Central Hepatectomy versus Major Hepatectomy for Centrally located Hepatocellular Carcinoma: A Propensity Score Matching Study.

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Running head: Centrally located hepatocellular carcinoma

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Synopsis: The study reviewed the surgical outcomes of centrally located hepatocellular carcinoma patients who underwent central hepatectomy or major hepatectomy.

ABSTRACT

Background: In terms of anatomical liver sectionectomy approaches, both a central hepatectomy (CH) and major hepatectomy (MH) are feasible options for a centrally located hepatocellular carcinoma (HCC).

Methods: We retrospectively reviewed the surgical outcomes of central HCC patients who underwent CH or MH. MH includes hemihepatectomy or trisectionectomy, whereas CH involves a left medial sectionectomy, right anterior sectionectomy, or central bisectionectomy. The surgical outcomes were compared before and after propensity score matching (PSM).

Results: A total of 233 patients were enrolled, including 132 in the CH group and 101 in the MH group. The MH group cases were pathologically more advanced and had poorer overall survival rates than the CH group. After PSM, 68 patients were selected into each group, both of which showed similar overall and recurrence free survival outcomes. The CH group showed a tendency for a longer operation time, however, other perioperative outcomes were similar between the two groups. Multivariate analyses of our matched HCC patients revealed that the type of surgery (CH or MH) was not an independent prognostic factor. More patients in the matched CH group experienced a repeat hepatectomy for recurrence and no patients in this group underwent a preoperative portal vein embolization.

Conclusions: The short- and long-term surgical outcomes of CH and MH for a centrally located HCC are similar under a matched clinicopathological background. CH has the

advantage of not requiring a preoperative portal vein embolization and increased chances of conducting a repeat hepatectomy for recurrence.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth-most common cancer in the world and the third highest cause of cancer-related mortality [1]. Hepatic resection is the established treatment of choice for HCC, and anatomical liver resection yields favorable results in these cases [2, 3]. Anatomical liver resection is a reasonable treatment option for HCC because it can effectively eradicate intrahepatic metastases through the portal venous system.

Centrally located HCCs are traditionally defined as HCCs located in the left medial section and/or right anterior section (

HCCs [4-6]. These studies have indicated that CH is an effective operative procedure for some patients with a central HCC. However, the CH and MH cohorts in those reports may have had different clinicopathological backgrounds, which will have caused a selection bias. In addition, the difference and significance of CH and MH for patients with a central HCC and with the same clinicopathological background remains unclear.

In our present study, we retrospectively reviewed a cohort of central HCC patients who underwent either CH or MH. We applied propensity score matching (PSM) to the clinicopathological features of these cases and then compared and assessed the short- and long-term outcomes of the CH or MH interventions.

PATIENTS AND METHODS

Between 2000 and 2019, 874 HCC patients underwent a liver resection at the Department of Gastroenterological Surgery I, Hokkaido University Hospital. Of these cases, 233 patients underwent an anatomical liver sectionectomy (either a left medial sectionectomy, right anterior sectionectomy, right/left hemihepatectomy, central bisectionectomy, or right/left trisectionectomy) for a centrally located HCC. In our present analysis, we defined a central location for a HCC as either the left medial section and/or right anterior section (i.e. , + I). We defined CH as an anatomical liver sectionectomy including a left medial sectionectomy, right anterior sectionectomy, or central

bisectionectomy (mesohepatectomy). We defined MH as an anatomical liver sectionectomy including a right/left hemihepatectomy or right/left trisectionectomy. Using these criteria, our study included 132 patients in the CH group and 101 patients in the MH group. Among these included cases there were 40 left medial sectionectomies, 58 right anterior sectionectomies, and 34 central bisectionectomies in the CH group, and 51 right hemihepatectomies, 39 left hemihepatectomies, 9 right trisectionectomies, and 2 left trisectionectomies in the MH group.

This study was approved by the institutional review board of Hokkaido University Hospital (approval number: 020-0219). All analyses in this study were performed in accordance with the ethical guidelines of Hokkaido University Hospital.

Preoperative management

The preoperative management of our patients was conducted as described in our previous report [7]. Briefly, we evaluated all patients by abdominal and chest computed tomography (CT) prior to surgery. We measured the liver parenchyma and tumor volumes using contrast-enhanced CT data and 3-dimensional workstations (Virtual Place Lexus; Medical Imaging Laboratory, AZE, Tokyo, Japan, and Synapse Vincent; Fujifilm Medical Co., Ltd., Tokyo, Japan), and thereby calculated the effective hepatic resection rate (%). The indocyanine green retention rate at 15 minutes (ICGR15) was measured to evaluate the functional liver reserve. We then used our algorithm which incorporates the ICGR15 and

remnant liver volume to determine the optimal operative procedure, as previously described [7]. If the ICGR15 is less than 15% and the resected liver volume is less than 60%, a hepatectomy of two or more sections (hemihepatectomy, central bisectionectomy, or trisectionectomy) can be performed. However, if the ICGR15 is less than 15% and the resected liver volume is greater than 60%, percutaneous transhepatic portal embolization (PTPE) is performed before surgery. For patients with an ICGR15 of 15-20%, a sectionectomy can be performed.

Surgical methods

The surgical methods used for the liver resection in our present cohort have been previously described [7]. Briefly, transection of the liver parenchyma was performed using the hook spatula of an ultrasonic harmonic scalpel (Ethicon EndoSurgery, San Angelo, TX) and either a DS3.0 Dissecting Sealer (Medtronic, Minneapolis, MN) or a bipolar cautery with a saline irrigation system. Inflow occlusion was applied in an intermittent manner, with 15 minutes of occlusion alternating with 5 minutes of reperfusion. The central venous pressure was maintained at < 5-cm H_2O during transection of the liver parenchyma to prevent venous hemorrhage. We defined anatomical resection in our current study as the anatomically complete removal of the lesion based on Couinaud's classification.

