

REVIEW ARTICLE

Update on perioperative management of patients undergoing surgery for liver cancer

Masaki Kaibori¹  | Kosuke Matsui¹  | Mitsuo Shimada²  | Shoji Kubo³  | Kiyoshi Hasegawa⁴ 

¹Department of Surgery, Kansai Medical University, Osaka, Japan

²Department of Surgery, Tokushima University, Tokushima, Japan

³Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan

⁴Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Correspondence

Masaki Kaibori, Department of Surgery, Kansai Medical University, 2-5-1 Shinmachi, Hirakata, Osaka 573-1191, Japan.

Email: kaibori@hirakata.kmu.ac.jp

Abstract

Hepatocellular carcinoma is often accompanied by chronic hepatitis or cirrhosis. Preoperative evaluation of liver function and postoperative nutritional management are critical in patients with hepatocellular carcinoma who undergo liver surgery. Although the incidence of postoperative complications and death has declined in Japan over the last 10 years, postoperative complications have not been fully overcome. Therefore, surgical procedures and perioperative management must be improved. Accurate preoperative evaluations of liver function, nutrition, inflammation, and body skeletal muscle are required. Determination of the optimal surgical procedure should consider not only tumor characteristics but also the physical reserve of the patient. Nutritional management of chronic liver disorders, especially maintaining protein synthesis for postoperative protein/energy, is important. Prophylactic antibiotics are recommended for short-term use within 24 hours after surgery. Abdominal drainage is recommended for patients with cirrhosis who may develop large amounts of ascites, who are at risk of postoperative bleeding, or who may have bile leakage due to a large resection area. Postoperative exercise therapy may improve insulin resistance in patients with chronic liver damage. Implementation of an early/enhanced recovery after surgery program is recommended to reduce biological invasive responses and achieve early independence of physical activity and nutrition intake. We review the latest information on the perioperative management of patients undergoing liver resection for hepatocellular carcinoma.

KEYWORDS

liver cancer, perioperative management, review, surgery

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide.¹ Although most affected patients are in Asia and Africa, HCC incidence and mortality rates are increasing in North America and Europe.^{2,3} In Japan, most HCCs occur in patients with chronic

hepatitis and liver cirrhosis induced by hepatitis B or C virus infection. Because of advances in perioperative management, anesthesia, and operative techniques, hepatectomy for HCC has become more common.⁴ However, the postoperative mortality rate remains higher than in patients with cirrhosis or chronic hepatitis undergoing other types of surgery. The morbidity rate of patients with cirrhosis undergoing liver

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. *Annals of Gastroenterological Surgery* published by John Wiley & Sons Australia, Ltd on behalf of The Japanese Society of Gastroenterology.

resection has been reported to range from 20% to 70%, with mortality rates of 5%-21%.⁵⁻¹⁰ Mortality rates at high-volume centers in Japan are usually much lower, <2%,¹¹⁻¹³ although morbidity rates remain relatively high. The postoperative course of these patients does not always proceed as expected, owing to various types of intraoperative stress, including blood loss and ischemia. These findings emphasize the importance of improving both surgical techniques and perioperative care in reducing the mortality and morbidity of patients with HCC undergoing liver resection. In this review, we outline the current status of and topics regarding the perioperative management of patients undergoing surgery for liver cancer based on recent evidence.

2 | ALGORITHM FOR THE TREATMENT OF HCC AND APPROPRIATE EVALUATION OF LIVER FUNCTION BEFORE HEPATECTOMY

With regard to the therapeutic strategy for HCC, the Barcelona Clinic Liver Cancer (BCLC) staging system recommended by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver is used worldwide.¹⁴ In Japan, the "treatment algorithm" described in the Clinical Guidelines for HCC is widely used to select the optimum treatment based on liver function and tumor status (Figure 1).¹⁵ The Japanese treatment algorithm differs markedly from the BCLC system with regard to HCC with concomitant portal hypertension.¹⁶ In the BCLC system, liver resection is not indicated if portal hypertension is present, and liver transplantation and radiofrequency ablation (RFA) are recommended. In contrast, liver resection is recommended based on the indocyanine green (ICG) retention rate at the 15-min (ICGR15) level in the Japanese treatment algorithm, and favorable outcomes have been reported.¹⁷ Liver resection for HCC is chosen based on the balance between tumor status and liver function. Resection exceeding the hepatic functional reserve with the goal of cancer cure may lead to liver failure, whereas insufficient resection due to excessive safety concerns may have a high risk of early recurrence. Therefore, it is important to select the optimum surgical procedure based on the extent of the tumor and the acceptable liver resection range. As the liver reserve classification for preoperative liver function evaluation, the Child classification and its modified Child-Pugh classification have been widely used worldwide. In particular, the presence or absence of ascites is used as an index of the degree of portal hypertension, and poor control of ascites is not indicated for surgery. In Europe and the United States, it has been common that B and C cases of the Child-Pugh classification are not indicated for surgery, and even in cases of Child-Pugh classification A, if portal hypertension coexists, hepatectomy is not indicated. This standard is adopted in the liver cancer treatment guidelines in Europe and the United States.¹⁴ In contrast, reports from Europe and the United States have stated that portal hypertension is not a contraindication for hepatectomy with more than two sections.¹⁸ It has been reported in Japan that reduced hepatectomy with portal hypertension is not contraindicated, because no increase in postoperative complications was observed.¹⁷ The ICG loading test and

technetium-99m-garactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy are the main quantitative preoperative evaluations of liver function for hepatectomy. Many studies of ICG load have found that it is a useful predictor of postoperative mortality.^{5,19} The ICG retention rate at 15 minutes (ICGR15) has been adopted as a factor in the evaluation of liver damage by the Japan Liver Cancer Study Group²⁰ and has become a standard evaluation of preoperative liver function. Yamanaka et al reported that the prediction score for the occurrence of postoperative liver failure as a surgical indication criterion, which consists of the ICGR15, amount of resection, and age, could accurately predict postoperative mortality.^{21,22} Takasaki et al proposed a standard that set a different permissible amount of hepatectomy for each value of the ICG loading test.²³ Postoperative liver failure and death within the permissible hepatectomy criteria were 2% and 0%, respectively, whereas for non-permissible hepatectomy, they were 23% and 1%, respectively.²⁴ The Makuuchi standard,²⁵ which is widely used in Japan, clearly indicates whether hepatectomy is indicated and the allowable range of resection based on ascites, total serum bilirubin level, and ICGR15 (Figure 2). It has been reported that 0% of surgical deaths occurred in 1056 patients who underwent hepatectomy in compliance with this standard.²⁶ Kokudo et al reported that the Albumin-Indocyanine Green Evaluation (ALICE) grade using the serum albumin level and ICGR15 is useful for predicting the occurrence of postoperative liver failure and survival.²⁷ The ALICE grade is superior to the Child-Pugh classification in predicting outcomes after hepatectomy and may be a more useful liver function evaluation classification when combined with the presence or absence of portal hypertension.^{28,29} It has been reported that ^{99m}Tc-GSA liver scintigraphy was superior to the ICGR15 in the histologic evaluation of liver damage.³⁰ Evaluation of functional residual liver volume calculated from ^{99m}Tc-GSA liver scintigraphy was more informative than residual liver volume evaluation from computed tomography (CT) for predicting postoperative complications and death in patients with HCC and liver damage.³¹ However, ^{99m}Tc-GSA liver scintigraphy has facility restrictions due to the use of nuclides. In the evaluation of preoperative liver function to decide the surgical indication, in addition to information such as the Child-Pugh classification obtained in daily clinical practice, including blood tests, many reports recommend the ICG load test as a quantitative test.¹⁵ For hepatectomy, it is considered appropriate to determine the indication based on the balance between the degree of liver damage estimated from the ICGR15 and the range of hepatectomy (the amount of resection required).

