Current topics in liver surgery

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Abstract
Liver resection is one of the main treatment strategies for liver malignancies. Mortality and morbidity of liver surgery has improved significantly with progress in selection criteria, development of operative procedures and improvements in perioperative management. Safe liver resection has thus become more available worldwide. We have identified four current topics related to liver resection (anatomical liver resection, laparoscopic liver resection, staged liver resection and chemotherapy-induced liver injury). The balance between treatment effect and patient safety needs to be considered when planning liver resection. Progress in this area has been rapid thanks to the efforts of many surgeons, and outcomes have improved significantly as a result. These topics remain to be solved and more robust evidence is needed. Precise selection of the optimal procedure and risk evaluation should be standardized with further development of each topic. The present article reviews these four current topics with a focus on safety and efficacy in recent series.

KEYWORDS
adverse event, mortality, surgical criteria, surgical treatment

1 | INTRODUCTION

Anatomical liver resection (AR) is believed to reduce the risk of intrahepatic metastases and recurrences attributable to the invasion of tumor cells in the nearby portal veins.1–5 Some studies have reported the benefits of AR compared with non-anatomical liver resection (NAR).6–11 but other research has failed to confirm the same results.12–15 Which category of patients is most effectively treated by AR thus remains controversial.

Laparoscopic liver resection became widespread in the 1990s and is now in common use. At first, this surgery was considered controversial, but constant improvements have been made in the procedure, techniques and surrounding materials such as energy devices, forceps and scopes. As a result, laparoscopic liver resection is now one of the standard options for liver malignancies, showing merits in the operation fields and degree of invasiveness. Recently, laparoscopic liver resection has shown superiority in terms of lower intraoperative blood loss, shorter length of hospital stay and same overall and disease-free survival compared to open liver resection.16–22 However, the underlying pathologies are heterogeneous, and previous studies have included small numbers of participants and differing complication rates.23–27 Recently, results from the first randomized controlled trial (RCT) and some large cohort studies have become available.28 Thus, more robust evidence with which to carry out laparoscopic liver resection as a standard treatment is now available.

Over the last two decades, patients with colorectal liver metastases (CRM) have shown marked improvements in long-term survival thanks to advances in chemotherapy and surgical techniques.29 However, the use of several cytotoxic agents has been associated with specific liver injuries.30–32 A deeper understanding of the mechanisms of action and side-effects of common agents is needed to achieve maximal oncological benefit while reducing adverse effects from CRM.
| First author | Year | Term | Study type | Patients | Procedure | Tumor size (cm) | Single tumor (%) | Morbidity (%) | Mortality (%) | 5-y survival (%) | Reference no. |
|--------------|------|------|------------|----------|------------|----------------|----------------|--------------|--------------|----------------|--------------|
| 1 Yamamoto   | 2001 | 1990-1994 | Retrospective | 90       | AR         | 2.7 (±1.0)a   | 95.1           | N.A.         | 1.1           | 67             | 14           |
|              |      |       |            | 114      | NAR        | 2.5 (±1.0)a   | 96.4           | N.A.         | 2.6           | 55.8           |              |
| 2 Hasegawa   | 2005 | 1994-2001 | Retrospective | 156      | AR         | 3.5 (1.2-20.5) | 100            | N.A.         | 0            | 66             | 44           |
|              |      |       |            | 54       | NAR        | 3 (1.2-17.0)   | 100            | N.A.         | 0            | 35             |              |
| 3 Capussotti | 2005 | 1985-2001 | Retrospective | 164      | AR         | 5.1a          | N.A.           | 37.2         | N.A.         | 33.9           | 6            |
|              |      |       |            | 52       | NAR        | 4.2a          | N.A.           | 38.5         | N.A.         | 39.3           |              |
| 4 Kaibori    | 2006 | 1992-2003 | Retrospective | 34       | AR         | 4.1 (±2.1)a   | 64.7           | 23.5         | 2.9           | 52.7           | 7            |
|              |      |       |            | 213      | NAR        | 3.3 (±2.3)a   | 72.7           | 25.8         | 1.9           | 46.2           |              |
| 5 Wakai      | 2007 | 1990-2004 | Retrospective | 95       | AR         | 3.5 (1.2-17.0)| 100            | 22           | 2            | 67             | 8            |
|              |      |       |            | 63       | NAR        | 3.0 (1.0-12.0) | 100           | 25           | 6            | 59             |              |
| 6 Yamashita  | 2007 | 1985-2004 | Retrospective | 201      | AR         | 2.9 (±0.1)a   | 100            | 8            | N.A.         | 76             | 9            |
|              |      |       |            | 120      | NAR        | 2.4 (±0.1)a   | 100            | 10.8         | N.A.         | 74             |              |
| 7 Cho        | 2007 | 1998-2001 | Retrospective | 99       | AR         | 3.5a          | 100            | 12.1         | 0.7           | 65.7           | 10           |
|              |      |       |            | 69       | NAR        | 3.1a          | 100            | 20.3         | 0.8           | 49.3           |              |
| 8 Eguchi     | 2008 | 1994-2001 | National survey | 2267     | AR         | 3.1           | 100            | N.A.         | 0.71          | 65.5           | 12           |
|              |      |       |            | 3514     | NAR        | 2.8           | 100            | N.A.         | 0.86          | 62.4           |              |
| 9 Kobayashi  | 2008 | 1990-2004 | Retrospective | 106      | AR         | 3.0 (1.1-14.0)| 100            | 17           | 0            | 54             | 11           |
|              |      |       |            | 127      | NAR        | 2.8 (1.0-14.5)| 100            | 21           | 0            | 61             |              |
| 10 Dahiya    | 2010 | 1983-2002 | Retrospective | 159      | AR         | N.A.          | N.A.           | 46           | 1.8           | 47.5           | 45           |
|              |      |       |            | 214      | NAR        | N.A.          | N.A.           | 42           | 0            | 49.4           |              |
| 11 Kamiyama  | 2010 | 1990-2006 | Retrospective | 169      | AR         | 3.1a          | 100            | N.A.         | N.A.         | 83             | 2            |
|              |      |       |            | 153      | NAR        | 2.6a          | 100            | N.A.         | N.A.         | 65.3           |              |
| 12 Kang      | 2010 | 1998-2005 | Retrospective | 146      | AR         | 2.8 (±0.8)a   | 100            | 17.8         | N.A.         | 48             | 3            |
|              |      |       |            | 21       | NAR        | 2.7 (±0.9)a   | 100            | 4.8          | N.A.         | 40             |              |
| 13 Yamazaki  | 2010 | 1994-2007 | Retrospective | 111      | AR         | 3.1a          | 100            | 46           | 1.8           | 47.5           | 4            |
|              |      |       |            | 98       | NAR        | 2.7a          | 100            | 42           | 0            | 49.4           |              |
| 14 Kudo      | 2014 | 2000-2012 | Retrospective | 121      | AR         | 3.3a          | 96             | N.A.         | 0.4 (total)  | 63             | 5            |
|              |      |       |            | 112      | NAR        | 2.6a          | 96             | N.A.         | 0            | 69             |              |
| 15 Okamura   | 2014 | 2002-2013 | Matched cohort | 64       | AR         | 3.0 (7.0-16.0)| 100            | 21.9         | 0            | 71             | 41           |
|              |      |       |            | 64       | NAR        | 2.5 (10.0-16.0)| 100           | 18.8         | 0            | 79.7           |              |