Postoperative data

Data on postoperative morbidity including pleural effusion, ascites, postoperative bleeding, surgical site infection, respiratory complications, posthepatectomy liver failure (PHLF), and bile leakage were collected for analysis. PHLF was diagnosed on the basis of the International Study Group of Liver Surgery definition [8]. Follow-up studies using CT or magnetic resonance imaging were conducted one month after the operation and at three-month intervals thereafter. Pathological liver fibrosis of the underlying liver was assessed according to the general rules for the clinical and pathological study of primary liver cancer set by the Liver Cancer Study Group of Japan, and divided into normal liver or mild fibrosis (f0–2) and advanced fibrosis (f3 and f4) [9].

Statistical analysis

Categorical variables were compared between the study groups using the Fisher exact test. Continuous variables were expressed as medians with ranges, and compared using the Mann-Whitney U test. The overall survival rates and recurrence-free survival rates were calculated using the Kaplan–Meier method and compared between the groups using the log-rank test. Potential prognostic factors were identified by univariate analysis using the log-rank test. Independent prognostic factors were evaluated using a Cox proportional-hazards regression model. Differences in the clinicopathological backgrounds between the CH and

MH groups were propensity score matched (PSM) at a 1:1 ratio. Eight variables (age, hepatitis B surface [HBs] antigen, platelet count, alpha-fetoprotein [AFP], tumor size, portal vein invasion, hepatic vein invasion, and bile duct invasion) were entered into the propensity score, and the caliper was set to 0.20. In this study, < 0.05 was considered statistically significant. All statistical analyses were performed using JMP version 14 for Windows (SAS Institute, Cary, NC).

RESULTS

Differences in the clinicopathological features and perioperative surgical outcomes in the HCC patients who underwent CH or MH before and after propensity score matching

The clinicopathological features of the centrally located HCC patients who underwent CH or MH are presented in Table 1. Sex, proportion of hepatitis C virus (HCV) antibody, albumin value, total bilirubin value, prothrombin time, ICGR15, pathological liver fibrosis, tumor number, histological differentiation, the hepatic artery invasion status, and the pathological surgical margin were similar between the CH and MH groups. On the other hand, significant differences were found between the groups in age, proportion of HBs antigen, platelet count, AFP expression, tumor size, portal vein invasion status, hepatic vein invasion status, and bile duct invasion status. We utilized PSM because of these clinicopathological differences. Sixty-eight patients in each group were matched in terms of their

clinicopathological variables (Table 1). The perioperative outcomes of the central HCC patients who underwent CH or MH are provided in Table 2. Prior to PSM, there were no significant differences found between the CH and MH groups in terms of operation time and blood loss. Prior to PSM also, in terms of postoperative complications, there were no significant differences between the CH and MH groups with respect to pleural effusion, ascites, postoperative bleeding, surgical site infection, respiratory complication, bile leakage, postoperative hospital stay, and postoperative mortality, although PHLF was more common in the MH group. After PSM, the CH group showed a tendency for a longer operation time, however, other perioperative outcomes were similar between the two groups (Table 2). In terms of preoperative PTPE, more patients in the MH group experienced this before surgery both before and after PSM (Table 2).

Prognostic outcomes in accordance with the surgical procedure before and after propensity score matching

Prior to PSM, the overall 5-year survival rates in the CH and MH groups were 71.8% and 57.1%, respectively (p=0.0262; Fig. 1a), and the 5-year recurrence-free survival rates were 35.2% and 33.6%, respectively (p=0.2013; Fig. 1b). After PSM, the overall 5-year survival rates in the CH and MH groups were 66.9% and 67.6%, respectively (p=0.7731; Fig. 1c), and the 5-year recurrence-free survival rates were 37.0% and 37.7%, respectively

(p=0.3900; Fig. 1d).

Risk factors for overall and recurrence-free survival in the propensity score-matched patients

In the propensity score-matched cohorts of centrally located HCC patients, univariate analysis revealed that albumin, tumor size, and portal vein invasion were significant prognostic indicators of overall survival and multivariate analysis revealed that tumor size and portal vein invasion were independent prognostic indicators of overall survival (Table 3). Univariate analysis of the matched patients also revealed that albumin, tumor number, tumor size, and portal vein invasion were significant prognostic factors for recurrence-free survival whereas multivariate analysis revealed tumor number and portal vein invasion as independent prognostic indicators of recurrence-free survival (Table 4). Notably, neither CH nor MH affected overall or recurrence-free survival outcomes in the central HCC cases after PSM.

Treatment for recurrences in the patients who underwent CH or MH

The treatments used for recurrences of the central HCCs in our current study series are listed in Table 5. Prior to PSM, there were no significant differences found in the number of treatments with respect to transcatheter arterial chemoembolization (TACE), radiation, local ablation therapy, and hepatic arterial infusion chemotherapy (HAIC). On the other hand,

more patients in the CH group underwent a rehepatectomy, whereas more cases in the MH group received systemic therapy. After PSM however, there were no significant differences evident in the number of cases that received TACE, systemic therapy, radiation, local ablation therapy, or HAIC, although more patients in CH group were given a rehepatectomy.