3 | NUTRITIONAL STATUS OF PATIENTS WITH LIVER CANCER

3.1 | Evaluation by biochemical and physical factors

Recent studies have proposed markers based on several nutritional or inflammation-based prognostic indicators of HCC. Nutritional or inflammation-based markers include the prognostic nutritional

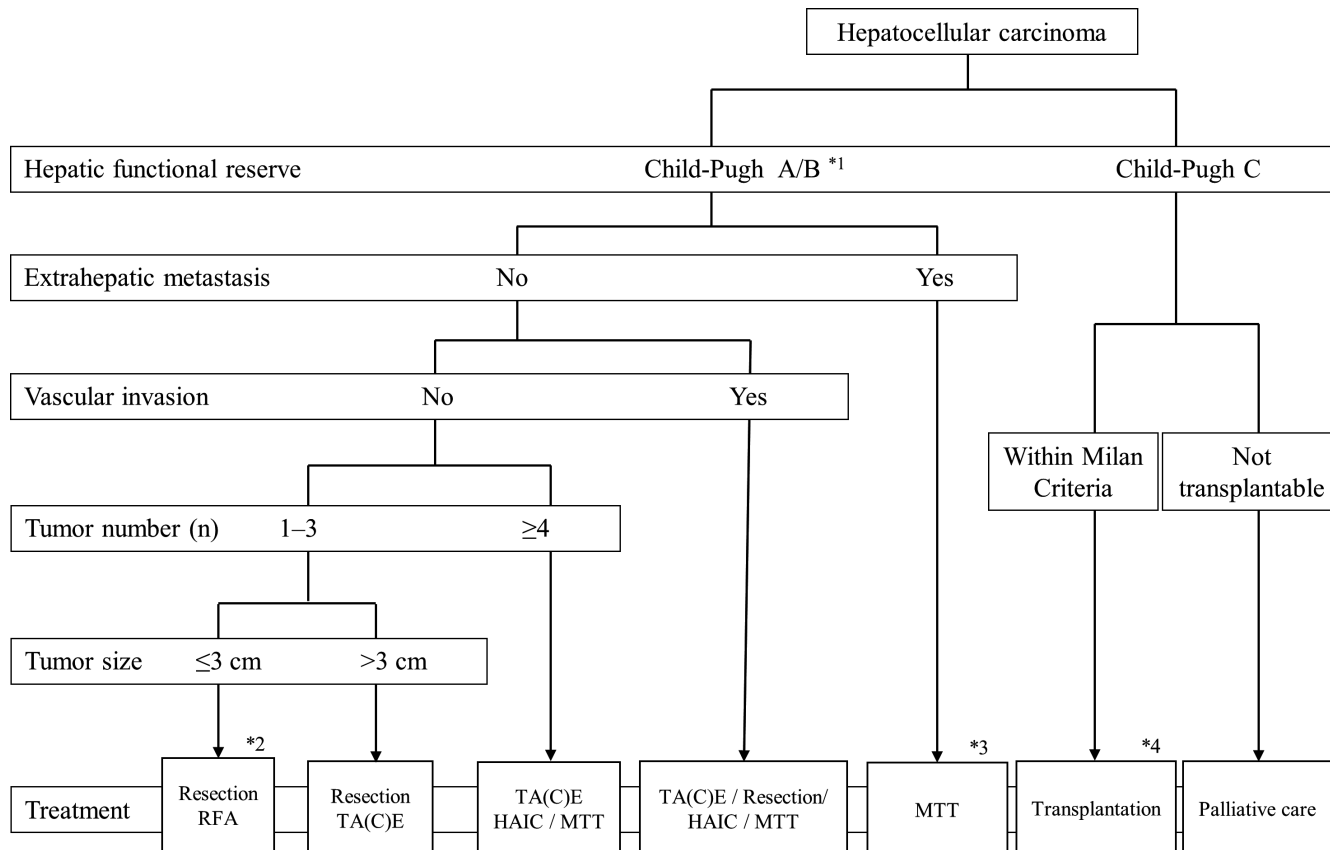


FIGURE 1 Algorithm for treatment in Japanese guidelines for hepatocellular carcinoma.¹⁵ This algorithm is simple and easy to memorize, consisting of five factors: (a) hepatic functional reserve; (b) extrahepatic metastasis; (c) vascular invasion, (d) tumor number; and (e) tumor size. *1: Assessment based on liver damage is recommended in the case of hepatectomy. *2: For a solitary hepatocellular carcinoma, resection is recommended as first-line therapy, and ablation as second-line therapy. *3: Patients with Child-Pugh A only. *4: Patients aged ≤ 65 y. HAIC, hepatic arterial infusion chemotherapy; MTT, molecular-targeted therapy; RFA, radiofrequency ablation; TA(C)E, transcatheter arterial (chemo) embolization

index,³²⁻³⁴ controlling nutritional status (CONUT) score,³⁵⁻³⁷ Glasgow prognostic score,³⁸ C-reactive protein (CRP)-to-albumin ratio (CAR),³⁹ neutrophil-to-lymphocyte ratio (NLR),⁴⁰ platelet-to-lymphocyte ratio (PLR),^{41,42} lymphocyte-to-monocyte ratio (LMR),^{43,44} and CRP-albumin-lymphocyte index.⁴⁵ Table 1 shows combined indices that can reportedly be used to estimate the nutritional or inflammatory status relevant to short- and long-term outcomes after hepatectomy for HCC. While some of the algorithms are complicated, CRP and serum albumin measurements are used more often as components of combined indices.³⁹

The use of sarcopenia to predict outcomes in patients with cancer has attracted more attention, including those with HCC⁴⁶⁻⁴⁸ or colorectal liver metastases (CRLM)^{49,50} undergoing hepatic resection. Previous studies also demonstrated that sarcopenia increased the risk of postoperative morbidity and longer hospital stay, as well as readmission rates, after partial liver resection for CRLM.^{51,52} Those studies focused only on skeletal muscle mass, as assessed by CT of skeletal muscle area. In contrast, a few reports have described the deterioration of muscle quality associated with muscle fat deposition. The usefulness of intramuscular adipose tissue content in hepatectomy for HCC^{53,54} and CRLM⁵⁵ has been reported.

Preoperative sarcopenia and/or intramuscular adipose tissue content might be considered a new selection criterion for hepatectomy in patients with liver cancer.

3.2 | Nutrition therapy

Because many cases of hepatectomy for HCC coexist with chronic hepatitis and cirrhosis, these patients often have energy/substrate metabolic disorders. Specifically, it has been reported that nutritional disorders occur frequently in patients with liver cirrhosis; 84% and 95% of patients with Child-Pugh classifications B and C, respectively, are undernourished, and 45% of patients with Child-Pugh classification A are also undernourished.⁵⁶ The main characteristic of nutritional disorders in patients with liver cirrhosis is malnutrition of protein and energy, and a decrease in the burning ratio of glucose as an energy-burning source and an increase in the burning ratio of fat are observed.⁵⁷ These nutritional disorders in patients with cirrhosis are closely related to the incidence of complications after hepatectomy, and the importance of perioperative nutrition therapy has been noted.⁵⁸ In principle, oral and enteral nutrition should be