(Continues)
Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a novel procedure to maximize remnant liver volume to carry out extended right liver resection such as right trisegmentectomy. However, according to the international ALPPS registry, more than 15% of ALPPS were done in patients who may have had no indications for two-stage hepatectomy. They cautioned against overuse of ALPPS and mentioned that the indications should be carefully considered. The indications for ALPPS should thus be reconsidered to balance safety and efficacy. To overcome the high morbidity after ALPPS, a modified procedure is now available.

2 | ANATOMICAL LIVER RESECTION IN HEPATOCELLULAR CARCINOMA

The concept of AR was proposed in the 1930s as a right or left hepatectomy. Thereafter, in 1985, Makuuchi described ultrasonically anatomical subsegmentectomy for hepatocellular carcinoma (HCC) in which every Couinaud’s segment could be completely removed. The 5-year survival rate was better in the AR group (35%) than in the enucleation group (66%, \( P < 0.05 \)). As a result, AR was considered theoretically effective for avoiding intrahepatic metastasis of cancer cells through the portal vein, with a preference for eradicating portal venous tumor extension in HCC. In contrast, AR requires the sacrifice of a large amount of liver parenchyma to guarantee eradication of potential vascular invasion and tumor spread through the portal vein. Some authors have described AR as too complex and offering no contribution to survival. Most previous studies have shown no clear evidence regarding the superiority of AR and some meta-analyses have also reported conflicting results.

The current series represents a review of AR between 2001 and 2015 (Table 1). We identified 18 studies on the surgical treatment of single lesions <5 cm in diameter. Most of these papers (13 studies) were retrospective with four matched cohorts and one national survey from Japan. Sufficient number of participants was included in each study. Morbidity rate ranged from 8% to 46% with AR and from 4.8% to 42% with NAR. No obvious difference in morbidity was seen between the two procedures. At the same time, mortality associated with liver resection has improved dramatically over the last two decades, implying that significant differences may not exist between procedures.

The survival benefit of AR remains controversial. In retrospective studies, 5-year overall survival has tended to be better with anatomical resection. However, a large cohort in a national survey from Japan demonstrated that AR showed superiority in neither overall survival nor disease-free survival compared to NAR. In subgroup analysis, superiority of AR was found only for tumors between 2 and 5 cm in diameter. Matched cohort studies showed that some populations (absence of vascular invasion, tumor diameter >2.0 cm, degree of differentiation) were associated with better 5-year overall survival following AR. Meta-analysis of both 5-year disease-free survival and 5-year overall survival has shown significantly better...
results with AR than with NAR. This result makes sense, in that HCC <2 cm are generally effectively treated with other treatment options such as radiofrequency ablation. In cases with tumors larger than 5 cm, the high frequency of vascular invasion may impede the local treatment effects of AR. AR thus appears to have limited beneficial effects on survival in all patients. Results from further clinical studies such as large RCT are awaited to clarify which categories are suitable for AR.

3 | LAPAROSCOPIC LIVER RESECTION

Use of laparoscopic surgery for digestive procedures has increased rapidly and the approach is now mainstream in this area. Laparoscopic surgery for hepatobiliary-pancreatic surgery has also spread quickly over the last decade, with the optimization of procedures and good selection criteria depending on tumor location contributing to improved effectiveness and safety. The merits of laparoscopic surgery in liver resection are thought to be the magnified view and reduced invasiveness of the operation. Compared to open liver resection, in recent reports, less blood loss from the hepatic veins during liver transection contributes to better surgical outcomes with laparoscopic surgery.

