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Gradual expansion of the indications for minimally invasive liver resection to include highly complex procedures may improve postoperative outcomes

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Abstract

Aim: Liver resection is performed in patients with benign and malignant liver tumors. Advancements in surgical instruments and improved perioperative management have enabled safe laparoscopic and robotic liver resections. Herein, we aimed to evaluate the patients who underwent minimally invasive liver resection (MISLR) and compare their short-term outcomes with those of patients who underwent open liver resection (OLR), according to surgical complexity.

Methods: Data of patients who underwent liver resection at our institution from January 2011 to August 2023 were obtained from a prospectively maintained database. We gradually expanded the indications for MISLR from technically less demanding procedures to intermediate- and high-complexity MISLRs. The procedures were categorized into three grades (low, intermediate, and high) according to the liver resection complexity classification.

Results: Of the 1,866 patients who underwent liver resection, 953 were included in the analysis. Of the 953 patients, 781 underwent OLR and 172 underwent MISLR. The operative time and estimated blood loss increased with the increase in surgical complexity in the MISLR group, which was similar to finding in the OLR group. The complication rate also increased with the increase in surgical complexity in the OLR group (low complexity vs. high



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complexity, 34.8% vs. 50.1%). However, the complication rate was steadily low and approximately 10% across all complexity grades in the MISLR group.

Conclusion: Careful selection and gradual expansion of the indications of MISLR may facilitate improved postoperative outcomes in patients undergoing highly complex MISLRs.

Keywords: Liver resection, laparoscopic liver resection, robot liver resection, the liver resection complexity classification

INTRODUCTION

Liver resection is a potentially curative treatment for liver malignancies, including hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and liver metastases^[1-3]. Liver resection is performed via a laparotomy due to its technical complexity for a laparoscopic approach. The liver is a blood-intensive organ, and intraoperative bleeding may cause fatal complications^[4]. Postoperative complications such as bile leakage are closely related to surgical manipulations, anesthesia, preoperative evaluation and preparation, and postoperative observation and management^[5]. Recently, advancements in surgical instruments and improved perioperative management have expanded the indications of minimally invasive liver resection (MISLR)^[6-8]. Our group has gradually expanded the indications of MISLR to include technically less demanding as well as technically complex procedures. Furthermore, the indications for MISLR have been carefully selected to preserve the patient's safety and improve the postoperative outcomes of MISLR when compared with those of open liver resection (OLR). MISLR is reportedly associated with lesser blood loss, lesser pain, and shorter hospital stays. However, no mortality and minimal complications should be prioritized when selecting a new approach over the established approach (i.e., MISLR instead of OLR). We hypothesized that our policy to gradually and carefully expand the indications for MISLR would not impair the postoperative outcomes of patients undergoing technically complex MISLR procedures. Thus, to this end, we aimed to assess the annual number of MISLRs performed and compare the outcomes of patients undergoing MISLR with those of patients undergoing OLR, according to surgical complexity.

METHODS

Study population

A prospectively compiled database was searched for patients who had undergone liver resection at The University of Tokyo from January 2011 to August 2023. Patients who had undergone liver resection in addition to other procedures such as resection of other organs, cyst fenestration, and stoma closure and patients who underwent associating liver partition with portal vein occlusion for staged hepatectomy, two-stage liver resection, and laparoscopic-assisted liver resection were excluded. The study was approved by The University of Tokyo's Review Board (No: 2158-10; January 19, 2023).

Indications for MISLR

Our group started performing laparoscopic liver resection (LLR) in January 2009 and robot liver resection (RLR) in December 2021. We categorized liver resection procedures using the liver resection complexity classification which has been validated for both OLR and MISLR [Figure 1]^[9-11]. We started performing LLR in patients undergoing low-complexity liver resections such as wedge resection and left lateral sectionectomy. Gradually, we expanded the indications of LLR to intermediate- and high-complexity liver resections such as segmentectomy, sectionectomy, and hemi-hepatectomy. The indication of liver resection and the selection of surgical approach (i.e., open vs. minimally invasive approach) were discussed in the group meeting.