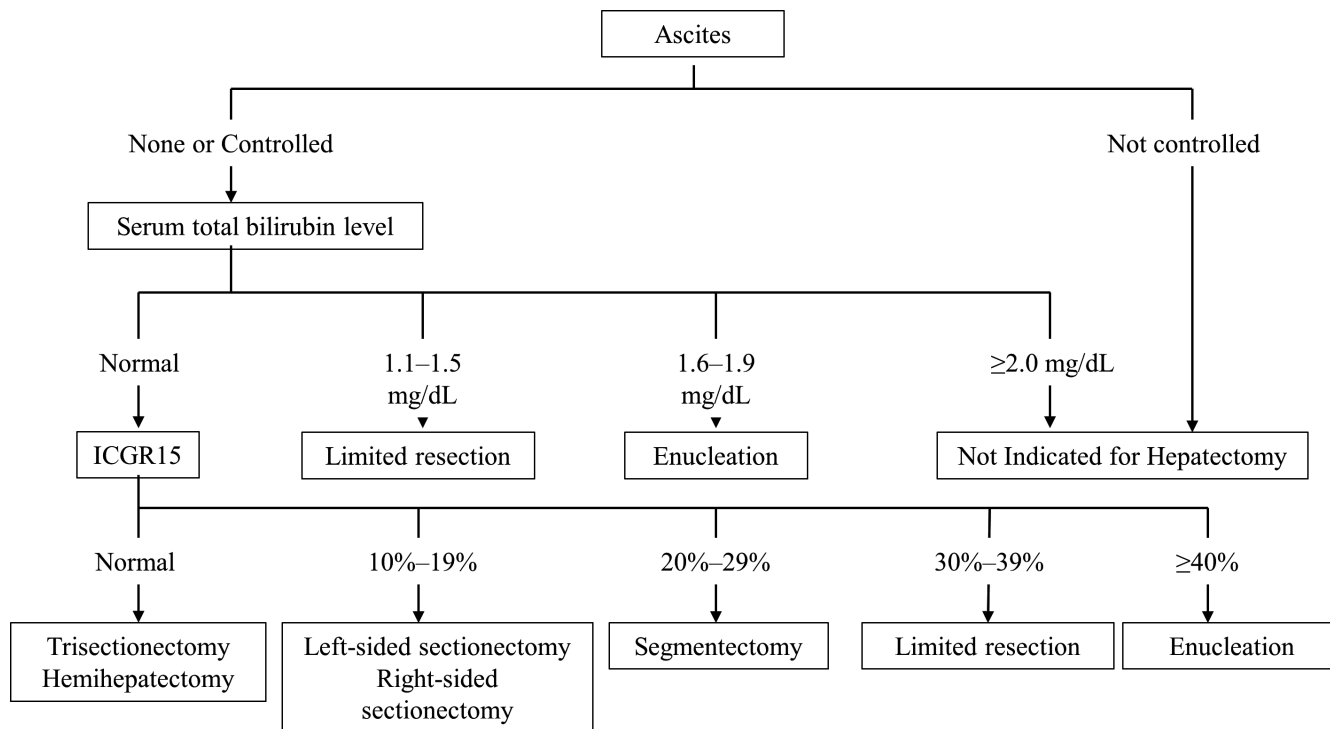


FIGURE 2 “Makuuchi’s criteria” as a surgical decision tree for liver resection. Makuuchi’s criteria include three factors: ascites, total serum bilirubin, and the ICGR15 (indocyanine green 15-min retention rate). This algorithm shows the maximal area for which an operation can be performed safely (modified ref. 25)

prioritized in nutrition therapy to maintain intestinal function. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines also recommend early oral nutrition for surgical patients to restore intestinal function, and early postoperative nutrition therapy for patients with liver cirrhosis to prevent postoperative complications.⁵⁹ The results of some studies on branched-chain amino acid (BCAA) administration and immunonutrition therapy (immunonutrition) in liver surgery complicated with liver cirrhosis are described as follows. Fan et al⁵⁸ reported a randomized controlled trial (RCT) of 124 patients who underwent hepatectomy for HCC who were divided into a perioperative nutrition therapy group that received an infusion of an emulsion of dextrose, BCAA, and medium-chain triglycerides and a non-nutrition therapy group. The frequency of postoperative complications was significantly reduced in the nutrition therapy group, and the incidence of infectious complications was 17% and 37% ($P = .02$) in the nutrition therapy and non-nutrition therapy groups, respectively. Furthermore, the effect of these nutrition therapies on postoperative complications was remarkable in patients with cirrhosis who underwent major hepatectomy. Shirabe et al reported an RCT of 26 patients who underwent hepatectomy in which nutritional components containing BCAAs were administered by intravenous or enteral routes. The incidence of infectious complications was 31% in the intravenous route group and 8% in the enteral route group, demonstrating the superiority of the enteral route as a nutritional route after hepatectomy.⁶⁰ Enteral nutrition may induce retention of the intestinal mucosa, activation of the immune system in the mesenteric lymph nodes, and increased IgA

production in patients with liver cirrhosis at high risk of bacterial translocation; therefore, the authors recommended enteral nutrition early after surgery. Recently, preoperative administration of BCAA in patients undergoing hepatic resection was shown to be effective for preventing ascites, plural effusion, or both, as well as for improving albumin metabolism and reducing the risk of complications and duration of hospital stay.^{61,62} Previous reports have addressed the effects of BCAA on HCC recurrence after surgery^{63,64}; however, no definitive conclusions have been reached. Hachiya et al reported the long-term prognosis of BCAA administration for patients with HCC who underwent hepatectomy.⁶⁵ They demonstrated that oral BCAA supplementation could not reduce the risk of recurrence after hepatic resection in HCC; however, the results suggested that BCAA supplementation may be beneficial for selected patients who were younger and had mildly impaired glucose tolerance.

Four studies on the efficacy of probiotics and prebiotics for patients who undergo hepatic resection have been published.⁶⁶⁻⁶⁹ A meta-analysis including these studies showed that administration of probiotics and/or prebiotics prior to the day of surgery decreases the infection rate post-liver resection and could shorten the duration of hospitalization and antibiotic use.⁷⁰ However, as the quality of the evidence was low, further research is required. There were three reports of perioperative immunonutrition therapy with omega-3 fatty acids.⁷¹⁻⁷³ Two RCTs showed that intravenous administration of omega-3 lipids for 5 days after hepatectomy improved postoperative liver function and suppressed the occurrence of complications.⁷² However, one RCT did not show these effects.⁷³

Index	Components (serum levels)	Results
PNI	Albumin, lymphocyte	PNI <44 was associated with higher transfusion rates and surgical outcomes, ³² PNI <45 was the most powerful predictor of complications after hepatic resection. ³³ Patients with PNI <37 were at high risk for early recurrence and poor survival. ³⁴
CONUT	Albumin, lymphocyte, total cholesterol	Early postoperative CONUT score >8 was identified as a risk factor for postoperative complication III-V. ³⁵ Preoperative CONUT scores >4 was predictive of worse OS and RFS. ³⁶ High CONUT score was an independent predictor of in-hospital mortality after hepatectomy. ³⁷
GPS	Albumin, C-reactive protein	An elevated GPS was an independent prognostic indicator for OS after hepatectomy. ³⁸
CRP/ALB ratio (CAR)	Albumin, C-reactive protein	High CAR (>0.027) was correlated with both poor OS and DFS. ³⁹
NLR	Neutrophil, lymphocyte	Preoperative plus postoperative ratio was a prognostic factor for OS. ⁴⁰
PLR	Platelet, lymphocyte	High PLR level (≥ 150) is a good indicator to predict recurrence beyond the Milan criteria. ⁴¹ High PLR indicates a higher rate of extrahepatic metastasis of HCC. ⁴²
LMR	Lymphocyte, monocyte	Both LMR and NLR might be preferable independent prognostic factors for DFS. ⁴³ Elevated preoperative LMR (≥ 4.01) was independently associated with poor OS and DFS. ⁴⁴
CRP-albumin-lymphocyte index	C-reactive protein, albumin, lymphocyte	OS and RFS were worse with an index of 5 or higher. ⁴⁵

Abbreviations: CAR, C-reactive protein (CRP) to albumin ratio; CONUT, controlling nutritional status; DFS, disease-free survival; GPS, Glasgow prognostic score; LMR, lymphocyte to monocyte ratio; OS, overall survival; PFS, progression-free survival; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index.

4 | PROPHYLACTIC ANTIBIOTICS

Hirokawa et al⁷⁴ reported the results of an RCT of the administration of prophylactic antibiotics to patients scheduled to undergo liver resection. The non-postoperative antibiotic group ($n = 95$) received 1.0 g of flomoxef sodium (FMOX) 30 minutes before surgery but was not given FMOX after surgery. The antibiotic group ($n = 95$) was given intravenous FMOX 1.0 g every 12 hours for 3 days after surgery. The groups did not differ significantly for signs of infection (21.3% vs 25.5%, $P = .61$), incidence of systemic inflammatory response syndrome (11.7% vs 17.0%, $P = .41$), infectious complications (7.5% vs 17.0%, $P = .07$), surgical site infection (SSI; 10.6% vs 13.8%, $P = .66$), and remote site infection (2.1% vs 8.5%, $P = .10$). Takayama et al⁷⁵ reported that the incidence of SSI was 9.5% and 9.8%, respectively, in a non-inferiority study comparing 232 patients who received 1 g of FMOX up to 6 hours after surgery (1-day group) and 235 patients who received it for

TABLE 1 Combined indices estimating nutritional or inflammatory status for liver cancer surgery

up to 2 days (3-day group; $P = .001$ for non-inferiority). In a retrospective study, after propensity score matching, there was no difference in the incidence of SSI and distant site infections when comparing administration of FMOX up to 24 hours after surgery and administration for 3 days after surgery in patients undergoing open and laparoscopic hepatic resection.⁷⁶ Based on these results, it is recommended that prophylactic antibiotics be administered within 24 hours after hepatectomy.

