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## Contents

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### EDITORIAL

- 6078** Kyoto classification of gastritis: Advances and future perspectives in endoscopic diagnosis of gastritis  
*Toyoshima O, Nishizawa T*

### OPINION REVIEW

- 6090** Current status of minimally invasive liver surgery for cancers  
*Morise Z*

### MINIREVIEWS

- 6099** Management of non-alcoholic fatty liver disease patients with sleep apnea syndrome  
*Sheng W, Ji G, Zhang L*

### ORIGINAL ARTICLE

#### Basic Study

- 6109** Differential analysis of intestinal microbiota and metabolites in mice with dextran sulfate sodium-induced colitis  
*Wang JL, Han X, Li JX, Shi R, Liu LL, Wang K, Liao YT, Jiang H, Zhang Y, Hu JC, Zhang LM, Shi L*
- 6131** *Salvia miltiorrhiza* extract may exert an anti-obesity effect in rats with high-fat diet-induced obesity by modulating gut microbiome and lipid metabolism  
*Ai ZL, Zhang X, Ge W, Zhong YB, Wang HY, Zuo ZY, Liu DY*

#### Retrospective Study

- 6157** Upper gastrointestinal endoscopic findings in celiac disease at diagnosis: A multicenter international retrospective study  
*Stefanolo JP, Zingone F, Gizzi C, Marsilio I, Espinet ML, Smecuol EG, Khaouli M, Moreno ML, Pinto-Sánchez MI, Niveloni SI, Verdú EF, Ciacci C, Bai JC*

### SCIENTOMETRICS

- 6168** Integrity of the editing and publishing process is the basis for improving an academic journal's Impact Factor  
*Wang JL, Li X, Fan JR, Yan JP, Gong ZM, Zhao Y, Wang DM, Ma L, Ma N, Guo DM, Ma LS*

### CORRECTION

- 6203** Correction to "MicroRNA-596 acts as a tumor suppressor in gastric cancer and is upregulated by promotor demethylation"  
*Zhang Z, Dai DQ*

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## Current status of minimally invasive liver surgery for cancers

Zenichi Morise

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### Abstract

Hepatocellular carcinoma (HCC) patients have chronic liver disease with functional deterioration and multicentric oncogenicity. Liver surgeries for the patients should be planned on both oncological effects and sparing liver function. In colorectal patients with post-chemotherapy liver injury and multiple bilateral tumors, handling multiple tumors in a fragile/easy-to-bleed liver is an important issue. Liver surgery for biliary tract cancers is often performed as a resection of large-volume functioning liver with extensive lymphadenectomy and bile duct resection/reconstruction. Minimally invasive liver surgery (MILS) for HCC is applied with the advantages of laparoscopic for cases of cirrhosis or repeat resections. Small anatomical resections using the Glissonian, indocyanine green-guided, and hepatic vein-guided approaches are under discussion. In many cases of colorectal liver metastases, MILS is applied combined with chemotherapy owing to its advantage of better hemostasis. Two-stage hepatectomy and indocyanine green-guided tumor identification for multiple bilateral tumors are under discussion. In the case of biliary tract cancers, MILS with extensive lymphadenectomy and bile duct resection/reconstruction are developing. A robot-assisted procedure for dissection of major vessels and handling fragile livers may have advantages, and well-simulated robot-assisted procedure may decrease the difficulty for biliary tract cancers.

**Key Words:** Minimally invasive liver surgery; Laparoscopic liver resection; Robot-assisted liver resection; Hepatocellular carcinoma; Colorectal liver metastases; Biliary tract carcinoma

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**Core Tip:** Minimally invasive liver surgery (MILS) for hepatocellular carcinoma is applied with the advantages of laparoscopic “caudal approach” for cases of cirrhosis or repeat resections. Small anatomical resections using newly developing approaches are under discussion. In many cases of colorectal liver metastases, MILS is applied combined with chemotherapy, owing to its advantage of better hemostasis. Two-stage hepatectomy and indocyanine green-guided tumor identification for multiple bilateral tumors are under discussion. In the case of biliary tract cancers, MILS with extensive lymphadenectomy and bile duct resection/reconstruction are developing. A robot-assisted procedure may have advantages.