Analysis of liver-only recurrence and extrahepatic recurrence in the patients who underwent CH or MH

Prior to PSM, liver-only recurrence occurred in 43 of 132 patients (32.5%) in the CH group and 27 of 101 patients (26.7%) in the MH group, respectively (p=0.3877). After PSM, liver-only recurrence occurred in 17 of 68 patients (25.0%) in the CH group and 22 of 68 patients (32.3%) in the MH group, respectively (p=0.4485). Prior to PSM, extrahepatic recurrence occurred in 28 of 132 patients (21.2%) in the CH group and 31 of 101 patients (30.6%) in the MH group, respectively (p=0.1281). After PSM, extrahepatic recurrence occurred in 15 of 68 patients (22.0%) in the CH group and 15 of 68 patients (22.0%) in the MH group, respectively (p=1.0000). Prior to PSM, the 5-year liver-only recurrence-free survival rates in the CH and MH groups were 37.2% and 36.5%, respectively (p=0.1186; Fig. 2a), and the 5-year extrahepatic recurrence-free survival rates were 52.7% and 44.2%, respectively (p=0.0188; Fig. 2b). After PSM, the 5-year liver-only recurrence-free survival rates in the CH and MH groups were 39.1% and 39.7%, respectively (p=0.3175; Fig. 2c), and

the 5-year extrahepatic recurrence-free survival rates were 51.7% and 53.0%, respectively (p=0.3478; Fig. 2d).

DISCUSSION

The central part of the liver includes a left medial section and right anterior section. Two types of anatomical liver sectionectomy can be carried out for patients with centrally located HCC although there have been few reports to date on this subject. A CH intervention for a central HCC is technically demanding due to the proximity of these lesions to important hilar structures and the need for two hepatic resection planes [10]. On the other hand, a hemihepatectomy or trisectionectomy carries a higher risk of PHLF due to the large liver parenchymal loss when using these methods [11]. In our present study, we investigated the effects of CH and MH in the treatment of a centrally located HCC in patients matched for their background clinicopathological characteristics. Our findings indicated that these alternative approaches produce similar short- and long-term surgical outcomes in this circumstance.

Anatomical liver resection has been established as a basic surgical procedure for HCC if functional liver reserve is preserved [12-16]. Anatomical liver resections involve the complete removal of the tumor-bearing portal territory of the liver and include segmentectomy, sectionectomy, hemihepatectomy, and trisectionectomy [17]. The smallest

anatomical liver resection unit is a segmentectomy, but it is rare to compare segmentectomy of with MH for a surgical indication of a central HCC because the tumor is often small and distant to the hilar structures in such cases. On the other hand, surgical indications for a sectionectomy and hemihepatectomy/trisectionectomy for central HCCs are often problematic. In terms of an anatomical liver sectionectomy, both CH and MH can be indicated for centrally located HCCs. There have been several previous reports on the short-term surgical outcomes of CH and MH [5] [6] [18]. However, these studies enrolled patients with different clinicopathological features and this may have resulted in a selection bias. In our current analysis, PHLF was more common in the MH group prior to PSM. The operation time for the CH group was longer than that of the MH group but other perioperative outcomes showed similar outcomes between these two groups after PSM. Hence, our present study data indicated similar short-term surgical outcomes for CH and MH for centrally located HCC under a matched clinicopathological background except for the operation time. In addition, more patients in our MH group underwent preoperative PTPE both before and after PSM. PTPE is a well-established procedure but can cause minor and major complications, albeit with a low probability [19]. CH is therefore worth considering because it typically will not require a prior PTPE.

Anatomic liver resection has generally been reported to improve the long-term outcomes for HCC patients [2, 3, 12-16], although there have been a few contrary findings in

this respect [20, 21]. Hasegawa et al. reported that anatomic resection for a single HCC yields more favorable results than a non-anatomic resection [2]. Huang et al. also reported that anatomic resection for HCC is superior to non-anatomic resection as it yields higher 5-year overall survival and disease-free survival rates and a lower overall recurrence rate [12]. However, the long-term surgical outcomes of anatomical resection for central HCCs remain unclear, and the impact of CH and MH for such lesions on the long-term prognosis remains controversial. In general, the choice of CH or MH for a centrally located HCC often depends on both tumor and patient factors. For example, if a large tumor is located in the central part of the liver, MH is often indicated because CH is a more technically demanding procedure for such cases. Large tumors are often accompanied by other negative prognostic factors such as vascular invasion [22]. By contrast, CH is often selected if the functional liver reserve is poor. Hence, it has been assumed that the clinicopathological features of CH and MH patient groups will be different. Several studies have analyzed the role of CH and MH on the long-term prognosis of patients with a central HCC [4-6]. However, a selection bias would have been unavoidable in these prior studies because most enrolled patients of different clinicopathological backgrounds. On the other hand, Li et al. reported previously after using their matching criteria that patients in the CH group had better overall survival rates but similar disease-free survival outcomes compared to MH-treated patients [23]. However, they included only right anterior sectionectomy and central bisectionectomy (mesohepatectomy)

cases, and no patients who received a left medial sectionectomy, in their CH group. Our current analyses have indicated that prior to PSM, overall survival outcomes were poorer in the MH group whereas recurrence-free survival rates were similar between the groups. Notably however, in our whole cohort before PSM, the MH cases were pathologically more advanced as indicated by higher AFP expression, a larger tumor size, a higher portal vein and hepatic vein invasion status, and a higher bile duct invasion status (Table 1). These pathological factors are already known to be associated with a poor prognosis in HCC [22, 24-27]. We performed PSM on the basis that matching evaluations are needed when there are background differences in the degree of pathological progression. Significantly, our CH group exhibited similar long-term surgical outcomes to the MH group after PSM. In addition, multivariate analyses of our matched HCC patients revealed that tumor size and portal vein invasion were independent prognostic factors for overall survival, and that tumor number and portal vein invasion were so for recurrence-free survival, whereas surgical procedures such as CH or MH was not. Thus, our present data indicated that the surgical intervention (i.e. CH or MH) does not affect the long-term prognosis of central HCC patients of the same clinicopathological background, and that the long-term surgical outcomes from CH and MH treatments of a central HCC are similar if the clinicopathological background is matched.