5 | PROPHYLACTIC ABDOMINAL DRAINAGE

Routine prophylactic abdominal drainage was unnecessary or contraindicated for patients who underwent elective hepatectomy in RCTs, because drain placement increased the frequency of drain-related complications, wound complications, sepsis and infectious

fluid retention, and significantly increased the length of hospital stay.⁷⁷⁻⁸⁰ On the other hand, in patients with liver cirrhosis accompanied by portal hypertension, one report recommended drain placement, because abdominal drainage reduced complications related to postoperative ascites and shortened the length of hospital stay.⁸¹ It was also reported that abdominal drainage should not be placed in patients unless they were at high risk of bleeding and bile leakage.⁸² Late-onset bile leakage, which could lead to serious complications, such as sepsis, occurred in patients without abdominal drainage.⁸³ Intra-abdominal infection should also be treated as soon as possible, because it may induce refractory bile leakage with serious complications. Some reports recommended drain placement in cases of therapeutic usefulness for bile leakage and intraperitoneal fluid retention due to drainage,^{84,85} for the possibility of predicting bile leakage by monitoring the bilirubin concentration in drainage,^{85,86} for patients at high risk of bile leakage, such as those with biliary tract reconstruction, exposure of major Glisson's capsule, and with bile leakage observed during surgery.⁸⁷ It was also reported that prophylactic abdominal drainage was not essential for living-donor liver transplant donor hepatectomy.⁸⁸ Unlike other abdominal organ resections, hepatectomy is often associated with chronic liver damage, and it is necessary to pay attention to bleeding, bile leakage, and intractable ascites. Regarding the pros and cons of drain placement during elective hepatectomy, RCTs have been performed since the 1990s, but they had some limitations, such as a small number of patients and the methods used for evaluation. Therefore, it was necessary to consider the degree of coexisting liver damage and the surgical procedure. More careful consideration is required for abdominal drainage in living-donor liver transplant donor surgery performed on healthy people, and it is also necessary to consider the pros and cons of drain placement in laparoscopic hepatectomy, which has been increasing in recent years. It is currently considered that the presence or absence of abdominal drainage in elective hepatectomy should be determined in consideration of the risk of bleeding and bile leakage. The Centers for Disease Control and Prevention (CDC) guidelines for prevention of SSI recommend "if a drain is needed, use a closed drain and remove it as soon as possible."⁸⁹ Some reports demonstrated that it is desirable to remove the drain within 2-3 days after surgery if there is no problem with the drainage properties.^{85,90,91}

6 | EXERCISE THERAPY

Dynamic assessment of preoperative exercise capacity may be a useful predictor of short- and long-term postoperative prognosis. Cardiopulmonary exercise (CPX) testing measures oxygen uptake at increasing levels of work and predicts cardiopulmonary performance under stress, such as after surgery. Among older patients undergoing major abdominal surgical procedures, most deaths from cardiopulmonary complications occur in those with an anaerobic threshold (AT) <11 mL/min/kg.^{92,93} The AT is defined as the point during exercise at which oxygen demand outstrips oxygen

delivery, and metabolism starts to become anaerobic. The AT is a measure of the ability of the cardiopulmonary system to deliver adequate oxygen to tissues, and it has the advantage of being independent of patient motivation. To date, few studies have examined the usefulness of pre- and postoperative CPX testing in patients undergoing hepatectomy.^{94,95} Recently, Kaibori et al reported that in patients with HCC and hepatic impairment undergoing liver resection, exercise significantly decreased body mass and fat mass, as well as insulin resistance, 6 months postoperatively.⁹⁶ Maintenance of postoperative physical strength and earlier resumption of daily activities could be possible by intensifying perioperative and postoperative exercise. An exercise program was tailored for each patient. Exercise was started as soon as possible after diagnosis, up to 1 month preoperatively, and was resumed from 1 week postoperatively and continued for 6 months. The program consisted of three 60-minute exercise sessions per week. Each session included 5 minutes of stretching exercises, 30 minutes of walking at an intensity based on the AT of each patient, 20 minutes of targeted stretching exercises, and 5 minutes of cooling down with stretching. Patients with HCC (N = 51) were randomized to receive diet therapy alone (n = 25) or exercise in addition to diet therapy (n = 26). Whole body mass and fat mass in the exercise group compared with the diet group were significantly decreased at 6 months postoperatively. Fasting serum insulin and the homeostasis model assessment score were also significantly decreased (Figure 3). At 6 months, the AT and peak oxygen consumption were significantly increased, while serum insulin and insulin resistance significantly improved in a high frequency exercise subgroup compared with a low frequency group (Figure 2).

7 | ENHANCED RECOVERY AFTER SURGERY

Fast-track or enhanced recovery after surgery (ERAS) programs following surgical interventions are now within the standard of care for patients with several surgical indications.⁹⁷⁻¹⁰¹ These programs use a multimodal approach to maximize effectiveness and minimize cost, thus optimizing perioperative care pathways.¹⁰² ERAS programs have been associated with reductions in complications, duration of hospital stay, and hospital costs in colorectal surgery.⁹⁷ Recently, ERAS programs have also been introduced in liver surgery. Wang et al demonstrated in a meta-analysis that the implementation of ERAS programs in liver surgery appears to be feasible and efficient and could significantly reduce overall morbidity, hospital stay and costs, intraoperative blood loss, and time to bowel function recovery without increasing rates of mortality, readmission, or transfusion.¹⁰³ They also found that ERAS programs reduced morbidity in open and laparoscopic surgery equally, whereas hospital stays were reduced more obviously in laparoscopic surgery. However, it is unclear why the implementation of ERAS programs resulted in the reduction of intraoperative blood loss, which is largely dependent on the surgical technique.

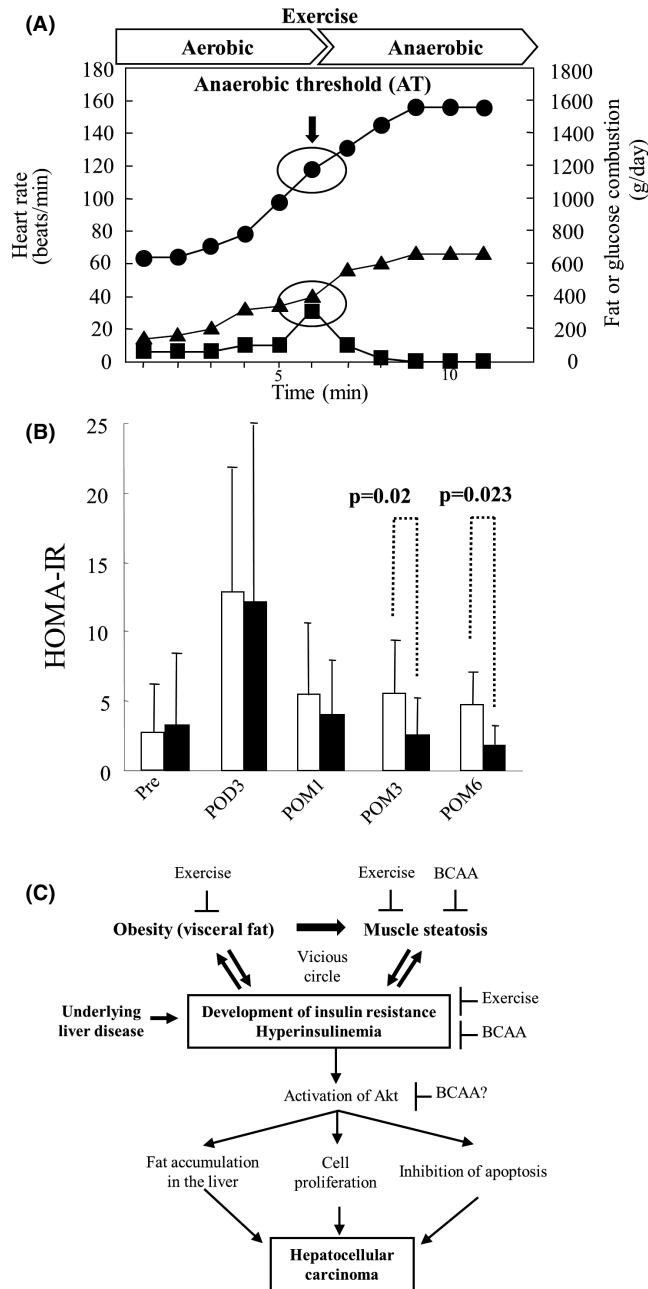


FIGURE 3 Exercise therapy. (A) Cardiopulmonary exercise test. The anaerobic threshold (AT) was set at the break point between carbon dioxide production and Vo_2 , or the point at which the ventilatory equivalent for oxygen and end-tidal oxygen partial pressure curves reached their respective nadirs before beginning to increase again. Thus, the AT was set at a maximum point of fat combustion. ● heart rate; ▲ glucose combustion; ■ fat combustion. (B) Effect of exercise on insulin resistance in patients with HCC with hepatic impairment. HOMA-IR in the diet group (□) and the exercise group (■). HOMA-IR, homeostasis model for assessment of insulin resistance; POD, postoperative day; POM, postoperative month. (C) Estimating the mechanism of hepatocellular carcinoma development due to exacerbation of insulin resistance. There is a vicious cycle among obesity, muscle steatosis, and the development of insulin resistance in patients with liver diseases. Exercise and/or BCAA therapy is considered to suppress the deterioration of the condition. Akt; protein kinase B; BCAA; branched-chain amino acid