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## INTRODUCTION

Liver surgery for cancer is mainly performed in patients with hepatocellular carcinoma (HCC), liver metastasis of colorectal carcinoma (CRCLM), or biliary tract carcinomas (BTC)[1-4]. It is usually performed as curative-intent liver resection (LR) without other comparable alternatives, except for ablation therapy for small HCC and liver transplantation for patients with severe cirrhosis and non-advanced HCC. However, LR for each disease has its own specificity based on disease characteristics and background liver condition. This editorial describes the characteristics of LR for each disease. Thereafter, the advantages, disadvantages, and current status of the minimally invasive approach for each disease, and its potential are discussed.

## LR FOR HCC

Patients with HCC mostly have a history of chronic liver disease (CLD), which causes functional deterioration and multicentric oncogenicity in the injured liver[1]. Therefore, depending on the tumor and pre-existing liver conditions, LR, ablation therapy, trans-arterial chemoembolization, liver transplantation, or recently emerged systemic chemo-immune therapy are chosen. The rates of LR application to primary HCC cases and the 5 year-survival rate thereafter are approximately 30% and 50%, respectively[1]. However, after a successful first treatment, many patients eventually enter a long-term treatment course with repeated treatments for recurrent/multicentric metachronous HCC raised from an oncogenic CLD background. One of the above-listed treatment options is selected based on the tumor and liver conditions of the patients at the time of each treatment. On LR indication, an evaluation of the liver function and, accordingly, estimation of resectable functional liver volume should be performed preoperatively[5], since HCC patients with CLD have a potential risk factor for postoperative morbidity and liver failure. Furthermore, potential repeated treatments over a long period of the treatment course should be considered in the treatment strategy of patients with HCC/CLD.

However, dissemination of cancer cells within the same portal territory as HCC tumors is well known, and anatomical resection of HCC is recommended[6]. Hemi-hepatectomy, sectionectomy, and sometimes segmentectomy, are widely accepted anatomical resections. However, since clear margins of segments one, five, six, and seven have sometimes been difficult to define, the Tokyo 2020 terminology of liver anatomy and resections was recently issued for segment or smaller anatomical resections[7]. These small anatomical resections and their combinations are under discussion for their oncological advantages. Liver surgeries for HCC patients should be planned to be appropriate in terms of both oncological effects on the currently existing HCC and sparing function of the liver with CLD, not only to minimize postoperative morbidity but also from the long-term perspective of potential repeated treatments.

## LR FOR CRCLM

LR is the only curative-intent treatment for patients with CRCLM, with a 5-year overall survival rate of approximately 40%-50%[3]. However, due to the advancement of chemotherapy over the last few decades, combination strategies with chemotherapy, including adjuvant, neoadjuvant, and conversion strategies, for expanding indications and improving outcomes have become increasingly common[3]. Based on the current situation, patients with multiple tumors in the bilateral lobes often undergo LR. Several procedures are advocated to ensure that extended LR for multiple tumors is feasible and safer,

such as residual liver hypertrophy with percutaneous transhepatic portal embolization (PTPE)[8,9], two-stage hepatectomy[10], or associating liver partition or portal vein embolization for staged hepatectomy (ALPPS)[11]. In contrast, parenchymal-sparing LR is recommended for tumors occurring in small numbers, since tumor cell spreading *via* the portal vein system is rare, contrary to HCC[12]. Repeat LR for resectable recurrences improves long-term outcomes[13], and parenchymal-sparing LR reportedly improves salvageability and survival at recurrence within the liver[14]. The background liver condition is usually not fibrotic without CLD but is often associated with post-chemotherapy liver injury, such as steatosis and congestion of microcirculation with sinusoidal obstructive syndrome[15,16]. Liver steatosis can lead to liver fragility during surgery and postoperative elevation of transaminase levels. Congestion of microcirculation with sinusoidal obstruction can cause increased blood loss during surgery and, sometimes, postoperative morbidity, including ascites, similar to portal hypertension in patients with cirrhosis[17].

## LIVER SURGERY FOR BTC

Liver surgery (LS) for BTC is performed in intrahepatic cholangiocarcinoma (ICC; peripheral and central types), perihilar cholangiocarcinoma, and gall bladder carcinoma[4]. Small peripheral ICC of the mass-forming type, often with CLD backgrounds and rarely with lymph node metastases, can be treated with an HCC-like approach, though it usually lacks an HCC-like tumor capsule with more invasive features than HCC[18]. Others have more aggressive features like spreading along the Glissonian pedicle with perineural, lymphatic, and venous invasions, as well as direct liver parenchymal invasion and lymph node metastases[4,18]. Since the invasion often involves hilar and intrahepatic Glissonian pedicles, LRs for those diseases sacrifice large volumes of functioning non-cancerous liver parenchyma to remove the cancer cells deeply infiltrated from the hilum into the peripheral Glissonian pedicle. PTPE is sometimes applied in such cases to enlarge the residual liver volume preoperatively[8]. Extensive lymphadenectomy and bile duct (sometimes including vasculature: Portal vein and hepatic artery) resection plus reconstruction are required. The patients mostly have a normal liver; however, sometimes damage from biliary obstruction may be present. In cases with jaundice, preoperative biliary drainage is needed[19].