The history of laparoscopic liver resection is relatively long, but marked differences can be seen in procedures, patient populations and outcomes between the most recent decade and previous years. We therefore reviewed a total of 23 recent reports concerning laparoscopic liver resection from 2008, comprising 13 matched cohort studies and nine retrospective studies and one RCT (Table 2).

The general indications for laparoscopic resection in each study were lesions <5 cm in diameter or systematic lobectomy. Among these, the consensus was reached that operation time was significantly longer, but blood loss was lower with laparoscopic surgery than with open liver resection. Morbidity appears to be better with laparoscopic liver resection, attributable to the lower rate of infectious subcutaneous complications following reductions in the length of the skin incision. The mortality rate with laparoscopic liver resection has now decreased and optimal safety is ensured in high-volume centers. Among the studies examined in this report, some authors noted that survival benefits did not differ between laparoscopic and open liver resection.

Recently, the results of a multi-institutional large cohort meta-analysis have become available. The mortality rate was only 0.4% (37 of 9527 patients), comparable to that in the Japanese national survey of open liver resection (0.4%-0.5%). In cases of minor resection, mean intraoperative blood loss was 322 mL with laparoscopic liver resection, and 572 mL with open conventional liver resection, whereas values of 619 and 1299 mL, respectively, were seen with major liver resection. The morbidity rate was significantly better with laparoscopic liver resection than with open liver resection for both minor (13.5% vs 30.5%) or major liver resection (22.4% vs 45.6%). However, blood loss with open liver resection in these studies seemed extraordinarily high in high-volume hepatobiliary centers.

Development of the laparoscopic surgery procedure shows non-inferiority even when HCC was in an unfavorable location. This Italian multicenter study mentioned that even with HCC located on the posterior segment, the procedure can be safely carried out with a conversion rate of 17.8%. In contrast, conversion as a result of unfavorable intraoperative events resulted in worse outcomes during laparoscopic liver resection. In tertiary referral centers, the conversion rate in laparoscopic surgery was 10% among 1184 major resections in 1996-2014 and 7.8% among 2861. A history of neoadjuvant chemotherapy, previous liver resection, extent of resection and difficult location are independent predictors of the need for conversion.

Recently, results from the RCT to compare laparoscopic and open liver resection for CRM have become available. In brief, median complexity score and tumor distribution were not statistically significant, but most of the participants in this study had fewer than two tumors and median resection volume was <100 g. Complication rate and postoperative hospital stay were significantly better in laparoscopic liver resection. Differing from the previous studies, operation time was not significantly longer but intraoperative blood loss was less with laparoscopic liver resection. These results suggest that laparoscopic liver resection is catching up with conventional open liver surgery in many regards and shows superiority when carried out for optimal tumor conditions. Future prospective studies will show which conditions are more favorable for laparoscopic and conventional open liver resection.

4 | ASSOCIATED LIVER PARTITION AND PORTAL VEIN LIGATION FOR STAGED HEPATECTOMY

Insufficient volume after liver resection is one of the independent predictors for postoperative liver failure and is closely related to high mortality. The current consensus is that more than 30% of normal liver parenchyma or more than 40% of diseased liver parenchyma should be preserved when planning operations to secure patient safety. Thus, liver functional reserve and parenchyma volume should be precisely evaluated.

When the volume of remnant liver parenchyma is small, portal vein embolization (PVE) before liver resection is recommended to increase the remnant liver parenchyma. This procedure is usually adopted in right liver resection and results in an approximately 10% increase in the volume of remnant liver. Lower limits for an indication of PVE are approximately 30% of the remnant parenchymal volume in normal liver and 40% in chronic liver disease. PVE is now widely accepted as a useful option for certain patients who may require extensive hepatectomy. When the estimated remnant liver volume after liver resection is approximately 30% of the total liver volume, ALPPS is planned to increase the volume of remnant liver. ALPPS involves simultaneous liver partition and
| First author | Year | Term | Study type | Patients | Disease | Procedure |
|--------------|------|------|------------|----------|---------|-----------|
| 1 Topal      | 2008 | 2002-2007 | Matched cohort | 76 | N.A. | OLR |
| 2 Tsinberg   | 2009 | 2006-2008 | Retrospective | 43 | Mixed | OLR |
| 3 Castaing   | 2009 | 1997-2007 | Matched cohort | 60 | CRM | OLR |
| 4 Dagher     | 2009 | 1998-2002 | Matched cohort | 50 | Mixed | OLR |
| 5 Sarpe      | 2009 | 1997-2007 | Matched cohort | 56 | HCC | OLR |
| 6 Ito        | 2009 | 1998-2008 | Matched cohort | 65 | Mixed | OLR |
| 7 Tranchart  | 2010 | 1999-2008 | Matched cohort | 42 | HCC | OLR |
| 8 Vanounou   | 2010 | 2002-2008 | Retrospective | 29 | Mixed | OLR |
| 9 Cannon     | 2012 | 1995-2010 | Matched cohort | 35 | CRM | OLR |
| 10 Johnson   | 2012 | 2004-2011 | Retrospective | 124 | Mixed | OLR |
| 11 Bhojani   | 2012 | 2006-2010 | Retrospective | 114 | Mixed | OLR |
| 12 Slim      | 2012 | 2008-2011 | Matched cohort | 46 | Mixed | OLR |
| 13 Gustafson | 2012 | 2006-2009 | Retrospective | 49 | Mixed | OLR |
| 14 Kobayashi | 2013 | 1997-2011 | Retrospective | 27 | HCC | OLR |
| 15 Medbery   | 2014 | 2008-2012 | Matched cohort | 57 | Mixed | OLR |
| 16 Komatsu   | 2016 | 2006-2014 | Matched cohort | 38 | HCC | OLR |
| 17 Ratti     | 2015 | 2011-2015 | Matched cohort | 147 | Mixed | OLR |
| 18 Nomi      | 2015 | 1998-2014 | Retrospective | 28 | Mixed | OLR |
| 19 Yoon      | 2017 | 2008-2015 | Matched cohort | 115 | HCC | OLR |
| 20 Cheung    | 2016 | 2004-2014 | Matched cohort | 330 | HCC | OLR |
| 21 Xiang     | 2016 | 2012-2015 | Retrospective | 207 | HCC | OLR |
| 22 Li        | 2017 | 2005-2010 | Retrospective | 87 | HCC | OLR |
| 23 Fretland  | 2018 | 2012-2016 | RCT | 144 | CRM | OLR |