of patients who underwent extended hepatectomy (defined as resection of more than two sections) for HCC coexistent with chronic hepatitis and cirrhosis, before and after the introduction of an ERAS program. Operating time and postoperative hospital stay were significantly shorter, and total volume infused during surgery was significantly lower for the ERAS group than for the control group. Although the percentage of patients with retention of abdominal drainage was significantly smaller in the ERAS group, the frequency of abdominal paracentesis in patients without intraoperative abdominal drainage was higher. Oral dietary intake and ability to walk stably occurred significantly earlier in the ERAS group. Postoperative serum concentrations of albumin and cholinesterase were significantly higher in the ERAS group than in the control group. We concluded that a multimodal ERAS program was feasible and effective for patients with chronic liver diseases undergoing extended liver resection for HCC.

We speculate that the spread of ERAS programs in hepatectomy in Japan will be as follows. There are 15 ERAS items essential for liver surgery: "Pre-admission counseling," "No bowel preparation," "Fluid and CHO-loading/no fasting," "No pre-anesthetic medication," "No routine nasogastric tubes postoperatively," "Epidural analgesia," "Short-acting anesthetic agent," "Avoidance of sodium/fluid overload," "Short incision," "Warm air body heating in theatre," "Early mobilization (routine mobilization care pathway)," "Non-opiate oral analgesics/NSAIDs," "Early feeding (stimulation of gut motility and perioperative oral nutrition)," and "Early removal of catheters." However, "No surgical drains," "Prevention of nausea and vomiting," and "Audit of compliance/outcome" are not yet widespread components of ERAS programs in Japan (Figure 4).

8 | CONCLUSIONS

This review summarizes a series of unique approaches to the perioperative management of patients with HCC undergoing liver resection based on the available evidence, with the goal of achieving "no

We consider that laparoscopic surgery, unlike open surgery, is effective for reduction in surgical bleeding because it requires minimal peeling due to the magnifying effect and reduces damage to tissues around the liver. The results of RCT and meta-analysis have shown that the introduction of ERAS programs reduced the frequency of complications as well as improved early postoperative recovery.¹⁰³⁻¹⁰⁷ Among programs, pain management is an important factor, and Hausken et al reported that intravenous patient-controlled analgesia (IV-PCA) was non-inferior to epidural anesthesia.¹⁰⁶ Most of the patients in these studies underwent hepatectomy for colorectal liver metastases. Few studies have analyzed the effect of ERAS programs on patients with diseased livers who underwent hepatectomy for HCC. Kaibori et al¹⁰⁵ compared clinicopathologic factors, surgical factors, and outcomes

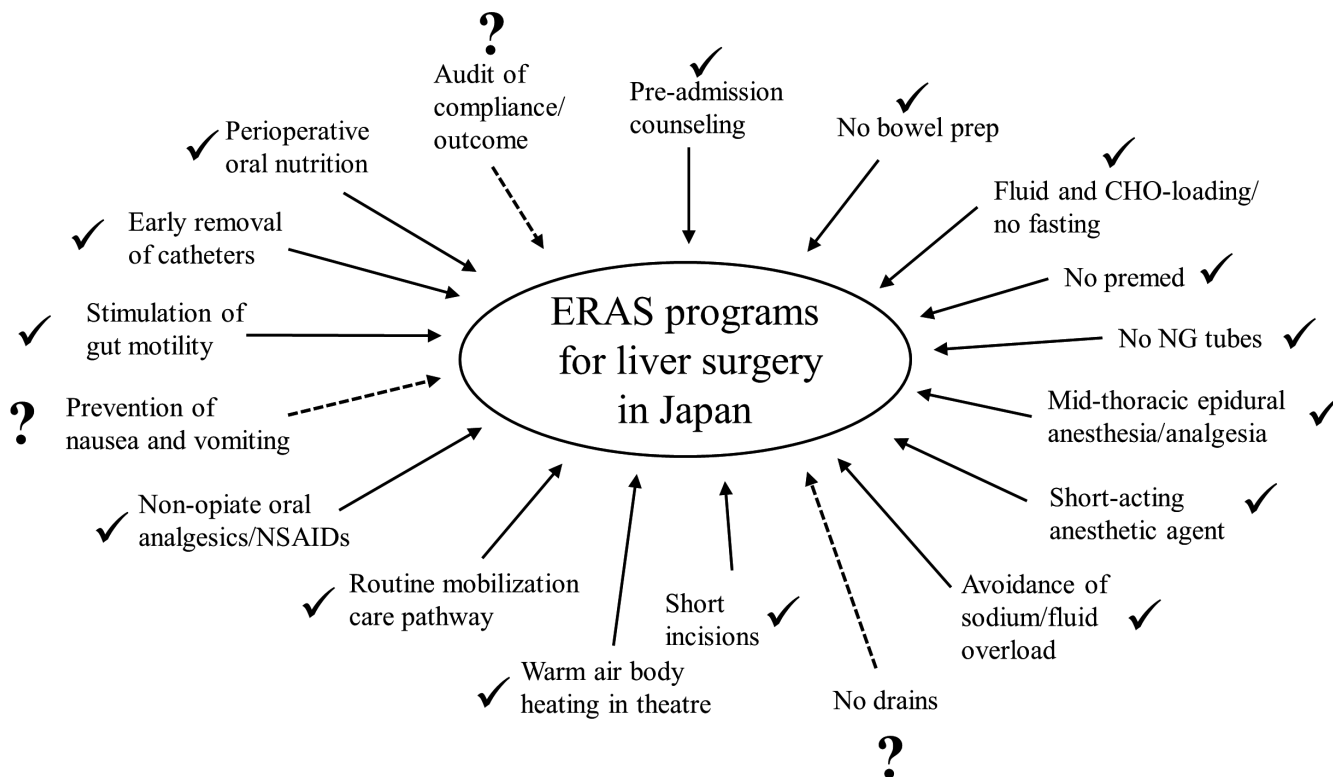


FIGURE 4 Enhanced recovery after surgery (ERAS) program items performed in patients undergoing hepatectomy in Japan. ERAS program items that have already been implemented at many facilities in Japan are marked with a check mark, and items that have not yet been implemented sufficiently are marked as question marks

mortality” and “minimal postoperative complications.” We believe that general perioperative management of patients undergoing surgery for liver cancer is basically the same, even when there is a wide variety of patient and surgical factors. Whether the associated liver disease is normal vs severe cirrhosis, and whether the surgery is laparoscopic vs open hepatectomy, we perform the perioperative management described above in the same way. New methods for the improvement of preoperative liver function and perioperative management are likely to facilitate expansion of the indication for liver resection.

ACKNOWLEDGEMENTS

We are indebted to the following surgeons for their excellent collection and management of the manuscripts: Satoru Imura (Department of Surgery, Tokushima University) and Shogo Tanaka (Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine).

DISCLOSURE

Funding: All authors hereby declare that there is no potential or actual personal, financial, or political interest related to this study.

Conflict of Interest: None.

Author Contribution: MK drafted and wrote the manuscript. KM, MS, SK, and KH participated in the study design and helped draft

the manuscript. All authors contributed to the interpretation of the findings, read, and approved the final manuscript.