## MINIMALLY INVASIVE LIVER SURGERY

Laparoscopic liver resection (LLR) emerged in the early 1990s, and its indications have expanded thereafter[20,21]. The cancers previously mentioned are all within the indication of LLR. Less intraoperative blood loss, shorter hospital stays, and less morbidity in some conditions with comparable long-term outcomes have been generally reported with LLR for HCC and CRCLM[22,23]. LLRs for BTC, especially for those requiring extensive lymphadenectomy and bile duct (and vasculature) resection plus reconstruction, are now in the developmental stage with some early reports[24]. Although laparoscopic techniques for liver parenchymal transection, mobilization, and hemostasis have been established, those for extensive lymphadenectomy and bile duct (and vasculature) resection plus reconstruction are performed only in specialized centers. Robot-assisted LLR is also in its developmental stage and is performed mainly in specialized centers[25]. Moreover, devices that can be used in robotic procedures are still limited. However, some of the robotic procedures, such as bile duct/vasculature resection plus reconstruction, are expected to have advantages due to increased dexterity from stable endo-wrist instruments and stable high-definition three-dimensional visualization.

### Minimally invasive LR for HCC

HCC with pre-existing CLD is thought to be the cancer for which the specific approach of minimally invasive LR (MILR) is most beneficial. In 2013, we presented the novel concept of the “caudal approach to LLR”[26]. Researchers followed[27,28] and defined the concept as a major conceptual changing of LLR in the statement of the 2<sup>nd</sup> international consensus conference[29]. LR is a procedure for handling the liver while it is protected inside the subphrenic “rib cage”. In open LR, the cage is opened with a large subcostal incision and the liver is mobilized. In LLR, the laparoscope and instruments get directly into the space from the caudal direction with minimal damage on the cage, and minimal mobilization and compression on the liver[30]. This leads to minimal damage to the adherent structures as well as the liver. Since HCC patients mostly have underlying CLD, they have a higher risk of post-LR morbidity. LR patients are exposed to three types of surgical stress: (1) General and whole-body surgical stress; (2) Decreased liver function from the decrease of functioning liver parenchyma after LR; and (3) Surgery-induced damage on the environment structures and residual liver (such as disruption of collateral vessels in CLD patients by laparotomy/dissection of peritoneal attachments and parenchymal damage by compression). The third type of surgical stress can be reduced by laparoscopic-specific caudal approach[26-28] in LLR for HCC/CLD patients and that decreases short-term morbidity[30]. We

evaluated the short-term outcomes of liver surface small LLR for patients with severe CLD and our findings showed comparable short-term outcomes to those from patients of mild-to-moderate liver dysfunction[31]. Direct access to the surface tumor and minimal dissection of attachments made this surgery possible. This setting of LR can be achieved only with a laparoscopic approach. An international retrospective study using propensity score matching analysis of Child-Pugh B patients who underwent LR has shown that LLR is beneficial for these patients[32]. Moreover, LLR is thought to be advantageous also in less post-LR liver functional deterioration for those patients by smaller damage caused in surgical manipulation[30]. It can be beneficial for long-term and repeated treatment courses for the patients.

The treatment of intrahepatic recurrence is also important. Modifications of the anatomy and the formation of adhesions make repeating LR more difficult. Laparoscopic surgeries make following procedures easier from reduced formation of adhesions[33]. Furthermore, LLR allows for better visibility and manipulation even in a small surgical field between adhesions[30]. It can lead to unnecessary of total adhesiolysis in repeat procedures. Our international retrospective study for repeat LR compared laparoscopic and open approaches[34] and showed that laparoscopic repeat LR is feasible and has the short-term advantages of less bleeding and morbidity for selected patients. The overall survival curves were clearly separated, with a better tendency in LLR, though the disease-free survival curves were overlapped. The post-LR overall survival of HCC/CLD patients is determined not only by the treatment results of the resected lesion but by those of metachronous lesions and liver insufficiency during the long-term course[35,36]. During the long course of repeated treatments, patients with HCC/CLD should have adequate residual liver function after each intervention, which enables them to get future repeat treatments. We hypothesized that better overall survival after laparoscopic procedure may be from less liver functional deterioration[30]. Accompanied with less adhesion, it can make the repeat treatments easy to access and decrease deceased patients by liver insufficiency. LLR with the specific caudal approach, performed as a unique strong local treatment, is beneficial for patients with HCC/CLD.