Currently, there are a wide variety of treatments for recurrent HCC, including resection, ablation, embolization, systemic therapy, and radiation [28]. Intrahepatic

recurrences is the most common type after a liver resection for HCC [27, 28]. Hence, effective treatments for intrahepatic recurrences are important for the management of HCC. Although there are various treatments such as ablation, embolization, and systemic therapy for recurrences of a HCC, repeat surgeries for such lesions contributes to the favorable prognosis in patients who are candidates for a hepatectomy [29]. There have been no prior studies that have analyzed the treatment of recurrences in patients with a centrally located HCC who underwent CH or MH. Our present study is therefore the first to do so. Our present results after PSM indicated that more of our CH patients experienced a repeat hepatectomy. It is assumed that local ablation therapy for recurrence after CH is difficult, because CH has two hepatic dissection planes, the intestinal tract often enters between the liver dissection planes, and gastrointestinal perforations can occur when the target nodule is adjacent to the intestine [30]. As a result, the use of a repeat hepatectomy for recurrence after CH may have increased. Furthermore, CH has been reported to have the advantage of leaving a sufficient liver parenchyma [10] which may underlie why there were many repeat hepatectomies in our CH group. In addition, our present results after PSM showed both liver-only recurrence and extrahepatic recurrence rate were similar between CH and MH groups. Taken together, the fact that repeat hepatectomy was more common in CH group was not because liver recurrence was more common in CH group, but because the sufficient remnant liver was preserved in CH group. Hence, by preserving the remnant liver parenchyma CH provides more opportunities

for a repeat hepatectomy after tumor recurrence.

This study had several limitations of note, including its retrospective nature and enrollment of patients from a single center. Surgical indications for a central HCC are related not only to tumor factors such as size and patient factors such as functional liver reserve, but also to the three-dimensional positional relationship between the tumor, hilar structures and hepatic veins. Hence, our current study was not able to completely match the patient backgrounds with respect to the positional relationship of the tumors. In addition, other anatomical factor and liver dysfunction also affect the choice of CH or MH. Patient-specific vasculature is related to surgical indication. In this study, factors related to liver function such as albumin, ICG R15, and pathological liver fibrosis were examined and matched, but not all liver functions were matched. However, this is still the first report on CH and MH for centrally located HCC cases that employed a PSM methodology and included treatments for recurrences. Our current analyses thus provide some important new insights into the surgical approaches for a central HCC.

In conclusion, the short- and long-term surgical outcomes of CH and MH for central HCC cases are similar under a matched clinicopathological background. The prognosis for a centrally located HCC mainly depends on pathological factors rather than the surgical intervention. Either CH or MH can be selected to treat a central HCC in terms of patient and tumor factors, but CH has the advantages of preserving the liver parenchyma,

avoidance of preoperative PTPE, and an increased the chance of conducting a repeat hepatectomy in the event of a recurrence.

References

1. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68:723-750.
2. Hasegawa K, Kokudo N, Imamura H, et al. Prognostic impact of anatomic resection for hepatocellular carcinoma. Ann Surg. 2005;242:252-259.
3. Kaibori M, Kon M, Kitawaki T, et al. Comparison of anatomic and non-anatomic hepatic resection for hepatocellular carcinoma. J Hepatobiliary Pancreat Sci. 2017;24:616-626.
4. Hu RH, Lee PH, Chang YC, Ho MC, Yu SC. Treatment of centrally located hepatocellular carcinoma with central hepatectomy. Surgery. 2003;133:251-256.
5. Chen X, Li B, He W, Wei YG, Du ZG, Jiang L. Mesohepatectomy versus extended hemihepatectomy for centrally located hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int. 2014;13(3):264-270.
6. Yang LY, Chang RM, Lau WY, Ou DP, Wu W, Zeng ZJ. Mesohepatectomy for centrally located large hepatocellular carcinoma: Indications, techniques, and outcomes. Surgery. 2014;156:1177-1187.

7. Kamiyama T, Nakanishi K, Yokoo H, et al. Perioperative management of hepatic resection toward zero mortality and morbidity: analysis of 793 consecutive cases in a single institution. J Am Coll Surg. 2010; 211:443-449.
8. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011 ;149:713-724.
9. Liver cancer study group of Japan. General Rules for the Clinical and Pathological Study of Primary Liver Cancer. 6th ed. Tokyo: Kanehara & CO., LTD.; 2015.
10. Mehrabi A, Mood ZA, Roshanaei N, et al. Mesohepatectomy as an option for the treatment of central liver tumors. J Am Coll Surg. 2008;207:499-509.
11. Orimo T, Kamiyama T, Kamachi H, et al. Predictive value of gadoxetic acid enhanced magnetic resonance imaging for posthepatectomy liver failure after a major hepatectomy. J Hepatobiliary Pancreat Sci. 2020;27:531-540.
12. Huang X, Lu S. A Meta-analysis comparing the effect of anatomical resection vs. non-anatomical resection on the long-term outcomes for patients undergoing hepatic resection for hepatocellular carcinoma. HPB (Oxford). 2017;19:843-849.
13. Kamiyama T, Nakanishi K, Yokoo H, Kamachi H, Matsushita M, Todo S. The impact of anatomical resection for hepatocellular carcinoma that meets the Milan criteria. J Surg Oncol. 2010;101:54-60.

14. Jung DH, Hwang S, Lee YJ, et al. Small Hepatocellular Carcinoma With Low Tumor Marker Expression Benefits More From Anatomical Resection Than Tumors With Aggressive Biology. Ann Surg. 2019;269:511-519.

15. Hokuto D, Nomi T, Yasuda S, et al. Does anatomic resection improve the postoperative outcomes of solitary hepatocellular carcinomas located on the liver surface? Surgery. 2018;163:285-290.

16. Aoki T, Kubota K, Hasegawa K, et al. Significance of the surgical hepatic resection margin in patients with a single hepatocellular carcinoma. Br J Surg. 2020;107:113-120.