ORCID

Masaki Kaibori <https://orcid.org/0000-0002-0577-3921>

Kosuke Matsui <https://orcid.org/0000-0002-7274-0177>

Mitsuo Shimada <https://orcid.org/0000-0003-1255-4783>

Shoji Kubo <https://orcid.org/0000-0002-4353-8033>

Kiyoshi Hasegawa <https://orcid.org/0000-0001-8734-740X>

REFERENCES

1. Bosch X, Ribes J, Borrás J. Epidemiology of primary liver cancer. *Semin Liver Dis.* 1999;19:271–85.
2. Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK 1979–94. *Lancet.* 1997;350:1142–3.
3. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med.* 1999;340:745–50.
4. Nanashima A, Nagayasu T. Development and clinical usefulness of the liver hanging maneuver in various anatomical hepatectomy procedures. *Surg Today.* 2016;46:398–404.
5. Fan ST, Lai EC, Lo CM, Ng IO, Wong J. Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. *Arch Surg.* 1995;130:198–203.
6. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. *Ann Surg.* 2000;232:10–24.

7. Yeh CN, Chen MF, Lee WC, Jeng LB. Prognostic factors of hepatic resection for hepatocellular carcinoma with cirrhosis: univariate and multivariate analysis. *J Surg Oncol*. 2002;81:195–202.
8. Benzoni E, Cojutti A, Lorenzin D, Adani GL, Baccarani U, Favero A, et al. Liver resective surgery: a multivariate analysis of post-operative outcome and complication. *Langenbecks Arch Surg*. 2007;392:45–54.
9. Chiappa A, Zbar AP, Audisio RA, Leone BE, Biella F, Staudacher C. Factors affecting survival and long-term outcome in the cirrhotic patient undergoing hepatic resection for hepatocellular carcinoma. *Eur J Surg Oncol*. 2000;26:387–92.
10. Farges O, Malassagne B, Flejoux JF, Balzan S, Sauvanet A, Belghiti J. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. *Ann Surg*. 1999;229:210–5.
11. Mizuguchi T, Kawamoto M, Meguro M, Okita K, Ota S, Ishii M, et al. Impact of aging on morbidity and mortality after liver resection: a systematic review and meta-analysis. *Surg Today*. 2015;45:259–70.
12. Makuuchi M. Remodeling the surgical approach to hepatocellular carcinoma. *Hepatogastroenterology*. 2002;49:36–40.
13. Taketomi A, Kitagawa D, Itoh S, Harimoto N, Yamashita Y, Gion T, et al. Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute's experience with 625 patients. *J Am Coll Surg*. 2007;204:580–7.
14. Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53:1020–2.
15. Kokudo N, Takemura N, Hasegawa K, Takayama T, Kubo S, Shimada M, et al. Clinical practice guidelines for hepatocellular carcinoma: the Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. *Hepatol Res*. 2019;49:1109–13.
16. Nakayama H, Takayama H. Role of surgical resection for hepatocellular carcinoma based on Japanese clinical guidelines for hepatocellular carcinoma. *World J Hepatol*. 2015;7:261–9.
17. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology*. 2008;134:1908–16.
18. Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G, et al. Is portal hypertension a contraindication to hepatic resection? *Ann Surg*. 2009;250:922–8.
19. Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. *Br J Surg*. 1997;84:1255–9.
20. Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer (4th, Japanese ed.). Kanehara-Shuppan; 2000.
21. Yamanaka N, Okamoto E, Kuwata K, Tanaka N. A multiple regression equation for prediction of posthepatectomy liver failure. *Ann Surg*. 1984;200:658–63.
22. Yamanaka N, Okamoto E, Oriyama T, Fujimoto J, Furukawa K, Kawamura E, et al. A prediction scoring system to select the surgical treatment of liver cancer. Further refinement based on 10 years of use. *Ann Surg*. 1994;219:342–6.
23. Takasaki K, Kobayashi S, Suzuki S, Muto H, Marada M, Yamana Y, et al. Predetermining postoperative hepatic function for hepatectomies. *Int Surg*. 1980;65:309–13.
24. Ariizumi S, Yamamoto M, Takasaki K. Right hepatectomy for hepatocellular carcinoma in patients with an indocyanine green retention rate at 15 minutes of 10% or higher. *Dig Surg*. 2009;26:135–42.
25. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, et al. Surgery for small liver cancers. *Semin Surg Oncol*. 1993;9:298–304.
26. Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, et al. One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg*. 2003;138:1198–206.
27. Kokudo T, Hasegawa K, Amikura K, Uldry E, Shirata C, Yamaguchi T, et al. Assessment of preoperative liver function in patients with hepatocellular carcinoma - The Albumin-Indocyanine Green Evaluation (ALICE) Grade. *PLoS One*. 2016;11:e0159530.
28. Russolillo N, Forchino F, Conci S, Mele C, Langella S, Ruzzenente A, et al. Validation of the albumin-indocyanine green evaluation model in patients with resected hepatocellular carcinoma and comparison with the albumin-bilirubin score. *J Hepatobiliary Pancreat Sci*. 2019;26:51–7.
29. Shirata C, Kokudo T, Arita J, Akamatsu N, Kaneko J, Sakamoto Y, et al. Albumin-Indocyanine Green Evaluation (ALICE) grade combined with portal hypertension to predict post-hepatectomy liver failure. *Hepatol Res*. 2019;49:942–9.
30. Kwon AH, Ha-Kawa SK, Uetsuji S, Inoue T, Matsui Y, Kamiyama Y. Preoperative determination of the surgical procedure for hepatectomy using technetium-99m-galactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy. *Hepatology*. 1997;25:426–9.
31. Hayashi H, Beppu T, Okabe H, Kuroki H, Nakagawa S, Imai K, et al. Functional assessment versus conventional volumetric assessment in the prediction of operative outcomes after major hepatectomy. *Surgery*. 2015;157:20–6.
32. Sim JH, Kim SH, Jun IG, Kang SJ, Kim B, Kim S, et al. The association between prognostic nutritional index (PNI) and intraoperative transfusion in patients undergoing hepatectomy for hepatocellular carcinoma: a retrospective cohort study. *Cancers (Basel)*. 2021;13:2508.
33. Nagata S, Maeda S, Nagamatsu S, Kai S, Fukuyama Y, Korematsu S, et al. Prognostic nutritional index considering resection range is useful for predicting postoperative morbidity of hepatectomy. *J Gastrointest Surg*. 2021;25:2788–2795.
34. Tanemura A, Mizuno S, Hayasaki A, Gyoten K, Fujii T, Iizawa Y, et al. Onodera's prognostic nutritional index is a strong prognostic indicator for patients with hepatocellular carcinoma after initial hepatectomy, especially patients with preserved liver function. *BMC Surg*. 2020;20:261. doi:10.1186/s12893-020-00917-2
35. Li L, Liu C, Yang J, Wu H, Wen T, Wang W, et al. Early postoperative controlling nutritional status (CONUT) score is associated with complication III-V after hepatectomy in hepatocellular carcinoma: A retrospective cohort study of 1,334 patients. *Sci Rep*. 2018;8:13406. doi:10.1038/s41598-018-31714-w
36. Harimoto N, Yoshizumi T, Inokuchi S, Itoh S, Adachi E, Ikeda Y, et al. Prognostic significance of preoperative controlling nutritional status (CONUT) score in patients undergoing hepatic resection for hepatocellular carcinoma: a multi-institutional study. *Ann Surg Oncol*. 2018;25:3316–23.
37. Takagi K, Umeda Y, Yoshida R, Nobuoka D, Kuise T, Fushimi T, et al. Preoperative controlling nutritional status score predicts mortality after hepatectomy for hepatocellular carcinoma. *Dig Surg*. 2019;36:226–32.
38. Abe T, Tashiro H, Kobayashi T, Hattori M, Kuroda S, Ohdan H. Glasgow prognostic score and prognosis after hepatectomy for hepatocellular carcinoma. *World J Surg*. 2017;41:1860–70.
39. Yamamoto M, Kobayashi T, Kuroda S, Hamaoka M, Okimoto S, Honmyo N, et al. Verification of inflammation-based prognostic marker as a prognostic indicator in hepatocellular carcinoma. *Ann Gastroenterol Surg*. 2019;3:667–75.
40. Wu M, Yang S, Feng X, Yu F, Liu X, Dong J. *Oncol Lett*. 2020;20:375. doi:10.3892/ol.2020.12238
41. Kaida T, Nitta H, Kitano Y, Yamamura K, Arima K, Higashi T, et al. Preoperative platelet-to-lymphocyte ratio can predict recurrence beyond the Milan criteria after hepatectomy for patients with hepatocellular carcinoma. *Hepatol Res*. 2017;47:991–9.
42. Chen Y, Zeng J, Guo P, Zeng J, Liu J. Prognostic significance of platelet-to-lymphocyte ratio (PLR) in extrahepatic metastasis of hepatocellular carcinoma after curative resection. *Cancer Manag Res*. 2021;13:1395–405.

