

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2023 April 27; 15(4): 495-744



REVIEW

- 495 Current and emerging therapeutic approaches for colorectal cancer: A comprehensive review
Kumar A, Gautam V, Sandhu A, Rawat K, Sharma A, Saha L
- 520 Harnessing interventions during the immediate perioperative period to improve the long-term survival of patients following radical gastrectomy
Liu LB, Li J, Lai JX, Shi S

MINIREVIEWS

- 534 Nutrition in acute pancreatitis
Gopi S, Saraya A, Gunjan D
- 544 Surgical treatment for recurrent hepatocellular carcinoma: Current status and challenges
Wang D, Xiao M, Wan ZM, Lin X, Li QY, Zheng SS
- 553 The spectrum of pneumatosis intestinalis in the adult. A surgical dilemma
Tropeano G, Di Grezia M, Puccioni C, Bianchi V, Pepe G, Fico V, Altieri G, Brisinda G
- 566 Surgical aspects of small intestinal neuroendocrine tumors
Kupietzky A, Dover R, Mazeh H
- 578 Tumor budding in gastric cancer
Xiao SM, Li J
- 592 Initial management of suspected biliary injury after laparoscopic cholecystectomy
Siki A, Ahola R, Vaalavuo Y, Antila A, Laukkarinen J

ORIGINAL ARTICLE**Basic Study**

- 600 Acinous cell AR42J-derived exosome miR125b-5p promotes acute pancreatitis exacerbation by inhibiting M2 macrophage polarization *via* PI3K/AKT signaling pathway
Zheng Z, Cao F, Ding YX, Lu JD, Fu YQ, Liu L, Guo YL, Liu S, Sun HC, Cui YQ, Li F

Case Control Study

- 621 Skeletal muscle mass and quality before preoperative chemotherapy influence postoperative long-term outcomes in esophageal squamous cell carcinoma patients
Ichinohe D, Muroya T, Akasaka H, Hakamada K

Retrospective Study

- 634 *In situ* subtotal spleen resection combined with selective pericardial devascularization for the treatment of portal hypertension
Li HL, Ning SL, Gao YJ, Zhou T, Chen YX
- 643 Risk factors for blood transfusion and its prognostic implications in curative gastrectomy for gastric cancer
Kawakami LE, Bonomi PB, Pereira MA, Carvalho FO, Ribeiro Jr U, Zilberstein B, Sampaio LR, Carneiro-D'Albuquerque LA, Ramos MFKP

Clinical Trials Study

- 655 Endoscopic ultrasound-guided intraportal injection of autologous bone marrow in patients with decompensated liver cirrhosis: A case series
Zheng SP, Deng AJ, Zhou JJ, Yuan LZ, Shi X, Wang F
- 664 Computed tomography perfusion in differentiating portal hypertension: A correlation study with hepatic venous pressure gradient
Dong J, Zhang Y, Wu YF, Yue ZD, Fan ZH, Zhang CY, Liu FQ, Wang L

Observational Study

- 674 Ligamentum teres hepatis as a graft for portal and/or superior mesenteric vein reconstruction: From bench to bedside
Zhu WT, Wang HT, Guan QH, Zhang F, Zhang CX, Hu FA, Zhao BL, Zhou L, Wei Q, Ji HB, Fu TL, Zhang XY, Wang RT, Chen QP
- 687 Efficacy and safety analysis of transarterial chemoembolization and transarterial radioembolization in advanced hepatocellular carcinoma descending hepatectomy
Feng R, Cheng DX, Song T, Chen L, Lu KP

Prospective Study

- 698 Effectiveness of a new approach to minimally invasive surgery in palliative treatment of patients with distal malignant biliary obstruction
Susak YM, Markulan LL, Lobanov SM, Palitsya RY, Rudyk MP, Skivka LM