17. Strasberg SM, Phillips C. Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. Ann Surg. 2013;257:377-382.

18. Xiao Y, Li W, Wan H, Tan Y, Wu H. Central hepatectomy versus major hepatectomy for patients with centrally located hepatocellular carcinoma: A meta-analysis. Int J Surg. 2018;52:297-302.

19. Abulkhir A, Limongelli P, Healey AJ, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg. 2008;247:49-57.

20. Marubashi S, Gotoh K, Akita H, et al. Anatomical versus non-anatomical resection for hepatocellular carcinoma. Br J Surg. 2015;102:776-784.

21. Hidaka M, Eguchi S, Okuda K, et al. Impact

of Anatomical Resection for Hepatocellular Carcinoma With Microportal Invasion (vp1): A Multi-institutional Study by the Kyushu Study Group of Liver Surgery. Ann Surg. 2020;271:339-346.

22. Wakayama K, Kamiyama T, Yokoo H, et al. Huge hepatocellular carcinoma greater than resection. J Surg Oncol. 2017;115:324-329.

23. Li W, Li L, Minigalin D, Wu H. Anatomic mesohepatectomy versus extended hepatectomy for patients with centrally locat ed hepatocellular carcinoma. HPB (Oxford). 2018;20:530-537.

24. Yang SL, Liu LP, Yang S, et al. -fetoprotein and prognosis after hepatectomy for hepatocellular carcinoma. Br J Surg. 2016 ;103:716-724.

25. Minagawa M, Makuuchi M, Takayama T, Ohtomo K. Selection criteria for hepatectomy in patients with hepatocellular carcinoma and portal vein tumor thrombus. Ann Surg. 2001; 233:379-384.

26. Kokudo T, Hasegawa K, Yamamoto S, et al. Surgical treatment of hepatocellular carcinoma associated with hepatic vein tumor thrombosis. J Hepatol. 2014; 61:583-588.

27. Orimo T, Kamiyama T, Yokoo H, et al. Hepatectomy for Hepatocellular Carcinoma with Bile Duct Tumor Thrombus, Including Cases with Obstructive Jaundice. Ann Surg Oncol. 2016;23:2627-2634.

28. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S.

Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis.

Ann Surg. 2015;261:947-955.

29. Yoh T, Seo S, Taura K, et al. Surgery for Recurrent Hepatocellular Carcinoma: Achieving

Long-term Survival. Ann Surg. 2019 Apr 30. doi: 10.1097/SLA.0000000000003358.

Online ahead of print.

30. Tateishi R, Shiina S, Teratani T, et al.

Percutaneous radiofrequency ablation for hepatocellular carcinoma.

An analysis of 1000 cases. Cancer. 2005 Mar 15;103(6):1201-1209.

Figure legend

Figure 1. (a) Overall survival rates in the MH group were poorer than those of the CH group prior to propensity score matching (PSM) analysis (p = 0.0262). (b) The recurrence-free survival rates in the CH and MH groups were similar before PSM analysis (p = 0.2013). (c) The overall survival rates in the CH and MH groups were similar after PSM analysis (p = 0.7731). (d) The recurrence-free survival rates in the CH and MH groups were similar after PSM analysis (p = 0.3900).

Figure 2. (a) The liver-only recurrence-free survival rates in the CH and MH groups were similar before PSM analysis (p = 0.1186). (b) The extrahepatic recurrence-free survival rates in the MH group were poorer than those of the CH group prior to propensity score matching (PSM) analysis (p = 0.0188). (c) The liver-only recurrence-free survival rates in the CH and MH groups were similar after PSM analysis (p = 0.3175). (d) The extrahepatic recurrence-free survival rates in the CH and MH groups were similar after PSM analysis (p = 0.3478).

Table 1 Clinicopathological features according to the operative procedure before and after propensity score matching (PSM) method

	Before PSM			After PSM		
Variable	CH group (n = 132)	MH group (n = 101)	p value	CH group (n = 68)	MH group (n = 68)	p value
Age†			0.0120			0.9462
	68 (39-86)	65 (33-85)		65.5 (39-82)	65 (33-85)	
Gender			1.0000			1.0000
Female	20	16		12	13	
Male	112	85		56	55	
HBs antigen			0.0285			0.7253
Negative	92	56		40	43	
Positive	40	45		28	25	
HCV antibody			0.2290			0.5252
Negative	93	79		56	52	
Positive	39	22		12	16	
Alb (g/dl)†			0.4817			0.7731
	4.2 (3.1-5.2)	4.2 (2.9-4.9)		4.2 (3.4-4.9)	4.2 (2.9-4.9)	
T-Bil (mg/dl)†			0.1682			0.3385
	0.7 (0.2-1.7)	0.7 (0.1-2.3)		0.7 (0.2-1.7)	0.6 (0.2-2.3)	
PT (%)†			0.9695			0.5495
	95.5 (52.6-124.8)	96.0 (54.5-126.8)		93.7 (52.6-124.8)	96.1 (54.5-122.2)	
Plt ($\times 10^4$			0.0100			0.7623
	17.2 (5.6-37.8)	19.2 (8.8-54.7)		17.1 (5.6-34.3)	17.5 (8.8-48.4)	
ICG R15 (%)†			0.1619			0.5807
	11.6 (2.9-86.7)	10.8 (1.4-54.0)		10.9 (2.9-86.7)	10.5 (2.5-54.0)	
Pathological liver fibrosis			0.8914			0.5827
f0-2	84	63		44	48	
f3, f4	48	38		24	20	
AFP (ng/ml)†			0.0025			0.2271
	7.7 (1.3-142448)	47.7 (1.7-1488000)		10.5 (1.6-142448)	25.1 (1.7-158732)	
Tumor number			0.4846			0.7157
Single	91	65		47	44	
Multiple	41	36		21	24	
Tumor size (cm)†			<0.0001			0.4552
	4.5 (1.2-15.2)	6.5 (0.6-22.5)		4.9 (1.4-15.2)	5.5 (0.7-18.0)	
Differentiation			0.2031			0.7537
Well	13	4		7	4	
Moderate	86	63		43	45	
Poor	32	32		17	17	
unknown	1	2		1	2	
Portal vein invasion			<0.0001			1.0000
Absence	103	53		44	45	
Presence	29	48		24	23	
Hepatic vein invasion			0.0230			0.5854
Absence	116	77		59	62	
Presence	16	24		9	6	
Hepatic artery invasion			0.1868			1.0000
Absence	132	99		68	68	
Presence	0	2		0	0	
Bile duct invasion			0.0071			0.7182
Absence	127	87		63	65	
Presence	5	14		5	3	
Pathological surgical margin			1.0000			0.3250
Negative	120	92		61	65	
Positive	12	9		7	3	