43. Yang T, Zhu J, Zhao L, Mai K, Ye J, Huang S, et al. Lymphocyte to monocyte ratio and neutrophil to lymphocyte ratio are superior inflammation-based predictors of recurrence in patients with hepatocellular carcinoma after hepatic resection. *J Surg Oncol*. 2017;115:718–28.
44. Yang YT, Jiang JH, Yang HJ, Wu ZJ, Xiao ZM, Xiang BD. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival compared to established biomarkers in HCC patients undergoing liver resection. *Sci Rep*. 2018;8:2535. doi:10.1038/s41598-018-20199-2
45. Iida H, Tani M, Komeda K, Nomi T, Matsushima H, Tanaka S, et al. Superiority of CRP-albumin-lymphocyte index (CALLY index) as a non-invasive prognostic biomarker after hepatectomy for hepatocellular carcinoma. *HPB (Oxford)*. 2021. doi:10.1016/j.hpb.2021.06.414. Online ahead of print.
46. Berardi G, Antonelli G, Colasanti M, Meniconi R, Guglielmo N, Laurenzi A, et al. Association of sarcopenia and body composition with short-term outcomes after liver resection for malignant tumors. *JAMA Surg*. 2020;155:e203336. doi:10.1001/jamasurg.2020.3336
47. Kobayashi A, Kaido T, Hamaguchi Y, Okumura S, Shirai H, Yao S, et al. Impact of sarcopenic obesity on outcomes in patients undergoing hepatectomy for hepatocellular carcinoma. *Ann Surg*. 2019;269:924–31.
48. Xu L, Jing Y, Zhao C, Zhang Q, Zhao X, Yang J, et al. Preoperative computed tomography-assessed skeletal muscle index is a novel prognostic factor in patients with hepatocellular carcinoma following hepatectomy: a meta-analysis. *J Gastrointest Oncol*. 2020;11:1040–53.
49. Runkel M, Diallo TD, Lang SA, Bamberg F, Benndorf M, Fichtner-Feigl S. The role of visceral obesity, sarcopenia and sarcopenic obesity on surgical outcomes after liver resections for colorectal metastases. *World J Surg*. 2021;45:2218–26.
50. Liu YW, Lu CC, Chang CD, Lee KC, Chen HH, Yeh WS, et al. Prognostic value of sarcopenia in patients with colorectal liver metastases undergoing hepatic resection. *Sci Rep*. 2020;10:6459. doi:10.1038/s41598-020-63644-x
51. Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB (Oxford)*. 2011;13:439–46.
52. Lodewick TM, van Nijnatten TJ, van Dam RM, van Mierlo K, Dello SA, Neumann UP, et al. Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases? *HPB (Oxford)*. 2015;17:438–46.
53. Hamaguchi Y, Kaido T, Okumura S, Ito T, Fujimoto Y, Ogawa K, et al. Preoperative intramuscular adipose tissue content is a novel prognostic predictor after hepatectomy for hepatocellular carcinoma. *J Hepatobiliary Pancreat Sci*. 2015;22:475–85.
54. Kaibori M, Ishizaki M, Iida H, Matsui K, Sakaguchi T, Inoue K, et al. Effect of intramuscular adipose tissue content on prognosis in patients undergoing hepatocellular carcinoma resection. *J Gastrointest Surg*. 2015;19:1315–23.
55. Horii N, Sawda Y, Kumamoto T, Tsuchiya N, Murakami T, Yabushita Y, et al. Impact of intramuscular adipose tissue content on short- and long-term outcomes of hepatectomy for colorectal liver metastasis: a retrospective analysis. *World J Surg Oncol*. 2020;18:68. doi:10.1186/s12957-020-01836-5
56. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. *Clin Gastroenterol Hepatol*. 2012;10:117–25.
57. Dudrick SJ, Kavic SM. Hepatobiliary nutrition: history and future. *J Hepatobiliary Pancreat Surg*. 2002;9:459–68.
58. Fan ST, Lo CM, Lai EC, Chu KM, Liu CL, Wong J, et al. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. *N Engl J Med*. 1994;331:1547–52.
59. Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirllich M, Kondrup J, et al. ESPEN Guidelines on Enteral Nutrition: Liver disease. *Clin Nutr*. 2006;25:285–94.
60. Shirabe K, Matsumata T, Shimada M, Takenaka K, Kawahara N, Yamamoto K, et al. A comparison of parenteral hyperalimentation and early enteral feeding regarding systemic immunity after major hepatic resection—the results of a randomized prospective study. *Hepatogastroenterology*. 1997;44:205–9.
61. Mizuguchi T, Kawamoto M, Meguro M, Nakamura Y, Harada K, Kukita K, et al. Prognostic impact of preoperative the branched-chain amino acid to the tyrosine ratio in hepatocellular carcinoma patients after initial hepatectomy. *J Gastrointest Surg*. 2011;15:1433–9.
62. Kikuchi Y, Hiroshima Y, Matsuo K, Kawaguchi D, Murakami T, Yabushita Y, et al. A randomized clinical trial of preoperative administration of branched-chain amino acids to prevent postoperative ascites in patients with liver resection for hepatocellular carcinoma. *Ann Surg Oncol*. 2016;23:3727–35.
63. Togo S, Tanaka K, Morioka D, Sugita M, Ueda M, Miura Y, et al. Usefulness of granular BCAA after hepatectomy for liver cancer complicated with liver cirrhosis. *Nutrition*. 2005;21:480–6.
64. Ichikawa K, Okabayashi T, Maeda H, Namikawa T, Iiyama T, Sugimoto T, et al. Oral supplementation of branched-chain amino acids reduces early recurrence after hepatic resection in patients with hepatocellular carcinoma: a prospective study. *Surg Today*. 2013;43:720–6.
65. Hachiya H, Aoki T, Iso Y, Shimizu T, Tago K, Park KH, et al. Effects of branched-chain amino acids on postoperative tumor recurrence in patients undergoing curative resection for hepatocellular carcinoma: A randomized clinical trial. *J Hepatobiliary Pancreat Sci*. 2020;27:819–29.
66. Sugawara G, Nagino M, Nishio H, Ebata T, Takagi K, Asahara T, et al. Perioperative synbiotic treatment to prevent postoperative infectious complications in biliary cancer surgery: a randomized controlled trial. *Ann Surg*. 2006;244:706–14.
67. Kanazawa H, Nagino M, Kamiya S, Komatsu S, Mayumi T, Takagi K, et al. Synbiotics reduce postoperative infectious complications: a randomized controlled trial in biliary cancer patients undergoing hepatectomy. *Langenbecks Arch Surg*. 2005;390:104–13.
68. Usami M, Miyoshi M, Kanbara Y, Aoyama M, Sakaki H, Shuno K, et al. Effects of perioperative synbiotic treatment on infectious complications, intestinal integrity, and fecal flora and organic acids in hepatic surgery with or without cirrhosis. *JPEN J Parenter Enteral Nutr*. 2011;35:317–28.
69. Rayes N, Pilarski T, Stockmann M, Bengmark S, Neuhaus P, Seehofer D. Effect of pre- and probiotics on liver regeneration after resection: a randomised, double-blind pilot study. *Benef Microbes*. 2012;3:237–44.
70. Gan Y, Su S, Li B, Fang C. Efficacy of probiotics and prebiotics in prevention of infectious complications following hepatic resections: systematic review and meta-analysis. *J Gastrointest Liver Dis*. 2019;28:205–11.
71. Wu Z, Qin J, Pu L. Omega-3 fatty acid improves the clinical outcome of hepatectomized patients with hepatitis B virus (HBV)-associated hepatocellular carcinoma. *J Biomed Res*. 2012;26:395–9.
72. Gong Y, Liu Z, Liao Y, Mai C, Chen T, Tang H, et al. Effectiveness of ω -3 polyunsaturated fatty acids based lipid emulsions for treatment of patients after hepatectomy: a prospective clinical trial. *Nutrients*. 2016;8:357. doi:10.3390/nu8060357
73. Seguin P, Locher C, Boudjema K, Hamon C, Mouchel C, Malledant Y, et al. Effect of a perioperative nutritional supplementation with oral impact in patients undergoing hepatic surgery for liver cancer: A prospective, placebo-controlled, randomized, double-blind study. *Nutr Cancer*. 2016;68:464–72.
74. Hirokawa F, Hayashi M, Miyamoto Y, Asakuma M, Shimizu T, Komeda K, et al. Evaluation of postoperative antibiotic prophylaxis