Randomized Controlled Trial

- 712 External use of mirabilite to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis in children: A multicenter randomized controlled trial
Zeng JQ, Zhang TA, Yang KH, Wang WY, Zhang JY, Hu YB, Xiao J, Gu ZJ, Gong B, Deng ZH

SYSTEMATIC REVIEWS

- 723 The global epidemiology of upper and lower gastrointestinal bleeding in general population: A systematic review
Saydam ŞS, Molnar M, Vora P

CASE REPORT

- 740 Idiopathic colopleural fistula presenting with lung abscess and refractory empyema: A case report
Wang CL, Cheng KC

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INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJGS* as 2.505; IF without journal self cites: 2.473; 5-year IF: 3.099; Journal Citation Indicator: 0.49; Ranking: 104 among 211 journals in surgery; Quartile category: Q2; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Rui-Rui Wu, Production Department Director: Xiang Li, Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastrointestinal Surgery

ISSN

ISSN 1948-9366 (online)

LAUNCH DATE

November 30, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Peter Schemmer

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

PUBLICATION DATE

April 27, 2023

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Surgical treatment for recurrent hepatocellular carcinoma: Current status and challenges

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Elshimi E, Egypt;
Kanno H, Japan

Received: December 6, 2022

Peer-review started: December 6, 2022

First decision: December 19, 2022

Revised: January 5, 2023

Accepted: March 21, 2023

Article in press: March 21, 2023

Published online: April 27, 2023



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Abstract

Primary liver cancer is the sixth most commonly diagnosed cancer and was the third leading cause of cancer deaths worldwide in 2020. It includes hepatocellular carcinoma (HCC) (representing 75%-85% of cases), intrahepatic cholangiocarcinoma (representing 10%-15% of cases), and other rare types. The survival rate of patients with HCC has risen with improved surgical technology and perioperative management in recent years; however, high tumor recurrence rates continue to limit long-term survival, even after radical surgical resection (exceeding 50% recurrence). For resectable recurrent liver cancer, surgical removal [either salvage liver transplantation (SLT) or repeat hepatic resection] remains the most effective therapy that is potentially curative for recurrent HCC. Thus, here, we introduce surgical treatment for recurrent HCC. Areas Covered: A literature search was performed for recurrent HCC using Medline and PubMed up to August 2022. Expert commentary: In general, long-term survival after the resection of recurrent liver cancer is usually beneficial. SLT has equivalent outcomes to primary liver transplantation for unresectable recurrent illness in a selected group of patients; however, SLT is constrained by the supply of liver grafts. SLT seems to be inferior to repeat liver resection when considering operative and postoperative results but has the major advantage of disease-free survival. When considering the similar overall survival rate and the current situation of donor shortages, repeat liver resection remains an important option for recurrent HCC.

Key Words: Hepatocellular carcinoma; Repeated liver resection; Salvage liver transplantation; Primary liver cancer

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Core Tip: This article reviews the previous literature reports on the statistics of surgical treatment of recurrent liver cancer, mainly including re-hepatectomy and salvage liver transplantation. This article focuses on the analysis and comparison of the respective advantages and disadvantages of these two methods and proposes a future vision.

Citation: Wang D, Xiao M, Wan ZM, Lin X, Li QY, Zheng SS. Surgical treatment for recurrent hepatocellular carcinoma: Current status and challenges. *World J Gastrointest Surg* 2023; 15(4): 544-552

URL: <https://www.wjgnet.com/1948-9366/full/v15/i4/544.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v15.i4.544>