Abbreviations: AFP, alpha-fetoprotein; Alb, Albumin; CH, central hepatectomy; HBs antigen, hepatitis B surface antigen; HCV antibody, hepatitis C virus antibody; ICG R15, indocyanine green retention rate at 15 min; MH, major hepatectomy; Plt, platelet; PSM, propensity score matching; PT, prothrombin time; T-Bil, Total bilirubin

† Expressed as median (range)

Table 2 Perioperative outcomes of HCC according to the operative procedure before and after PSM method

		Before PSM			After PSM		
Variable		CH group (n = 132)	MH group (n = 101)	p value	CH group (n = 68)	MH group (n = 68)	p value
Operation time (min)†				0.2338			0.0015
		334 (201-588)	325 (171-911)		336 (239-588)	311 (171-611)	
Blood loss (ml)†				0.9765			0.0740
		430 (0-2620)	430 (0-35820)		465 (20-2620)	345 (0-4635)	
PTPE				0.0004			0.0279
	no	132	92		68	62	
	yes	0	9		0	6	
Postoperative complication							
Pleural effusion				1.0000			1.0000
	no	129	98		66	67	
	yes	3	3		2	1	
Ascites				0.2601			1.0000
	no	129	101		67	68	
	yes	3	0		1	0	
Postoperative bleeding				1.0000			1.0000
	no	129	98		66	66	
	yes	3	3		2	2	
Surgical site infection				1.0000			1.0000
	no	131	100		68	68	
	yes	1	1		0	0	
Respiratory complication				0.5067			1.0000
	no	130	101		67	68	
	yes	2	0		1	0	
PHLF				0.0280			0.5313
	no	128	90		64	61	
	yes	4	11		4	7	
Bile leakage				0.1494			0.2428
	no	118	96		59	64	
	yes	14	5		9	4	
Postoperative hospital stay (days)†				0.4108			0.0821
		16 (8-95)	15 (7-63)		16 (8-95)	15 (7-63)	
Mortality				1.0000			1.0000
	no	132	101		68	68	
	yes	0	0		0	0	

Abbreviations: CH, central hepatectomy;HCC, hepatocellular carcinoma; MH, major hepatectomy; PHLF, posthepatectomy liver failure; PSM, propensity score matching; PTPE, percutaneous transhepatic portal embolization

† Expressed as median (range)

Table 3 Univariate and multivariate analyses of overall survival

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Age (≥60 vs. <60 years)	1.016	0.509–1.920	0.9601	-		
Gender (male vs. female)	0.972	0.473–2.261	0.9443	-		
HBs antigen (positive vs. negative)	0.650	0.331–1.218	0.1825	-		
HCV antibody (positive vs. negative)	1.004	0.450–2.018	0.9906	-		
Alb (<3.5 vs. ≥3.5 g/dl)	3.553	1.342–7.863	0.0136	1.475	0.503–3.864	0.4565
T-Bil (≥1.0 vs. <1.0 mg/dl)	1.647	0.739–3.310	0.2079	-		
PT (≥70 vs. <70 %)	0.295	0.106–1.227	0.0853	-		
Plt (≥15 vs. 15 $\times 10^4$	0.928	0.478–1.886	0.8284	-		
ICG R15 (≥10 vs. <10 %)	0.873	0.446–1.632	0.6783	-		
AFP (≥20 vs. <20 ng/ml)	1.474	0.802–2.725	0.2094	-		
Liver fibrosis (f0-2 vs. f3,4)	0.737	0.375–1.380	0.3463	-		
Tumor number (multiple vs. single)	1.520	0.796–2.816	0.1983	-		
Tumor size (≥10 vs. <10 cm)	3.277	1.692–6.121	0.0007	2.872	1.337–5.776	0.0081
Differentiation (poor vs. well-mod)	1.001	0.466–1.969	0.9957	-		
Portal vein invasion (positive vs. negative)	2.076	1.104–3.834	0.0239	1.984	1.054–3.669	0.0340
Hepatic vein invasion (positive vs. negative)	1.416	0.419–3.606	0.5329	-		
Bile duct invasion (positive vs. negative)	2.318	0.555–6.526	0.2148	-		
Surgical procedure (MH vs. CH)	1.093	0.593–2.013	0.7732	-		

Abbreviations: AFP, alpha-fetoprotein; Alb, Albumin; CH, central hepatectomy; HBs antigen, hepatitis B surface antigen; HCV antibody, hepatitis C virus antibody; ICG R15, indocyanine green retention rate at 15 min; MH, major hepatectomy; Plt, platelet; PSM, propensity score matching; PT, prothrombin time; T-Bil, Total bilirubin