- after liver resection: a randomized controlled trial. *Am J Surg.* 2013;206:8–15.
75. Takayama T, Aramaki O, Shibata T, Oka M, Itamoto T, Shimada M, et al. Antimicrobial prophylaxis for 1 day versus 3 days in liver cancer surgery: a randomized controlled non-inferiority trial. *Surg Today.* 2019;49:859–69.
 76. Shinkawa H, Tanaka S, Takemura S, Amano R, Kimura K, Nishioka T, et al. Giving short-term prophylactic antibiotics in patients undergoing open and laparoscopic hepatic resection. *Ann Gastroenterol Surg.* 2019;3:506–14.
 77. Belghiti J, Kabbej M, Sauvanet A, Vilgrain V, Panis Y, Fekete F. Drainage after elective hepatic resection. A randomized trial. *Ann Surg.* 1993;218:748–53.
 78. Liu CL, Fan ST, Lo CM, Wong Y, Ng IO-L, Lam C-M, et al. Abdominal drainage after hepatic resection is contraindicated in patients with chronic liver diseases. *Ann Surg.* 2004;239:194–201.
 79. Sun HC, Qin LX, Lu L, Wang L, Ye QH, Ren N, et al. Randomized clinical trial of the effects of abdominal drainage after elective hepatectomy using the crushing clamp method. *Br J Surg.* 2006;93:422–6.
 80. Kim YI, Fujita S, Hwang VJ, Nagase Y. Comparison of abdominal drainage and no-drainage after elective hepatectomy: a randomized study. *Hepatogastroenterology.* 2014;61:707–11.
 81. Fuster J, Llovet JM, Garcia-Valdecasas JC, Grande L, Fondevila C, Vilana R, et al. Abdominal drainage after liver resection for hepatocellular carcinoma in cirrhotic patients: a randomized controlled study. *Hepatogastroenterology.* 2004;51:536–40.
 82. Arita J, Sakamaki K, Saiura A, Konishi M, Sakamoto Y, Hashimoto M, et al. Drain placement after uncomplicated hepatic resection increases severe postoperative complication rate: A Japanese multi-institutional randomized controlled trial (ND-trial). *Ann Surg.* 2021;273:224–31.
 83. Kaibori M, Shimizu J, Hayashi M, Nakai T, Ishizaki M, Matsui K, et al. Late-onset bile leakage after hepatic resection. *Surgery.* 2015;157:37–44.
 84. Kyoden Y, Imamura H, Sano K, Beck Y, Sugawara Y, Kokudo N, et al. Value of prophylactic abdominal drainage in 1269 consecutive cases of elective liver resection. *J Hepatobiliary Pancreat Sci.* 2010;17:186–92.
 85. Tanaka K, Kumamoto T, Nojiri K, Takeda K, Endo I. The effectiveness and appropriate management of abdominal drains in patients undergoing elective liver resection: a retrospective analysis and prospective case series. *Surg Today.* 2013;43:372–80.
 86. Torzilli G, Olivari N, Del Fabbro D, Gambetti A, Leoni P, Gendarini A, et al. Bilirubin level fluctuation in drain discharge after hepatectomies justifies long-term drain maintenance. *Hepatogastroenterology.* 2005;52:1206–10.
 87. Hirokawa F, Hayashi M, Miyamoto Y, Asakuma M, Shimizu T, Komeda K, et al. Re-valuation of the necessity of prophylactic drainage after liver resection. *Am Surg.* 2011;77:539–44.
 88. Liu CL, Fan ST, Lo CM, Chan SC, Yong BH, Wong J. Safety of donor right hepatectomy without abdominal drainage: a prospective evaluation in 100 consecutive liver donors. *Liver Transpl.* 2005;11:314–9.
 89. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection. Hospital infection control practices advisory committee. *Infect Control Hosp Epidemiol.* 1999;1999(20):250–78.
 90. Mitsuka Y, Yamazaki S, Yoshida N, Masamichi M, Higaki T, Takayama T. Prospective validation of optimal drain management “the 3x3 rule” after liver resection. *World J Surg.* 2016;40:2213–20.
 91. Hokuto D, Nomi T, Yasuda S, Kawaguchi C, Yoshikawa T, Ishioka K, et al. The safety of the early removal of prophylactic drainage after liver resection based solely on predetermined criteria: a propensity score analysis. *HPB (Oxford).* 2017;19:359–64.
 92. Older P, Hall A, Hader R. Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. *Chest.* 1999;116:355–62.
 93. Older P, Smith R, Courtney P, Hone R. Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. *Chest.* 1993;104:701–4.
 94. Dunne DF, Jack S, Jones RP, Jones L, Lythgoe DT, Malik HZ, et al. Randomized clinical trial of prehabilitation before planned liver resection. *Br J Surg.* 2016;103:504–12.
 95. Kasivisvanathan R, Abbassi-Ghadi N, McLeod AD, Oliver A, Rao Baikady R, Jhanji S, et al. Cardiopulmonary exercise testing for predicting postoperative morbidity in patients undergoing hepatic resection surgery. *HPB (Oxford).* 2015;17:637–43.
 96. Kaibori M, Ishizaki M, Matsui K, Nakatake R, Yoshiuchi S, Kimura Y, et al. Perioperative exercise for chronic liver injury patients with hepatocellular carcinoma undergoing hepatectomy. *Am J Surg.* 2013;206:202–9.
 97. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ, Delaney CP. Enhanced recovery pathways optimize health outcomes and resource utilization: A meta-analysis of randomized controlled trials in colorectal surgery. *Surgery.* 2011;149:830–40.
 98. Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg.* 2009;144:961–9.
 99. Leibman BD, Dilliogluligil O, Abbas F, Tanli S, Kattan MW, Scardino PT. Impact of a clinical pathway for radical retropubic prostatectomy. *Urology.* 1998;52:94–9.
 100. Niino T, Hata M, Sezai A, Yoshitake I, Unosawa S, Shimura K, et al. Optimal clinical pathway for the patient with type B acute aortic dissection. *Circ J.* 2009;73:264–8.
 101. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. *Cochrane Database Syst Rev.* 2011;(2):CD007635. doi:10.1002/14651858
 102. Hall TC, Dennison AR, Biku DK, Metcalfe MS, Garcea G. Enhanced recovery programmes in hepatobiliary and pancreatic surgery: A systematic review. *Ann R Coll Surg Engl.* 2012;94:318–26.
 103. Wang C, Zheng G, Zhang W, Zhang F, Lv S, Wang A, et al. Enhanced recovery after surgery programs for liver resection: a meta-analysis. *J Gastrointest Surg.* 2017;21:472–86.
 104. Noba L, Rodgers S, Chandler C, Balfour A, Hariharan D, Yip VS. Enhanced recovery after surgery (ERAS) reduces hospital costs and improve clinical outcomes in liver surgery: a systematic review and meta-Analysis. *J Gastrointest Surg.* 2020;24:918–32.
 105. Kaibori M, Matsui K, Ishizaki M, Iida H, Yoshii K, Asano H, et al. Effects of implementing an “enhanced recovery after surgery” program on patients undergoing resection of hepatocellular carcinoma. *Surg Today.* 2017;47:42–51.
 106. Hausken J, Fretland ÅA, Edwin B, Andersen MH, Dagenborg VJ, Bjørnelv GMW, et al. Intravenous patient-controlled analgesia versus thoracic epidural analgesia after open liver surgery: a prospective, randomized, controlled, noninferiority trial. *Ann Surg.* 2019;270:193–9.
 107. Melloul E, Hübner M, Scott M, Snowden C, Prentis J, Dejong CH, et al. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. *World J Surg.* 2016;40:2425–40.

How to cite this article: Kaibori M, Matsui K, Shimada M, Kubo S, Hasegawa K. Update on perioperative management of patients undergoing surgery for liver cancer. *Ann Gastroenterol Surg.* 2022;6:344–354. doi:10.1002/ags3.12529