However, LLR also has certain disadvantages. Disorientation can be easily happened due to lack of fine perceptible sensation and overview of the whole surgical field, and difficulty in performing precise intraoperative ultrasonography. Simulation and navigation from pre- and intra-operative imaging studies have been used to overcome these disadvantages. Well-simulated small anatomical resections in LLR can secure the tumor location in the resected area and provide adequate surgical margins, and lead to less postoperative bile leakage and less residual ischemic/congestive parenchyma, which possibly leads to recurrence[37]. For HCC for which anatomical resection is recommended, there are several reports of LLR that can lead to new developments, such as landmark (hepatic veins, *etc.*)-guided small anatomical resection[38], indocyanine green (ICG)-guided anatomical resection and tumor identification [39], and LLR with a Glissonian approach to more peripheral smaller branches from the hilum (cone unit resection)[40]. Robot-assisted LLR is an important emerging tool under discussion[25,41]. It could be advantageous, for example, in cases exposing a wide range of Glissonian pedicles and major hepatic veins.

### **MILR for CRCLM**

As mentioned before, patients with post-chemotherapy liver injury and those with multiple tumors in bilateral lobes increasingly undergo MILR with recent advancements in neoadjuvant/conversion chemotherapy[15,16]. Handling multiple tumors in a fragile/easy-to-bleed liver is an important issue.

In MILR for CRCLM, disorientation can be easily happened due to lack of fine perceptible sensation and overview of the whole surgical field, and difficulty in performing precise intraoperative ultrasonography, as mentioned in MILR for HCC. Simulation and navigation from pre- and intraoperative imaging studies to assure tumors in the resected area with enough surgical margin are important. Landmark (such as hepatic veins)-oriented small anatomical resection[38], ICG-guided anatomical resection and tumor identification[39], and LLR with a Glissonian approach to more peripheral smaller branches from the hilum[40,42] are also applied to CRCLM. However, because the liver does not have CLD and the need for anatomical resection is low, LR for CRCLM with a large number of tumors is often planned as a combination of large anatomical resection plus partial resections or multiple partial resections. For the combination of large anatomical resection plus partial resections, the application of two-stage hepatectomy or ALPPS in MILR is now advocated[43,44]. For multiple partial resections, ICG-guided tumor identification is reported to be effective in addition to conventional intraoperative navigation[45,46].

In terms of handling fragile and easy-to-bleed injured liver after chemotherapy, bleeding can be controlled more easily in LLR than in open procedures by optimal visualization and pneumoperitoneum accompanied by Pringle's maneuver. However, handling a fragile liver can sometimes be difficult due to congenital motion restrictions in LLR, especially in complicated resections. Robot-assisted LLR may give us a chance to overcome this difficulty with its advantages, such as increased dexterity from stable endo-wrist instruments.

Theoretically, early recovery after MILR can be advantageous when it enables the earlier introduction of adjuvant chemotherapy. Although there are no solid data on the combination of MILR and chemotherapy, the combination of these treatments is a matter of further investigation.

### Minimally invasive liver surgery for BTC

BTC is an emerging indication of minimally invasive liver surgery (MILS) under discussion[47]. Surgery for BTC consists of three different procedures: LR, lymphadenectomy, and resection plus reconstruction of the bile duct (and vasculature). The laparoscopic procedure for LR has already been established during its application in HCC and CRCLM. Lymphadenectomy around the hepatic hilum and hepatoduodenal ligaments is often performed in laparoscopic pancreatic surgery[48,49]. Laparoscopic resection plus reconstruction of the bile duct (and vasculature) for malignant diseases should be added to MILS for BTC, although there are reports of bile duct resection plus reconstruction for benign diseases[50].