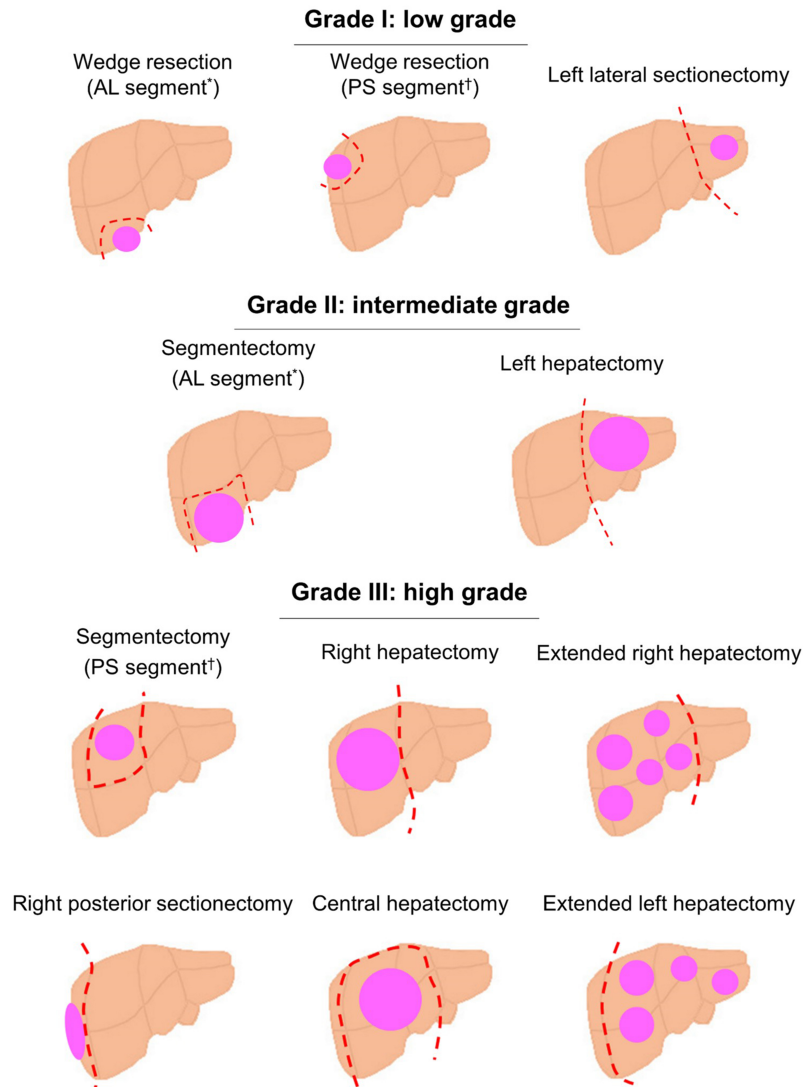


Figure 1. Three-level liver resection complexity classification. [†]AL segments are defined as Couinaud segments 2, 3, 4b, 5, and 6. [†]PS segments are defined as Couinaud segments 1, 4a, 7, and 8. AL: Anterolateral; PS: posterosuperior. Citation with permission^[12]. Copyright 2020, Clinics in liver disease.

Surgical procedure

We used a J-shaped or inverse L-shaped incision in most patients undergoing OLR and a midline or subcostal incision in others. For patients undergoing MISLR, we used a reduced port approach^[13]. A multiple access device was placed at the umbilicus via a 4-cm incision, and a camera port and assistant port were created. On the basis of the tumor location, 2–3 trocars were placed via these ports. The clamp crushing method was used in all the approaches. The intermittent inflow occlusion method (15 min of clamping followed by 5 min of release) was used for all the patients undergoing OLR in general. In contrast, it was used in selected patients undergoing LLR and RLR because pneumoperitoneum helps to control bleeding^[14]. A drainage tube was generally placed.

Definition

Surgical margin was determined on the basis of pathological evaluation. The complications were graded using Clavien–Dindo (CD) classification^[15].