Data are expressed as median (range).
CRM, colorectal metastasis; HCC, hepatocellular carcinoma; LLR, laparoscopic liver resection; OLR, open liver resection.
*Mean.
| Tumor size (cm) | Op. time (min) | Blood loss (mL) | Morbidity (%) | Mortality (%) | 5-y survival (%) | Reference no. |
|-----------------|----------------|----------------|--------------|--------------|-----------------|---------------|
| N.A.            | N.A.           | 300 (5-4000)   | 28.9         | N.A.         | N.A.            | 16            |
| 4.2 (±0.3)      | 172 (±12)      | 299.6 (±33.6)  | 16           | 0            | N.A.            | 24            |
| 3.9 (±2.7)      | 201 (±15)      | 122.5 (±45.4)  | 13           | 0            | N.A.            |               |
| 4.0 (8.0-16.0)  | N.A.           | N.A.           | N.A.         | N.A.         | 45              | 17            |
| 3.0 (5.0-8.0)   | N.A.           | N.A.           | N.A.         | N.A.         | 74              |               |
| 4.9 (±3.2)      | 328 (±10.6)    | 735.2 (±74.4)  | 34           | 2            | N.A.            | 23            |
| 4.3 (±7.6)      | 360 (±20.3)    | 519.5 (±93.4)  | 9            | 0            | N.A.            |               |
| 4.3            | N.A.           | N.A.           | N.A.         | N.A.         | N.A.            | 53            |
| 3.4 (0.9-13.0)  | 138³           | 200            | 43           | N.A.         | 56.2 (3 y)      | 18            |
| 3.3 (0.4-14.4)  | 170³           | 100            | 14           | N.A.         | 72.3 (3 y)      |               |
| 3.7³           | 221³           | 723.7³         | 40.4         | 2.4          | 37.2            | 19            |
| 3.6³           | 233³           | 364.3³         | 21.4         | 2.4          | 45.6            |               |
| 4.1 (±3.6)     | 249³           | N.A.           | 24           | 0            | N.A.            | 25            |
| 5.1 (±2.9)     | 245³           | N.A.           | 16           | 0            | N.A.            |               |
| 4 (±2)³        | N.A.           | 392 (±324)     | 49           | 0.7          | 37              | 20            |
| 4 (±3)³        | N.A.           | 202 (±180)     | 23           | 0            | 36              |               |
| 5.72³          | 234³           | 833 (±1008)    | 10.4         | 0.8          | N.A.            | 58            |
| 5.37³          | 238³           | 697 (±739)     | 6.8          | 1.1          | N.A.            |               |
| 3.6 (0.8-16.7) | 270 (137-500)  | 250³           | 25           | 0            | N.A.            | 59            |
| 4.5 (0.9-19.0) | 240 (128-605)  | 500³           | 39           | 2            | N.A.            |               |
| 4.3 (1.2-9)    | 170 (85-315)   | 200 (50-2000)  | 39.1         | 2.2          | N.A.            | 54            |
| 3.2 (1.3-8.3)  | 155 (45-400)   | 100 (10-800)   | 17.4         | 0            | N.A.            |               |
| 5.1³           | N.A.           | N.A.           | 48.8         | 4.1          | 89.8 (1 y)      | 26            |
| 2.6³           | N.A.           | N.A.           | 22.2         | 0            | 85.2 (1 y)      |               |
| 2.0³           | 185 (120-430)  | 450 (50-2200)  | 0            | 0            | 62 (3 y)        | 27            |
| 2.2³           | 198 (45-394)   | 110 (0-1180)   | 0            | 0            | 50 (3 y)        |               |
| 8              | 222            | 737            | 44           | 4            | N.A.            | 55            |
| 5.9            | 175            | 214            | 28           | 5            | N.A.            |               |
| 9.2            | 295            | 113            | 61           | 0            | 77.2            | 21            |
| 6.7            | 371            | 190            | 32           | 0            | 85.4            |               |
| 6              | 200            | 268            | 26           | 0            | N.A.            | 56            |
| 5              | 259            | 208            | 22           | 2            | N.A.            |               |
| N.A.           | 273            | 423            | 57           | 4            | N.A.            | 60            |
| N.A.           | 279            | 465            | 55           | 3            | N.A.            |               |
| 5.8³           | 202            | 136³           | 17           | 0            | 100 (2 y)       | 57            |
| 3.1³           | 33             | 125³           | 5            | 0            | 88.8 (2 y)      |               |
| 2.9 (0.8-10.0) | 255 (45-912)   | 410 (20-5000)  | 24.4         | N.A.         | 67.4            | 22            |
| 2.6 (0.6-10.0) | 185 (50-756)   | 150 (10-1500)  | 10           | N.A.         | 83.7            |               |
| 6.9 (±1.5)³    | 236 (117-466)  | 456 (50-2000)  | 35.7         | 1            | 82.2 (3 y)      | 61            |
| 6.7 (±1.5)³    | 234 (105-501)  | 481 (80-3000)  | 20.3         | 0.8          | 81.4 (3 y)      |               |
| 2.3 (±0.5)³    | 140 (±52.9)    | 85 (10-275)    | 73.6         | N.A.         | 72.4            | 62            |
| 2.0 (±0.5)³    | 129 (±41.8)    | 79 (20-200)    | 42.9         | N.A.         | 77.4            |               |
| N.A.           | 120 (106-134)  | 200 (126-273)  | 31           | 1            | N.A.            | 28            |
| N.A.           | 123 (108-138)  | 300 (224-375)  | 19           | 0            | N.A.            |               |
portal vein ligation prior to the liver resection. ALPPS provides great regeneration within the short term, but indications for this procedure are now controversial because of high mortality and morbidity.