INTRODUCTION

In every nation on earth, cancer is the main cause of mortality and a significant roadblock to raising life expectancy[1]. In 2020, primary liver cancer, which is the sixth most often diagnosed cancer, was the third greatest cause of cancer deaths globally[2]. It includes hepatocellular carcinoma (HCC) (representing 75%-85% of cases), intrahepatic cholangiocarcinoma (representing 10%-15% of cases), and other rare types. At present, the diagnosis of HCC is usually based on the standards established by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases[3]. Curative treatment for HCC modalities includes resection, ablative therapies (such as radiofrequency ablation, percutaneous ethanol injection, and liver transplantation), and palliative treatment [including trans-arterial chemoembolization (TACE) and targeted systemic chemotherapy with sorafenib][4]. Guidelines from countries worldwide recommend surgical resection as the preferred course of treatment for individuals with resectable tumors[5-7]. With more advanced surgical techniques and postoperative care in recent years, the survival rate of patients with HCC has increased, although long-term survival following surgical resection is still hampered by the high tumor recurrence rate[8-11]. Even after surgical resection, which is thought to be the most radical therapy, the recurrence rate has been reported to exceed 50%[12-14].

Recurrent cancers in liver remains have been treated using the therapeutic techniques frequently utilized for original tumors, such as TACE, radiotherapy, local ablative therapy, surgical resection, and liver transplantation[15]. Nonsurgical options are commonly indicated for the treatment of recurrent HCC since second procedures are frequently unacceptably risky due to the presence of multiple tumors or inadequately preserved liver function. The most effective treatment that may be curative for recurrent HCC remains surgical excision [either salvage liver transplantation (SLT) or repeat hepatic resection] for resectable recurrent liver cancer[16]. Here, we aimed to introduce surgical treatment for recurrent HCC.

RECURRENCE OF HCC

The recurrence of HCC can be either intrahepatic or extrahepatic. The rate of extrahepatic recurrence is far lower compared to that of intrahepatic recurrence. Extrahepatic metastasis is usually considered a late systemic disease[17]. Therefore, patients with extrahepatic recurrence usually receive systemic chemotherapy or supportive treatment only[18-20]. The most frequent kind of recurrent HCC, which is observed in 68%-96% of cases, is intrahepatic recurrence[17,21-23]. Clinically, intrahepatic recurrence is generally attributed to two alternative mechanisms: (1) Intrahepatic metastasis from a primary site; and (2) metachronous multicentric carcinogenesis[24]. Numerous studies have demonstrated that microvascular invasion is a major predictor of tumor recurrence and overall survival (OS) following surgical resection and liver transplantation for HCC[25-29]. According to several studies, there is a larger likelihood of microvascular invasion when there is a higher tumor burden (measured in terms of size and quantity)[30,31]. The alpha-fetoprotein level, transfusion, tumor grade, macroscopic portal vein involvement, the existence of satellite nodules, and positive surgical margin are additional recurrence predictors noted by other research[27,32].

REPEATED LIVER RESECTION

A treatment that may be curative for liver tumors is hepatic resection, which gives patients a possibility of long-term survival. Several treatment centers currently recommend repeating hepatectomy as the first line of therapy for recurrent HCC because it is secure and has comparable survival rates to the first hepatectomy[17]. The majority of patients with intrahepatic recurrence, however, are thought to be unsuitable for repeat hepatectomy[33]. At present, there is no uniform, standard for indicating re-hepatectomy; however, the basic principle is the same. Specifically, currently used standards include a Grade A Child-Pugh score of liver function, sufficient volume of residual liver, recurrent tumors are single or multiple nodules confined to one lobe or liver segment, and there is no invasion of the main blood vessels and bile ducts of the hepatic portal[34]. Repeat hepatectomy is performed 7%-30% of the time to treat HCC recurrence[33,35]. The multifocality, location, and degree of cirrhosis have all been linked to the poor incidence of resectability in individuals with intrahepatic recurrence[36].

The first study of second hepatic resections for recurrent HCC in nine patients without single surgical mortality was reported by Nagasue *et al*[37] in 1986. This study showed that repeated hepatic resection was a feasible and beneficial therapeutic approach for patients with recurrent HCCs in the liver residual [37]. Subsequently, several studies reported the feasibility of repeated hepatectomies for intrahepatic HCC recurrence, with it increasing survival time with no significant increase in morbidity and mortality rates[38-41]. According to Wu *et al*[41], therapy of recurrent HCC with a second hepatectomy was successful, even in cases of the disease's second and third occurrences.