Table 1. Demographics and clinicopathologic characteristics between OLR and MISLR groups

	OLR N = 781	MISLR N = 172	P-value
Age, median (IQR), year	69 (61-75)	68 (59-76)	0.625
Sex, n (%)			0.449
Male	554 (70.9)	117 (68.0)	
Female	227 (29.1)	55 (32.0)	
BMI, median (IQR), kg/m²	22.9 (20.6-25.3)	23.0 (21.0-25.9)	0.333
Child-pugh-score, n (%)			> 0.999
A	770 (98.6)	170 (98.8)	
B	11 (1.4)	2 (1.2)	
ICG-R15, median (IQR), %[‡]	9.7 (6.6-14.2)	9.9 (5.7-14.0)	0.391
History of abdominal surgery, n (%)	364 (46.6)	89 (51.7)	0.222
ASA, n (%)			0.075
1	114 (14.6)	23 (13.4)	
2	567 (72.6)	115 (66.9)	
3	99 (12.7)	33 (19.2)	
4	1 (0.1)	1 (0.6)	
Diagnosis, n (%)			0.061
HCC	470 (60.2)	89 (51.7)	
ICC	70 (9.0)	12 (7.0)	
CLM	164 (21.0)	45 (26.2)	
NENM	3 (0.4)	2 (1.2)	
Others [†]	74 (9.5)	24 (14.0)	

[‡]Data missing on ICG-R15 for four patients in OLR group. [†]Including non-colorectal liver metastases, focal nodular hyperplasia, hepatic hemangioma, bile duct stones, angioliopoma, angiomyolipoma, mucinous cystic neoplasm, neurofibroma, and inflammation tissue. OLR: Open liver resection; MISLR: minimally invasive liver resection; IQR: interquartile range; BMI: body mass index (calculated as weight in kilograms divided by height in meters squared); ICG-R15: indocyanine green retention rate at 15 minutes; ASA: American Society of Anesthesiologists; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; CLM: colorectal liver metastases; NENM: neuroendocrine neoplasm metastases.

Statistical analysis

Categorical variables were expressed in numbers and percentages, and assessed with Pearson's Chi-squared test or Fisher's exact test. Continuous variables were expressed as median values with the interquartile range (IQR), and assessed with Kruskal-Wallis test. Cochran-Armitage test was used for a trend test of binary variables, and Jonckheere-Terpstra test was used for a trend test of continuous variables. Statistical analysis was conducted with R software (The R Foundation).

RESULTS

Study population

Of the 1,866 patients who underwent liver resection, 953 met the inclusion criteria [Supplementary Figure 1]. Of the 953 included patients, 781 underwent OLR (grade I, $n = 224$; grade II, $n = 172$; grade III, $n = 385$) and 172 underwent MISLR (grade I, $n = 105$; grade II, $n = 47$; grade III, $n = 20$). The demographic and clinicopathologic characteristics did not significantly differ between the groups [Table 1]. Both groups included 50%-70% of patients with primary liver cancer and 20%-30% of patients with metastatic liver cancer.

Annual number of MISLRs performed according to complexity grades

The indications for MISLR had expanded from low-complexity resections to intermediate- and high-complexity resections. The proportion of grade II (intermediate-complexity) resections has increased since