We reviewed the current series concerning ALPPS from 2012. There were 18 retrospective studies, including three multicenter studies (Table 3). However, the number of participants in each study was small. We compared the current results of the five PVE papers in the same term as references. The most common current indication for ALPPS was multiple CRM, which suggests that most patients have good liver functional reserve. In contrast, the common indications for PVE were Klatskin tumor, HCC and colorectal metastasis. Rates of increase in liver volume were surprisingly different. With the ALPPS procedure, median rate of increase in remnant liver parenchyma over the first 2 weeks ranged from 48% to 113.1%, compared to 7.4% to 12% with PVE.

The most concerning problems in ALPPS are morbidity and mortality. Morbidity rate in ALPPS ranged from 15.3% to 92%, and mortality rate ranged from 0% to 29%. Severe complications appeared to be frequent after this procedure. In the first ALPPS procedures, intraoperative blood loss to partition the liver parenchyma was too high, ranging from 100 to 725 mL. Meta-analysis confirmed the results of operation-related outcomes. This procedure is therefore considered to be under development and modifications of the procedure and revision of its indications will be required in order to improve safety.

To obtain safe procedures, some modifications to the original ALPPS have been advocated including an anterior approach with complete parenchymal division down to the IVC, an in situ split using an anterior approach followed by PVE by interventional radiology, and partial transection using the anterior approach. These modified techniques have contributed to decreases in the mortality and morbidity of ALPPS. Recently, an analysis of the international ALPPS registry cautioned against overuse of ALPPS. One-third of ALPPS procedures for CRM were carried out without objective indications. Thus, keeping to strict indications for ALPPS would mean the procedure is done only when tri-segmentectomy is needed for the purposes of addressing a wide tumor distribution.

### 5 | CHEMOTHERAPY-ASSOCIATED LIVER DAMAGE

Systemic chemotherapy has no doubt changed the current strategy for patients with advanced CRM. The prognosis has improved significantly on the basis of current combination chemotherapies (5-fluorouracil, and oxaliplatin or irinotecan) with

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**TABLE 3** Associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) and portal vein embolization (PVE)

| First author       | Year  | Term       | No. of patients | Procedure | Study type       |
|--------------------|-------|------------|-----------------|-----------|-----------------|
| 1 Schnitzbauer     | 2012  | 2007-2011  | 25              | ALPPS     | Retrospective   |
| 2 Torres           | 2013  | 2011-2012  | 39              | ALPPS     | Retrospective   |
| 3 Nadalin          | 2014  | 2010-2013  | 15              | ALPPS     | Retrospective   |
| 4 Robles           | 2014  | 2011-2013  | 22              | ALPPS     | Retrospective   |
| 5 Schadde          | 2014  | 2012-2013  | 202             | ALPPS     | Retrospective (multicenter) |
| 6 Kremer           | 2015  | 2011-2014  | 19              | ALPPS     | Retrospective   |
| 7 Hernandez-Alejandro | 2015 | 2012-2013 | 14              | ALPPS     | Retrospective   |
| 8 Truant           | 2015  | 2011-2013  | 62              | ALPPS     | Retrospective   |
| 9 Alvarez          | 2015  | 2011-2014  | 30              | ALPPS     | Retrospective   |
| 10 Lang            | 2015  | 2007-2014  | 16              | ALPPS     | Retrospective   |
| 11 Chan            | 2016  | 2013-2015  | 17              | ALPPS     | Retrospective   |
| 12 Rasok           | 2016  | 2012-2014  | 36              | ALPPS     | Retrospective (multicenter) |
| 13 Serenari        | 2016  | 2012-2014  | 50              | ALPPS     | Retrospective (multicenter) |
| 14 Sakuhara        | 2012  | 1999-2009  | 143             | PVE       | Retrospective   |
| 15 Leung           | 2014  | 1999-2012  | 153             | PVE       | Retrospective   |
| 16 Shindoh         | 2014  | 1995-2012  | 358             | PVE       | Retrospective   |
| 17 Sofue           | 2014  | 2007-2011  | 83              | PVE       | Retrospective   |
| 18 Cazejust        | 2015  | 2009-2013  | 63              | PVE       | Retrospective   |

Data are expressed as median (range).