Surgeries for small peripheral mass-forming ICC rarely with lymph node metastases and early-stage gall bladder carcinoma without invasion to the hepatic hilum or hepato-duodenal ligament (candidates for radical cholecystectomy) requires only peripheral LR and mild lymphadenectomy. They are the first good candidates for the MILS application. On the other hand, advanced gallbladder carcinoma, central (invasive) ICC, and perihilar carcinoma with pedicle invasions and a high potential for lymph node metastases should be handled with a complicated combination of LR, extended lymphadenectomy, and resection plus reconstruction of the bile duct (and vasculature). There are only a few reports of MILS applications in those conditions[24,51]. Among these, minimally invasive surgery for perihilar carcinoma is the most difficult. Bile duct dissection, division, and reconstruction should be performed at the more peripheral part of the small-sized bile duct to obtain a cancer-free margin. Under laparoscopic conditions, disorientation is easy to occur due to the lack of good overview/tactile sensation and motion restriction is also a congenital problem. Setting an adequate resection line without cancer invasion and performing reconstruction of the small orifice of the residual bile duct is more difficult than the open procedure. From this perspective, a well-simulated and planned robot-assisted procedure may be a potential tool to overcome this situation.

## CONCLUSION

MILS for HCC with CLD background and recommendation for anatomical resection has been established and applied to most cases with advantages in cirrhotic patients and repeat LR by laparoscopic specific “caudal approach”. Small anatomical resections using Glissonian approach, ICG-guided approach, landmark (*i.e.*, hepatic vein)-guided approach are under discussion and developments. Robot-assisted procedure for long range dissection of major vessels may have advantages.

MILS for CRCLM with combination treatments to chemotherapy has been established and applied to many cases with the advantage in better hemostasis by pneumoperitoneum and optimal visualization. LLRs with two-stage hepatectomy, ALPPS, ICG-guided tumor identification are under discussion and developments. Robot-assisted procedure for handling the fragile liver after chemotherapy may have advantages.

MILS for BTC with spreading invasion along Glissonian pedicle, lymph node metastases and direct invasion to liver parenchyma is developing, especially for extensive lymphadenectomy and bile duct (vasculatures) resection /reconstruction, and possible in experienced center. Well simulated and planned robot-assisted procedure may decrease the difficulty in setting tumor free resection line and reconstruction of small bile duct orifice (Table 1).

**Table 1 Summary of current status of minimally invasive liver surgery for cancers**

Disease	Backgrounds of disease and liver for surgery	Status of minimally invasive liver resection
HCC	Chronically injured background of liver[1,2]: (1) Deteriorated liver function-postoperative morbidity; and (2) Multicentric carcinogenesis-repeated treatments  Anatomical resection[6]	Established/applied with some merit to most cases[21,29]: Advantages in LR of LC patients[30,31] and repeat LR[30,34] by laparoscopic specific “caudal approach”[26-28]  Under discussion and development: (1) Small anatomical resection using Glissonian approach[40,42], ICG-guided approach[39], hepatic vein-guided approach[38]; and (2) Robot for long-range dissection of major vessels?
CRCLM	Combination treatments with chemotherapy[3]: (1) Multiple bilateral tumors-TSH[10], ALPPS[11]; and (2) Injured liver-fragility from steatosis[15], easy bleeding form congestion[16,17]  Parenchymal sparing resection[12,14]	Established/applied to many cases[20,23]: Advantages of better hemostasis[20,29] by pneumoperitoneum/optimal visualization  Under discussion and development: (1) LLR with TSH[43], ALPPS[44] -possible in experienced centers; (2) ICG-guided tumor identification [39,45]; and (3) Robot for handling the fragile liver?
BTC	Spreading invasion along Glissonian pedicle[4], LN metastases and direct invasion to liver parenchyma: (1) Extended LR of normal	Developing and possible in specialized center[24]: (1) Lymphadenectomy and bile duct (vasculature) resection/reconstruction in



liver-PTPE[8]; (2) Lymphadenectomy; and (3) Bile duct (vasculature) resection/reconstruction-Needs of setting tumor free resection line and reconstruction of small bile duct orifice

specialized center[24,51]; and (2) Difficulties in setting tumor free resection line and reconstruction of small bile duct orifice: Well simulated robot-assisted procedure?

HCC: Hepatocellular carcinoma; CRCLM: Liver metastasis of colorectal carcinoma; BTC: Biliary tract carcinomas; LR: Liver resection; LLR: Laparoscopic liver resection; LC: Liver cirrhosis; ICG: Indocyanine green; TSH: Two-stage hepatectomy; ALPPS: Associating liver partition or portal vein embolization for staged hepatectomy; PTPE: Percutaneous transhepatic portal embolization; LN: Lymph node.

## FOOTNOTES

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