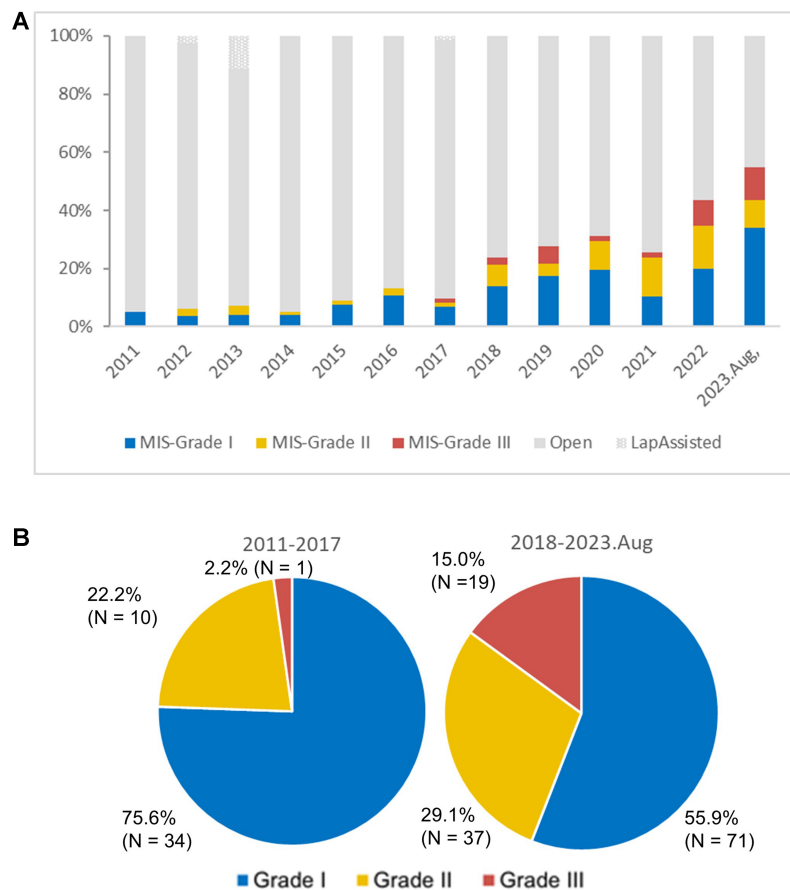


Figure 2. (A) Annual number of LR cases by each complexity grade and (B) proportion of MISLR cases of each complexity grade in 2011-2017 and 2018-2023 Aug. MIS: Minimally invasive surgery; LapAssisted: laparoscopic assisted; Aug: August; LR: liver resection; MISLR: minimally invasive liver resection.

2018, and the proportion of grade III (high-complexity) resections has risen since 2022 [Figure 2]. During 2011-2017, 24.4% of the MISLRs were grade II and III procedures, and this proportion increased to 44.1% during 2018-2023.

Comparison of the surgical and postoperative outcomes between the OLR and MISLR groups

The proportion of liver resections according to complexity was significantly different between the OLR and MISLR groups. The proportion of grade I and III procedures was the highest in the MISLR and OLR groups, respectively [Table 2]. Bile leakage, pulmonary complications and surgical site infection were significantly less in the MISLR group than in the OLR group [Table 2]. The operative time, blood loss, complication rate, and length of hospital stay were significantly lower in the MISLR group than in the OLR group [Supplementary Figure 2]. In the OLR group, the operative time, blood loss, complication rate, and length of hospital stay increased significantly with higher surgical complexity (from grade I to III resection, trend $P < 0.001$) [Supplementary Figure 3]. In the MISLR group, the operative time and blood loss increased significantly as the surgical complexity rose (from grade I to grade III resection, trend $P < 0.001$) [Supplementary Figure 4]. However, the complication rate and length of hospital stay were similar in the MISLR group across all grades of surgical complexity [Supplementary Figure 4].

Table 2. Surgical and postoperative outcomes between OLR and MISLR groups

	OLR N = 781	MISLR N = 172	P-value
Liver resection complexity classification, n (%)			< 0.001
Grade I	224 (28.7)	105 (61.0)	
Grade II	172 (22.0)	47 (27.3)	
Grade III	385 (49.3)	20 (11.6)	
Conversion to open approach, n (%)	-	7 (4.1)	-
Use of inflow occlusion, n (%)	732 (93.7)	100 (58.1)	< 0.001
Duration of inflow occlusion, median (IQR), min[‡]	56 (40-76)	60 (40-90)	0.179
Blood transfusion, n (%)	113 (14.5)	3 (1.7)	< 0.001
Surgical margin status, positive, n (%)[†]	124 (16.2)	14 (8.2)	0.008
Complication, n (%)			
Bile leakage	59 (7.6)	4 (2.3)	0.012
Hepatic insufficiency	1 (0.1)	0 (0)	> 0.999
Pulmonary complication	74 (9.5)	2 (1.2)	< 0.001
SSI	32 (4.1)	1 (0.6)	0.022
90-day mortality, n (%)	2 (0.3)	0(0)	-

[‡]Assessed with 732 patients in OLR and 100 patients in MISLR group undergoing inflow occlusion. [†]Data missing on surgical margin status, positive for 15 patients in OLR group, and two patients in MIS group. OLR: Open liver resection; MISLR: minimally invasive liver resection; IQR: interquartile range; SSI: surgical site infection.

Comparison of the surgical and postoperative outcomes between the OLR and MISLR groups according to the complexity grade

The surgical and postoperative outcomes were compared between the OLR and MISLR groups according to patients undergoing grade I resection [Figure 3], grade II resection [Figure 4], or grade III resection [Figure 5]. The operative time in patients undergoing grade I, II, and III resections was similar between the OLR and MISLR groups [Figures 3A, 4A, and 5A]. However, the blood loss, complication rate, and length of hospital stay were significantly lower in patients undergoing grade I-III procedures in the MISLR group than in the OLR group (all $P < 0.05$) [Figures 3-5].

