1 | 30      | –            |
| 16  | F   | 73      | HCC           | S4 partial resection   | 1 | 25      | +            |
| 17  | M   | 68      | HCC           | S8 partial resection   | 1 | 20      | +            |
| 18  | M   | 69      | HCC           | S8 partial resection   | 1 | 22      | +            |
| 19  | M   | 73      | HCC           | S2 partial resection   | 1 | 18      | +            |
| 20  | M   | 73      | HCC           | S3 partial resection   | 1 | 22      | +            |
| 21  | M   | 60      | Met           | S6 partial resection   | 1 | 25      | –            |
| 22  | M   | 64      | Met           | S6 partial resection   | 1 | 32      | –            |
| 23  | M   | 83      | Met           | S2,S3 partial resection | 2 | 18, 20  | –            |
| 24  | F   | 78      | HCC           | S2 partial resection   | 1 | 22      | +            |

HCC: Hepatocellular carcinoma; ICC: Intrahepatic cholangiocarcinoma; Met: metastasis; HALS: Hand-assisted laparoscopic surgery; TANKO: single-port surgery
Table 3

Short-term results of the LLR group and LapRH group

|                     | LapPLR     | LapRH     | p Value |
|---------------------|------------|-----------|---------|
| Age                 | 69 (37–84) | 69 (53–83) | 0.96    |
| Gender (M/F)        | 69/48      | 43/28     | 0.83    |
| Operation time (min)| 257 (57–836) | 228 (125–751) | 0.80    |
| Bleeding (mL)       | 248 (0–2885) | 70 (0–1500)   | 0.76    |
| Postop. hospital stay (days) | 12 (4–48) | 8 (6–20) | 0.23    |