Table 4 Univariate and multivariate analyses of recurrence free survival

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Age (≥60 vs. <60 years)	1.176	0.698–1.918	0.5294	-		
Gender (male vs. female)	1.209	0.675–2.360	0.5394	-		
HBs antigen (positive vs. negative)	1.156	0.719–1.840	0.5436	-		
HCV antibody (positive vs. negative)	0.616	0.315–1.104	0.1075	-		
Alb (<3.5 vs. ≥3.5 g/dl)	2.727	1.051–5.823	0.0404	2.429	0.926–5.666	0.0690
T-Bil (≥1.0 vs. <1.0 mg/dl)	1.072	0.533–1.961	0.8326	-		
PT (≥70 vs. <70 %)	0.537	0.196–2.215	0.3406	-		
Plt (≥15 vs. 15 $\times 10^4$	0.846	0.513–1.451	0.5333	-		
ICG R15 (≥10 vs. <10 %)	1.126	0.696–1.795	0.6225	-		
AFP (≥20 vs. <20 ng/ml)	1.557	0.979–2.418	0.0612	-		
Liver fibrosis (f0-2 vs. f3,4)	0.991	0.651–1.567	0.9727	-		
Tumor number (multiple vs. single)	1.968	1.211–3.161	0.0067	1.814	1.109–2.941	0.0181
Tumor size (≥10 vs. <10 cm)	1.846	1.020–3.159	0.0430	1.727	0.907–3.093	0.0933
Differentiation (poor vs. well-mod)	1.508	0.887–2.472	0.1247	-		
Portal vein invasion (positive vs. negative)	2.050	1.255–3.305	0.0046	2.231	1.358–3.636	0.0017
Hepatic vein invasion (positive vs. negative)	0.744	0.260–1.669	0.5054	-		
Bile duct invasion (positive vs. negative)	0.614	0.150–1.651	0.3739	-		
Surgical procedure (MH vs. CH)	1.224	0.769–1.951	0.3913	-		

Abbreviations: AFP, alpha-fetoprotein; Alb, Albumin; CH, central hepatectomy; HBs antigen, hepatitis B surface antigen; HCV antibody, hepatitis C virus antibody; ICG R15, indocyanine green retention rate at 15 min; MH, major hepatectomy; Plt, platelet; PSM, propensity score matching; PT, prothrombin time; T-Bil, Total bilirubin

Table 5 Treatment for recurrence of central located HCC before and after PSM method

	Before PSM			After PSM		
Number of treatment	CH group (n = 132)	MH group (n = 101)	p value	CH group (n = 68)	MH group (n = 68)	p value
Rehepatectomy			0.0158			0.0302
0	111	96		56	65	
1	15	5		9	3	
≥2	6	0		3	0	
TACE			0.8888			0.8544
0	69	54		39	39	
1	23	15		9	7	
≥2	40	32		20	22	
Systemic therapy			0.0020			0.1126
0	93	52		45	39	
1	18	13		12	8	
≥2	21	36		11	21	
Radiation			0.1457			0.2802
0	118	91		63	61	
1	10	3		3	1	
≥2	4	7		2	6	
Local ablation therapy			0.6821			0.7830
0	106	83		57	57	
1	15	8		6	4	
≥2	11	10		5	7	
HAIC			0.2417			1.0000
0	129	94		65	66	
1	2	3		2	1	
≥2	1	4		1	1	

Abbreviations: CH, central hepatectomy; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; MH, major hepatectomy; PSM, propensity score matching; TACE, transcatheter arterial chemoembolization