DISCUSSION

Our group has gradually expanded the indications for MISLR over ten years to include low-complexity liver resections and intermediate/high-complexity liver resections. This may enhance the safety of patients undergoing MISLR. The estimated blood loss and complication rate were lower and hospital stay was shorter in the MISLR group than in the OLR group in patients undergoing grade I-III resection [Figures 3-5].

Our data suggest that careful patient selection for a minimally invasive approach and gradual expansion of indications for MISLR to technically demanding procedures may lower the postoperative complication rate and shorten the hospital stay in patients undergoing grade II (intermediate complexity) and grade III (high complexity) liver resection. In the OLR group, the rate of CD grade \geq II complications demonstrated an increasing trend as the surgical complexity increased [Supplementary Figure 3]. However, in the MISLR group, the rate of CD grade \geq II complications was similar and approximately 10% in patients undergoing grade I, II, and III resections [Supplementary Figure 4]. As a European multi-institution study suggested, a long implementation process is necessary to allow for standardization and implementation to mastery^[16].

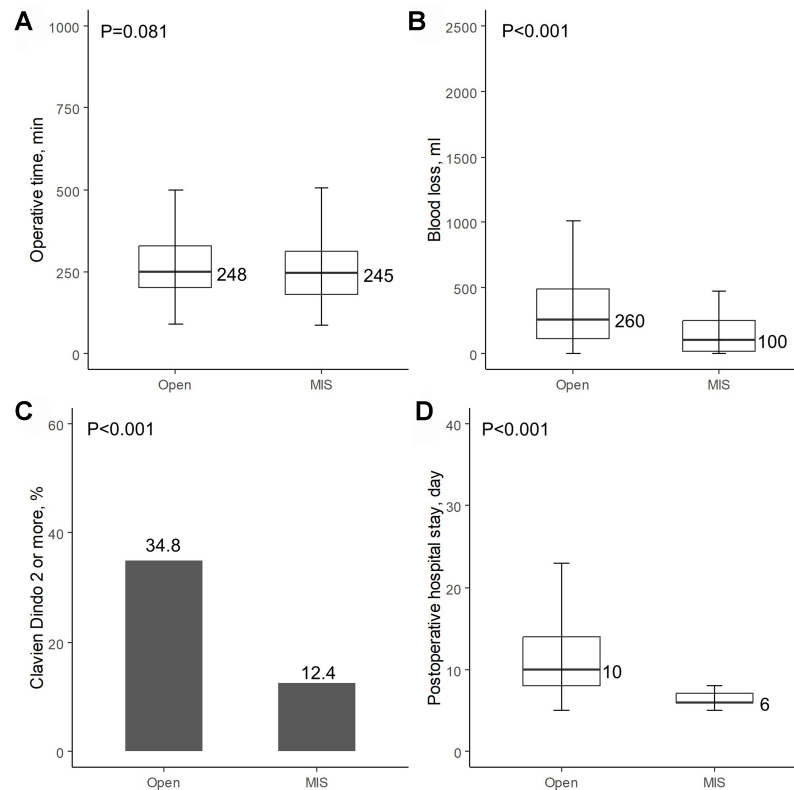


Figure 3. Surgical and postoperative outcomes compared between OLR and MIS groups in grade I. (A) Operation time is not significantly different; (B) Blood loss, (C) complication of Clavien Dindo 2 or more, and (D) postoperative hospital stay are better in MIS group. The numbers of cases of complication of Clavien Dindo 2 or more were 78 cases (34.8%) in OLR and 13 cases (12.4%) in MIS group (C). OLR: Open liver resection; MIS: minimally invasive surgery.