CRM, colorectal metastasis; HCC, hepatocellular carcinoma.

*Mean.

*Transfusion rate (%).
humanized monoclonal antibodies. As a result, liver resection provides potential “cure” in 10%-30% of patients with initially unresectable CRM.29 However, giving long-term chemotherapy induces chronic liver damage and is considered harmful for the prospects of future liver resection. Oxaliplatin-induced liver damage is termed “blue liver,” pathologically appearing as sinusoidal obstruction29-31,94 and nodular regenerative hyperplasia in the liver parenchyma.33 Irinotecan-induced liver damage is called “yellow liver,” representing steatosis or steatohepatitis in liver parenchyma.94,95 The parenchymal damage from chemotherapy negatively influences the postoperative outcomes. However, the pathophysiological background to such damage remains insufficiently understood.

### 5.1 Sinusoidal injury

Sinusoidal obstruction syndrome (SOS) was first described in patients given pyrrolizidine alkaloids.96 The key pathological feature is sinusoidal dilatation with hepatocyte atrophy. SOS is categorized into four grades (0-3) according to pathological changes, depending on the duration of chemotherapy. SOS progresses to perisinusoidal fibrosis and nodular regenerative hyperplasia. Oxaliplatin increases the risk of developing sinusoidal injury by approximately 2.22- to 4.36-fold when patients receive more than six cycles of chemotherapy.96

| Disease (%) | Increased liver volume (%) | Blood loss in liver partition (mL) | Time from treatment to assessment (days) | Morbidity (%) | Mortality (%) | Reference no. |
|-------------|---------------------------|----------------------------------|--------------------------------------|--------------|--------------|---------------|
| CRM (56)    | 74 (21 to 192)            | 320 (150-7500)                  | 9                                    | 64           | 12           | 34            |
| CRM (82)    | 83 (47 to 212)            | N.A.                             | 14                                   | 59           | 12.8         | 73            |
| CRM (33)    | 87 (23.8 to 161)          | N.A.                             | 13                                   | 67           | 29           | 74            |
| CRM (77.3)  | 61 (33 to 189)            | 100 (0-900)                      | 7                                    | 63           | 9            | 75            |
| CRM (58)    | 86                       | N.A.                             | 10                                   | 40           | 9            | 76            |
| CRM         | 74 (±35)                  | 1380 (200-700)                  | 8                                    | 68           | 16           | 77            |
| CRM (80.6)  | 93 (±28)                  | 725 (±85)                       | 8                                    | 36           | 0            | 78            |
| CRM (63)    | 48 (15.3 to 192)          | 494 (±35)                       | 8                                    | 80.6         | 12.9         | 79            |
| CRM (64)    | 89.7 (21 to 287)          | N.A.                             | 6                                    | 53           | 6.6          | 80            |
| CRM (56.3)  | 113.1 (38.6 to 207.7)     | N.A.                             | 9                                    | 64           | 12.5         | 81            |
| HCC         | 48.7                      | 500 (100-2000)                  | 8                                    | 15.3         | 7.7          | 82            |
| CRM (69.4)  | 67 (17 to 238)            | 675 (150-5600)                  | 6                                    | 92           | 0            | 83            |
| CRM (44)    | N.A.                      | N.A.                             | N.A.                                 | 54           | 20           | 84            |
| Klatskin (47.6) | 10.7 (±6.7)  | –                                 | 17                                   | 6.3          | 0            | 85            |
| CRM (89.5)  | 9.64 (6.75 to 12.36)      | –                                 | 27                                   | 56.8         | 1.3          | 86            |
| CRM (60.6)  | N.A.                      | –                                 | 32                                   | 25.8         | 3.8          | 87            |
| Klatskin (44.6) | 12 (5 to 8)   | –                                 | 17                                   | 5            | 0            | 88            |
| HCC (63.3)  | 11 (±7)                   | –                                 | 24                                   | 11.1         | N.A.         | 89            |

### 5.2 Hepatic steatosis and hepatitis

Liver steatosis and steatohepatitis induced by chemotherapy are thought to be mainly induced by irinotecan regimens. Postoperative risks appear to differ between steatosis and steatohepatitis. The pathological features vary from simple steatosis to steatohepatitis, hepatic fibrosis and cirrhosis, depending on the duration of parenchymal injury. The most widely used grading system was proposed by Kleiner et al, which categorizes features into four grades depending on the degree of steatosis (<5%, 5%-33%, 33%-66% and >66%).97 Steatohepatitis progresses to hepatic fibrosis and cirrhosis. Some reports have described high-grade steatosis as associated with a threefold increase in postoperative mortality.98 However, whether hepatic steatosis alone increases the risk of postoperative mortality remains controversial. In contrast, steatohepatitis is known to increase the risk of postoperative mortality when the patient receives more than 7.5 cycles of chemotherapy. Body mass index is one surrogate marker for high risk of hepatic steatohepatitis.99