Figure. 1

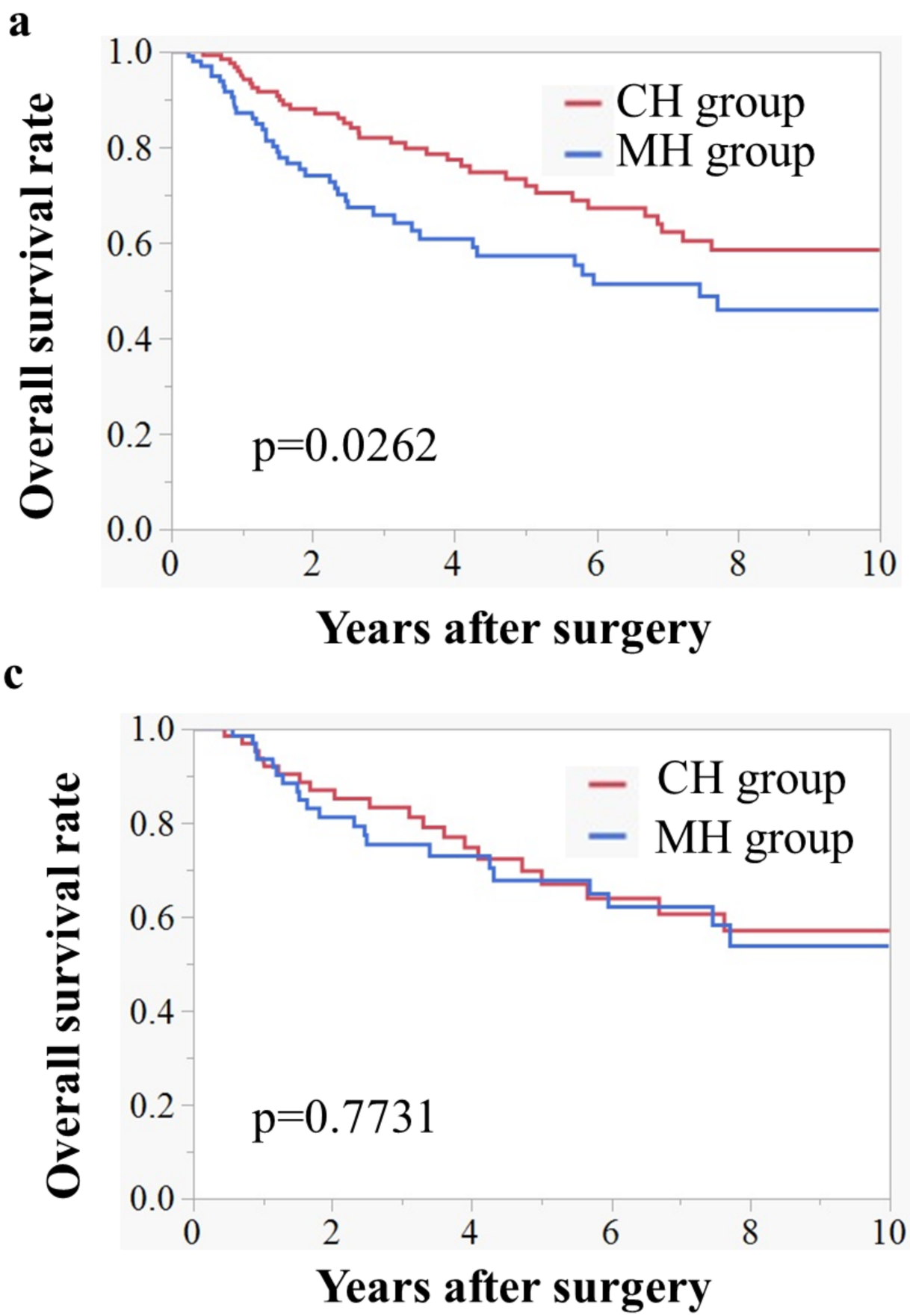
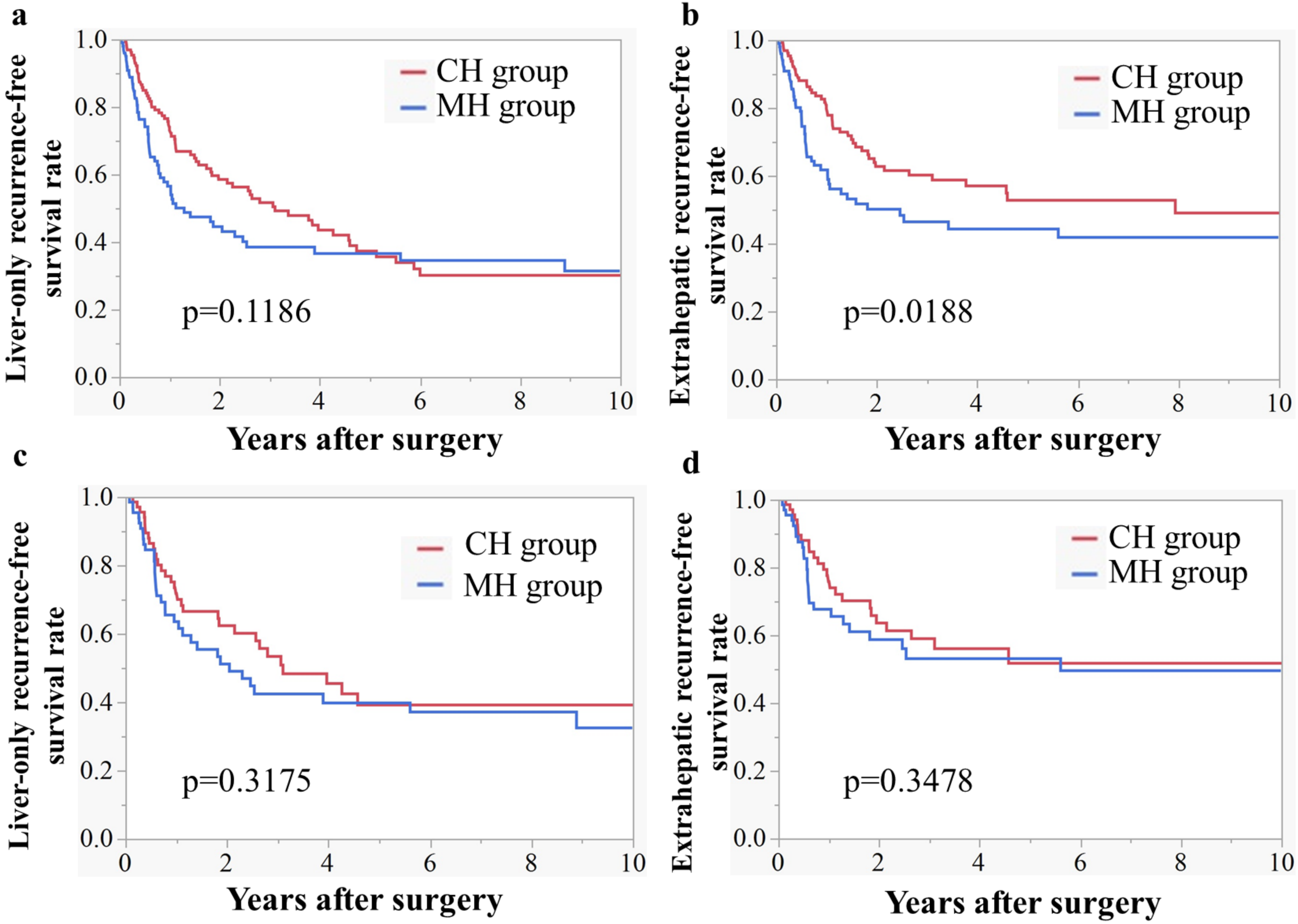

a
Overall survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
CH group
MH group
p=0.0262
Years after surgery
b
Recurrence-free survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
CH group
MH group
p=0.2013
Years after surgery
c
Overall survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
CH group
MH group
p=0.7731
Years after surgery
d
Recurrence-free survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
CH group
MH group
p=0.3900
Years after surgery

Figure. 2


a
Liver-only recurrence-free survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
CH group
MH group
p=0.1186
Years after surgery
b
Extrahepatic recurrence-free survival rate
CH group
MH group
p=0.0188
Years after surgery
c
Liver-only recurrence-free survival rate
CH group
MH group
p=0.3175
Years after surgery
d
Extrahepatic recurrence-free survival rate
CH group
MH group
p=0.3478
Years after surgery