Minor/major classification has been traditionally used on the basis that a resection of ≥ 3 contiguous Couinaud segments is defined as a major resection^[11]. New classifications for MISLR were reported by Ban *et al.*, Wakabayashi *et al.*, Kawaguchi *et al.*, Hasegawa *et al.*, and Halls *et al.* according to the difficulty of MISLR^[9,17-20]. The classifications proposed by Ban *et al.*, Wakabayashi *et al.*, Hasegawa *et al.*, and Halls *et al.* score MISLR procedures according to an index scale^[11,17-20]. The three-level complexity classification proposed by Kawaguchi *et al.* is simple and based on the type of liver resection procedures. Different from other classifications, this classification was originally developed for MISLR, and was subsequently validated for OLR^[11] and RLR^[21]. We used this classification in our current study because it was the only new classification validated for both MISLR and OLR. Russolillo *et al.* demonstrated that the classifications proposed by Kawaguchi *et al.* and Hasegawa *et al.* predicted the technical complexity of MISLR better than classification proposed by Halls *et al.*^[22]. Goh *et al.* reported that the classifications proposed by Wakabayashi *et al.*, Hasegawa *et al.*, and Kawaguchi *et al.* were significantly associated with surgical complexity and postoperative outcomes; however, the classification proposed by Halls *et al.* was not associated with postoperative outcomes^[23]. The analysis of the area under the curve of the receiver operating characteristic curve demonstrated that the three-level complexity classification was significantly better than the minor/major classification for both OLR and MISLR in terms of predicting the operative time, estimated blood loss, and postoperative complications^[10,11]. Furthermore, for MISLR, the classification by Kawaguchi *et al.* was similar to that by Wakabayashi *et al.* in terms of predicting the estimated blood loss and

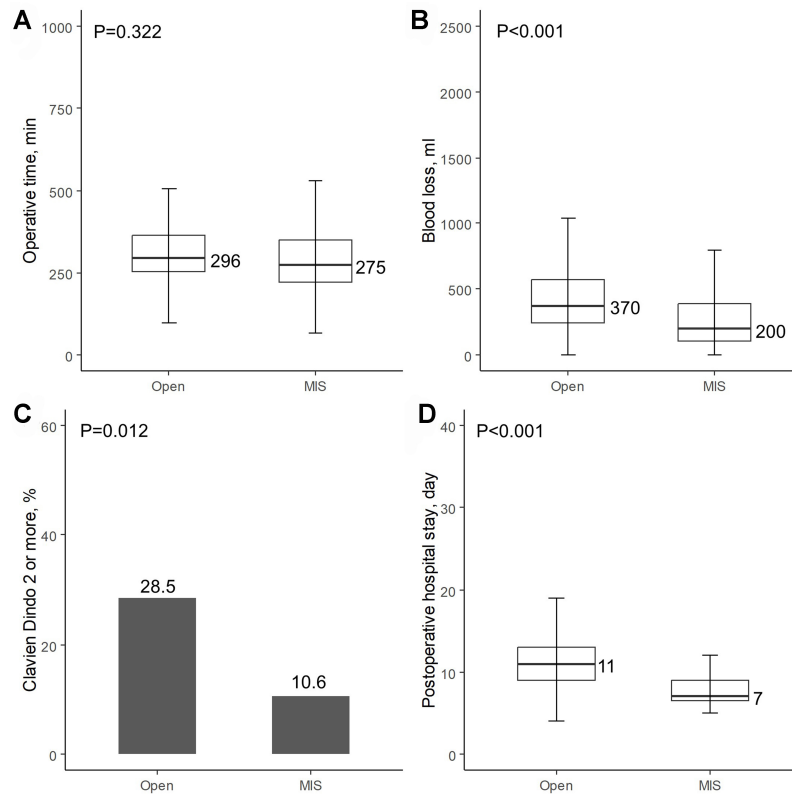


Figure 4. Surgical and postoperative outcomes compared between OLR and MIS groups in grade II. (A) Operation time is not significantly different; (B) Blood loss, (C) complication of Clavien Dindo 2 or more, and (D) postoperative hospital stay are better in MIS group. The numbers of cases of complication of Clavien Dindo 2 or more were 49 cases (28.5%) in OLR and 5 cases (10.6%) in MIS group (C). OLR: Open liver resection; MIS: minimally invasive surgery.

postoperative complications and associated with scores of the classification by Wakabayashi *et al.*^[10]. The classification by Kawaguchi *et al.* is reportedly useful in everyday clinical practice for evaluating training pathways with graduated autonomy in liver resection^[24], assessing outcomes stratified by surgical complexity^[25-27], adjusting imbalance of surgical complexity between groups using propensity score matching^[28], and reporting intergroup differences in surgical complexity in real-world patients regardless of geographical location^[11].