The surgical procedure for liver resection is still challenging and associated with complications[20,42, 43]. The more times a hepatectomy is performed, the more challenging resection is[19,38,39,44-49]. Compared to HCC patients that undergo primary hepatectomy, repeat hepatectomy has a higher risk of complications. Such complications include intra-abdominal adhesions caused by the previous hepatectomy, poorer systemic conditions, progressive deterioration of liver function in patients with cirrhosis, inconsistent liver regeneration, and new growth of intrahepatic vascular structures since the previous hepatectomy[41].

Laparoscopic hepatectomy is now frequently accepted as a minimally invasive method for curing HCC[50-52]. When compared to open liver resection, laparoscopic liver surgery is consistently associated with lower complication rates, less intraoperative bleeding, and a shorter hospital stay[53]. For patients with recurring HCC, Chan *et al*[54] demonstrated that laparoscopic re-resection is possible and secure. The authors identified no discernible differences in patient characteristics, preoperative liver function, and tumor features between laparoscopic and open groups, with the laparoscopic group's perioperative blood loss being considerably reduced (100 *vs* 314 mL; $P = 0.014$). Moreover, both the morbidity rate (18.2 *vs* 4.5%; $P = 0.199$) and the length of hospitalization (6 *vs* 5 d; $P = 0.831$) were comparable. Laparoscopic and open groups had three-year OS rates of 60.0% and 89.3%, respectively ($P = 0.279$)[54].

Nonetheless, existing data cannot confirm whether repeated hepatectomy is superior to other methods used to treat recurrent HCC. Due to selection bias, the prognosis of repeated hepatectomy compared with other treatment methods might not be valid. Patients that do not undergo repeated hepatectomy might have poor liver function reserves, or tumor recurrence might be too serious. Repeated hepatectomy as well as alternative treatment methods for recurrent HCC require prospective randomized studies. For patients with primary and secondary liver recurrences, repeated hepatectomy is still the preferred treatment for recurrent liver cancer.

SLT

Since the first attempted human liver transplantation was reported in 1963 by Starzl *et al*[55], surgical techniques and perioperative patient care for liver transplantation have improved, resulting in it now being a common and routine operation. The use of SLT to treat recurrent HCC following primary liver resection has recently been suggested as a way to increase the duration that HCC patients survive[56]. SLT was initially proposed by Majno *et al*[56] and involves the resection or ablation of the primary tumor, followed by transplantation when recurrence develops.

SLT has gained popularity as surgical technology has advanced because of its effectiveness, which is on par with primary transplantation[57,58]. SLT makes it possible for patients to have prompt, efficient, and secure therapy for HCC. Hepatectomy patients who do not have recurrence are exempt from the need for liver transplantation, which helps to address the scarcity of organ donors. SLT is thought to be comparable to primary liver transplantation and has a respectable long-term survival rate, despite the fact that HCC tends to have more aggressive tumor biology[59-61]. In comparison to repeated liver resection or other salvage therapy for HCC recurrence, SLT may also result in higher long-term survival [62-64]. This suggestion was supported in the published meta-analysis by Zheng *et al*[65].

The indications for SLT differ among studies, especially regarding the acceptable extent of recurrent HCC lesions[48,66-68]. It is still controversial what definition is meant by "transplantability criteria in SLT," which refers to standards identifying the individuals who would benefit most from

transplantation for HCC recurrence following hepatectomy[60,69]. The majority of research concurs that a decent post-SLT survival rate may be attained using the Milan criteria for patients with limited recurrence[70]. Zhang *et al*[71] studied the Milan criteria, the University of California San Francisco (UCSF) criteria, and the model for end-stage liver disease (MELD) score to find predictors for SLT. According to the author, the MELD score, Milan, and UCSF criteria were effective at estimating the outcome of SLT. The author emphasized in particular that SLT could be conducted with a favorable prognosis when the Milan criteria were met by the recurring HCC lesions. De Haas claimed that patients with better MELD scores, no preoperative TACE, no postoperative complications following the first hepatectomy, and low T-stage in the excised specimen are the best candidates for SLT[72]. There was no discernible difference in OS and disease-free survival (DFS) rates between the SLT and primary liver transplantation (PLT) groups when Liu *et al*[73] examined the effectiveness of SLT for patients with recurrent HCC following hepatectomy using UCSF criteria.