We reviewed 11 papers to assess the relationship between postoperative morbidity and perioperative chemotherapy from 2003 (Table 4). These included 10 retrospective studies30–33,94,100–104 and one RCT.29 The number of participants in each study varied. Most patients in the chemotherapy group were given systemic preoperative chemotherapy for metastasis from colorectal cancer. The data suggested that irinotecan-based chemotherapy was closely associated
with development of steatohepatitis.\textsuperscript{105} Presence of steatohepatitis has been shown to increase postoperative morbidity and mortality in non-alcoholic steatohepatitis (NASH) patients.\textsuperscript{106} The pathological feature of chemotherapy-induced liver damage resembles that in NASH patients. Some authors have cautioned that long-term chemotherapy-induced steatohepatitis is thus a risk for postoperative mortality. However, the optimal method for estimating liver functional reserve and how far liver resection can be safely carried out remains unconfirmed. Interruption of chemotherapy is reported to improve liver function (indocyanine green [ICG] retention rate at 15 minutes value from 17.7\% to 11.6\%) within 4 weeks.\textsuperscript{107} Therefore, estimation by ICG may be of value to estimate chemotherapy-induced liver damage.

Whether preoperative chemotherapy increases intraoperative blood loss is a controversial issue. Intraoperative blood loss is significantly greater in pathological high-grade SOS than in low-grade SOS.\textsuperscript{31} This difference may reflect the hepatic venous pressure gradient and parenchymal stiffness, and the increasing rate of SOS is associated with morbidity after liver resection. Rate of increase in splenic volume and decrease in platelet count are predictive of SOS.\textsuperscript{108-111} Reportedly, 75\% of patients who received adjuvant chemotherapy had increased splenic volume and 40\% of patients did not recover after discontinuation of chemotherapy.\textsuperscript{99,111} Giving bevacizumab in combination with systemic chemotherapy reduces the occurrence of SOS.\textsuperscript{112} However, the duration and extent to which liver function can recover remains unclear.

**6 | CONCLUSION**

Liver resection has gained wide use with more precise preoperative evaluation of hepatic functional reserve and tumor status.

### Table 4: Chemotherapy-induced perioperative risk

| First author | Year | Term | Study type | Patients | Setting | Tumor diameter (cm) |
|--------------|------|------|------------|----------|---------|-------------------|
| 1 Parikh     | 2003 | 1997-2002 | Retrospective | 34 | Preoperative chemo (CPT-based) | 2.0 (0.8-6.5) |
|              |      |        |            | 47 | Surgery alone | 4.3 (0.9-10.3) |
| 2 Fernandez  | 2005 | 2001-2003 | Retrospective | 14 | Preoperative chemo (OX- or CPT-based) + surgery | N.A. |
|              |      |        |            | 14 | Surgery alone | N.A. |
| 3 Karoui     | 2006 | 1998-2002 | Retrospective | 45 | Preoperative chemo + major surgery | 3.0 (±1.7)\textsuperscript{a} |
|              |      |        |            | 22 | Major surgery | 2.6 (±2.3)\textsuperscript{b} |
| 4 Sahajpal   | 2007 | 2001-2003 | Retrospective | 53 | Preoperative chemo + surgery | 4.5 |
|              |      |        |            | 43 | Surgery alone | 5.8 |
| 5 Nordlinger | 2008 | 2000-2004 | RCT | 182 | Perioperative chemo (OX-based) | N.A. |
|              |      |        |            | 182 | Surgery alone | N.A. |
| 6 Hubert     | 2010 | 2000-2006 | Retrospective | 72 | Perioperative chemo (OX-based) | N.A. |
|              |      |        |            | 18 | Surgery alone | N.A. |
| 7 Kishi      | 2010 | 1999-2007 | Retrospective | 157 | Preoperative short-term chemo + surgery | 2.1 (0.4-14.0) |
|              |      |        |            | 62 | Preoperative chemo long-term chemo + surgery | 2.7 (0.4-10.5) |
| 8 Soubrane   | 2010 | 1998-2007 | Retrospective | 13 | Preoperative chemo (SOS low-grade) + surgery | 6.3 (total length)\textsuperscript{a} |
|              |      |        |            | 38 | Preoperative chemo (SOS high-grade) + surgery | 7.9 (total length)\textsuperscript{a} |
| 9 Pessaux    | 2010 | 200-2009 | Retrospective | 26 | Preoperative chemo (Cmab) + surgery | 4.8\textsuperscript{b} |
|              |      |        |            | 26 | Preoperative chemo (without Cmab) + surgery | 4.3\textsuperscript{b} |
| 10 Makowiec  | 2011 | 2001-207 | Retrospective | 68 | Preoperative chemo + surgery | N.A. |
|              |      |        |            | 34 | Surgery alone | N.A. |
| 11 van der Pool | 2012 | 2003-2008 | Retrospective | 53 | Preoperative chemo (OX-based) + surgery | 3.5 (1-7) |
|              |      |        |            | 51 | Preoperative chemo (OX-based + Bmab) + surgery | 2.8 (1-18) |

Data are expressed as median (range).

CPT, irinotecan; DFS, disease-free survival; OX, oxaliplatin; RCT, randomized controlled trial; SOS, sinusoidal occlusion syndrome.