A limitation of this study is that it was a single-center retrospective study. Furthermore, the background demographics were not completely balanced between the groups. Additionally, repeat hepatectomy was not assessed in the study. The current study does not show how much experiences of OLR and MISLR are needed to safely expand the indication of MISLR toward grade II and III procedures. As such, careful selection and indication expansion are needed. A recent study of our group with the cumulative sum analysis showed that 40 cases of low complexity grade I procedures before starting intermediate complexity grade II procedures, and 30 cases of intermediate complexity grade II procedures before starting high

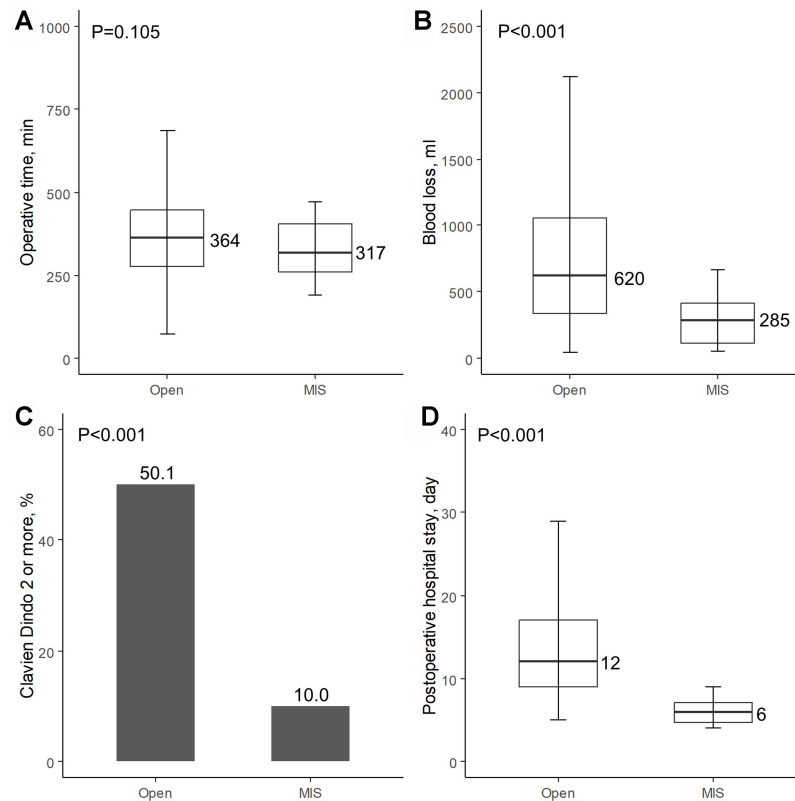


Figure 5. Surgical and postoperative outcomes compared between OLR and MIS groups in grade III. (A) Operation time is not significantly different; (B) Blood loss, (C) complication of Clavien Dindo 2 or more, and (D) postoperative hospital stay are better in MIS group. The numbers of cases of complication of Clavien Dindo 2 or more were 193 cases (50.1%) in OLR and 2 cases (10.0%) in MIS group (C). OLR: Open liver resection; MIS: minimally invasive surgery.

complexity grade III procedures may ensure a safe implementation of high complexity LLR procedures^[29]. Nonetheless, our study emphasized the importance to assess outcomes of liver resection by taking into account the difference in intergroup liver resection complexity. Finally, although the rate of intermediate- or high-complexity MISLRs increased, the majority of the highly complex liver resections classified as grade III procedures were performed via OLR.

In conclusion, careful selection and gradual expansion of MIRLR ensured the implementation of MISLR for highly complex liver resections without mortality. The postoperative complications of intermediate- and high-complexity resections were similar to those of low-complexity resections in patients undergoing MISLR. However, the postoperative complications increased with the rise in surgical complexity in patients undergoing OLR. MISLR should be used for liver resections if there are no contraindications.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Sawa Y, Kawaguchi Y

Performed data acquisition and provided administrative, technical, and material support: Sawa Y, Kawaguchi Y, Miyata A, Nishioka Y, Ichida A, Akamatsu N, Kaneko J, Hasegawa K

Availability of data and materials

Authors agree to make data and materials supporting the results or analyses presented in their paper available upon reasonable request.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

This research was conducted in accordance with the Declaration of Helsinki and approved by The University of Tokyo's Review Board (No: 2158-10; January 19, 2023). Informed consent of patients for the current study was obtained in the form of an opt-out on the website (<http://www.u-tokyo-hbp-transplant-surgery.jp/about/clinical.html>).

Consent for publication

Not applicable.

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