Previous studies showed that the average operating time lasts 7-10 h[74-76], with an average blood loss of 1.5-3 L[74-77]. Hu *et al*[76] observed a variety of postoperative complications in their review of 888 SLT cases, including intra-abdominal collection or abscesses and intra-abdominal hemorrhage (31% and 7% of patients, respectively). The authors also recorded postoperative infections in 30% of patients. There were 18%, 3%, and 4%, respectively, of biliary complications, renal failure, and vascular problems [76]. The range of postoperative mortality was 2.1% to 11.8%[74,77]. The rates of five-year DFS (37.8%-86%)[68,76-79] and five-year OS (46.6%-88%)[68,74-77] are very different among studies.

COMPARATIVE STUDY OF REPEATED LIVER RESECTION AND SLT

The statistics on survival after the surgical treatment of recurrent liver cancer in recent years are shown in Table 1. SLT and re-resection for recurrent HCC had comparable survival results, according to a cohort study by Chan *et al*[80]. The authors also demonstrated a relationship between poor DFS and preoperative serum alpha-fetoprotein (AFP) levels and the time to recurrence. SLT may thus be more suitable for patients who have a late recurrence and low serum AFP levels[80]. Furthermore, Lim *et al* [81] showed that five-year OS was similar for SLT and second resection strategies; however, SLT achieved better DFS, which might be attributed to several factors. To be more precise, SLT may: (1) Use complete hepatectomy to achieve the safest resection margin; (2) remove clinically undetectable distant micrometastases from the leftover liver; and (3) treat underlying liver disease, avoiding the emergence of HCC in the liver that remains[81]. Patients in the SLT group also had fewer procedures and treatments, and likely had a better quality of life compared to those in the second resection group[81]. Kostakis *et al*[82] backed up this claim by demonstrating that SLT has a clear benefit over recurrent liver resection (RLR) in terms of DFS. The authors did note, however, that SLT seemed to yield less favorable surgical and postoperative outcomes than RLR.

Re-resection has two clear advantages over SLT. First, the technique is not overly complex, and it is a therapy option that is readily available. Second, there are no opportunistic infection risks or immunosuppression-related risks[15]. A recommendation for the second resection first and SLT for unresectable recurrent illness may lessen the strain on the organ donor pool without reducing the likelihood of long-term survival[15].

CONCLUSION

In general, after the second resection for recurrent HCC, long-term survival rates are favorable. SLT has equivalent outcomes to primary liver transplantation for unresectable recurrent illness in a selected group of patients; however, SLT is constrained by the supply of liver grafts. In terms of surgical and postoperative outcomes, SLT appears to be inferior to repeat liver resection; nevertheless, it offers a sizable benefit in terms of DFS compared to repeat liver resection. Repeat liver resection is still an essential option for treating recurrent HCC when taking into account the similar OS rate and current donor scarcity.

The most crucial method for extending patients' life following hepatectomy at the moment is the aggressive treatment of postoperative intrahepatic recurrence. The outcome for long-term survival following resection of recurring liver cancer is generally favorable for resectable cancer. SLT offers outcomes comparable to primary liver transplantation for unresectable recurring illnesses but is constrained by the lack of liver transplant donor availability. Recent advances in systemic and loco-regional treatments for patients with unresectable and advanced HCC have resulted in improved response rates[83]. Consequently, selected patients with initially unresectable HCC have been given the opportunity to achieve adequate tumor downstaging to undergo surgical resection, a "conversion therapy" strategy[83]. For originally unresectable recurrent liver cancer, the potential of "conversion therapy" in transforming some unresectable patients into resectable patients is worth further clinical research. In addition to surgical treatment, TACE, RF ablation, and other forms of local ablation (such as microwave and high-intensity focused ultrasound) are used to treat recurrent liver cancer. It is still