\textsuperscript{a}Mean.

\textsuperscript{b}Transfusion rate (%).
We now have the Japanese treatment algorithm to aid in decision-making for the surgical treatment of HCC, backed up by robust evidence.\textsuperscript{113} Anatomical resection for HCC is a more complex procedure that results in greater intraoperative blood loss and longer operation time. Overall survival from HCC is multifactorial, but a significant positive impact on survival has been observed in anatomical resection. However, no RCT have determined whether anatomical resection is an essential technique for HCC. The results of our ongoing RCT might allow the establishment of optimized procedures.

There is currently no doubt that laparoscopic liver surgery offers comparable mortality to open liver resection when the optimal location and procedure are selected.\textsuperscript{22,28,57,61,62} Laparoscopic liver resection is technically demanding and requires technical command of both liver and laparoscopic surgery. Recently, consensus guidelines to determine suitable tumor location and optimal procedure for laparoscopic liver resection have been developed. A pre-registration system has also been available since 2015 to ensure safety and to maintain the quality of laparoscopic liver resection.\textsuperscript{46,114,115}

High morbidity and mortality rates remain the most critical problem in ALPPS, which is now a widely accepted option for “marginal resectable” patients with Klatskin tumor or multiple CRM. However, we must keep in mind that patients with primary unresectable CRM experience a high rate of recurrence and receive long-term chemotherapy. Thus, careful evaluation for chemotherapy-induced liver injury is needed to maintain quality for ALPPS. Use of a risk score for ALPPS and further refinement of the indications for ALPPS are warranted.\textsuperscript{35,116} To overcome these problems, a pre-registration system is now available and may provide a way to obtain safer indications for ALPPS.\textsuperscript{117}

| Single tumor (%) | Blood loss (mL) | Morbidity (%) | Mortality (%) | DFS | 5SU | Reference no. |
|------------------|----------------|--------------|--------------|-----|-----|---------------|
| 60               | 500\textsuperscript{a} | 29           | 0            | N.A. | N.A. | 33            |
| 27               | 425\textsuperscript{a} | 49           | 0            | N.A. | N.A. |               |
| N.A.             | N.A.           | N.A.         | 0            | N.A. | N.A. | 94            |
| N.A.             | N.A.           | N.A.         | 0            | N.A. | N.A. |               |
| N.A.             | 44.5\textsuperscript{b} | 37.8         | 0            | N.A. | N.A. | 100           |
| N.A.             | 45.5\textsuperscript{b} | 13.6         | 0            | N.A. | N.A. |               |
| N.A.             | 1242\textsuperscript{a} | 39.6         | 0            | N.A. | N.A. | 101           |
| N.A.             | 1245\textsuperscript{a} | 51.2         | 0            | N.A. | N.A. |               |
| 51               | N.A.           | 25           | 1            | 28.1 (3 y) | N.A. | 29            |
| 52               | N.A.           | 16           | 1            | 36.2 (3 y) | N.A. |               |
| 47               | 225 (150-1600) | 57.3         | 0            | N.A. | N.A. | 30            |
| 73               | 600 (150-4700) | 50           | 3            | N.A. | N.A. |               |
| 36               | 230 (10-1500)  | 3.8 (liver insufficiency) | N.A. | N.A. | N.A. | 102           |
| 31               | 200 (20-3100)  | 11.3 (liver insufficiency) | N.A. | N.A. | N.A. |               |
| N.A.             | 483 (±328)\textsuperscript{a} | 23.1         | 0            | N.A. | N.A. | 31            |
| N.A.             | 880 (±960)\textsuperscript{a} | 26.3         | 5.3          | N.A. | N.A. |               |
| 88.5             | 1019 (±1597)\textsuperscript{a} | 34.6         | 0            | N.A. | N.A. | 103           |
| 88.5             | 708 (±452)\textsuperscript{a} | 30.8         | 0            | N.A. | N.A. |               |
| N.A.             | N.A.           | 50           | 6            | N.A. | N.A. | 104           |
| N.A.             | N.A.           | 44           | 2            | N.A. | N.A. |               |
| N.A.             | 32\textsuperscript{b} | 32.1         | N.A.         | 32 (3 y) | N.A. | 32            |
| N.A.             | 29\textsuperscript{b} | 25.5         | N.A.         | 23 (3 y) | N.A. |               |

\textsuperscript{a}Mean.  
\textsuperscript{b}Transfusion rate (%).

Data are expressed as median (range).

CPT, irinotecan; DFS, disease-free survival; OX, oxaliplatin; RCT, randomized controlled trial; SOS, sinusoidal occlusion syndrome.
Current chemotherapies are obviously powerful, but are closely associated with liver injury, which is regimen-specific. 118 We should keep in mind that preoperative long-term chemotherapy is a risk factor for liver injury. Thus, in cases of major liver resection in patients who have received long-term chemotherapy, precise evaluation of liver functional reserve and volume should be carried out.

We have presented topics on the current treatment strategies for liver cancers, showing that surgery has the power to dramatically improve prognosis and the primary option of choice. It is important to take into account the balance between tumor distribution and difficulty of operation. Consideration of the advantages of techniques and treatment effects is important and the method of the operation should not be the purpose of the treatment. Safety is the first priority in surgical treatment and should be refined using high-level evidence as it becomes available.

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