Table 1 Statistics showing survival after surgical treatment of recurrent liver cancer based on published studies spanning 1989 to 2017

Ref.	Study design	Study period	n	Treatment	DFS rate (1-, 3-, 5-yr)	OS rate (1-, 3-, 5-yr)	DSS rate (1-, 3-, 5-yr)
Guerrini <i>et al</i> [84], 2014	Retrospectivecohort	2000-2011	28	SLT	95.1%, 80.6%, 80.6%	85.1%, 66.4%, 49.2%	NA
Qu <i>et al</i> [75], 2015	Retrospectivecohort	2000-2011	111	SLT	NA	75.5%, 56.3%, 49.1%	NA
Yamashita <i>et al</i> [62], 2015	Retrospectivecohort	1989-2012	13	SLT	NA, NA, 81%	NA, NA, 75%	NA
Lim <i>et al</i> [81], 2017	Retrospectivecohort	1994-2011	17	SLT	NA, 80%, 72%	NA, 71%, 71%	NA
Chan <i>et al</i> [3], 2019	Retrospectivecohort	2005-2017	59	SLT	84.8%, 68.2%, 68.2%	NA	95.7%, 74.4%, 66.7%
Yoon <i>et al</i> [85], 2022	Retrospectivecohort	2005-2017	42	SLT	91.6%, 78.6%, 76.8%	NA	98.8%, 90.7%, 87.0%
Minagawa <i>et al</i> [47], 2003	Retrospectivecohort	1994-2000	67	RLR	50%, 21%, 17%	93%, 70%, 56%	NA
Itamoto <i>et al</i> [38], 2007	Retrospectivecohort	1990-2004	84	RLR	56%, 25%, 10%	88%, 67%, 50%	NA
Wu <i>et al</i> [41], 2009	Retrospectivecohort	1990-2007	149	RLR	NA, NA, 31.8%	NA, NA, 56.4%	NA
Faber <i>et al</i> [86], 2011	Retrospectivecohort	1990-2009	27	RLR	NA	96%, 70%, 42%	NA
Yamashita <i>et al</i> [62], 2015	Retrospectivecohort	1989-2012	146	RLR	NA, NA, 16%	NA, NA, 61%	NA
Lim <i>et al</i> [81], 2017	Retrospectivecohort	1994-2011	80	RLR	NA, 22%, 18%	NA, 82%, 71%	NA

DFS: Disease-free survival; OS: Overall survival; DSS: Disease-specific survival; SLT: Salvage liver transplantation; RLR: Repeated liver resection; NA: Not available.

necessary to continue exploring how to formulate a reasonable treatment plan on the premise of fully evaluating the status of patients.

Most existing reports on the surgical treatment of recurrent liver cancer are retrospective, with limitations, such as case selection bias, to varying degrees. Thus, it is necessary to raise the standard of clinical evidence-based medicine in the surgical treatment of recurring liver cancer. More clinical studies, especially randomized prospective studies, are required to confirm the safety and effectiveness of the surgical treatment of recurring liver cancer, and to improve guidance on the surgical treatment of recurring liver cancer.

FOOTNOTES

Author contributions: All authors contributed to data collection, analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval to the version to be published, and agree to be responsible for all aspects of the work.

Supported by the Jinan Microecological Biomedicine Shandong Laboratory, No. JNL-2022022C; and the Health Commission of Zhejiang Province, No. JBZX-202004.

Conflict-of-interest statement: The authors report no conflicts of interest in this work.

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Country/Territory of origin: China

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S-Editor: Yan JP

L-Editor: A

P-Editor: Yan JP

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