Anatomic resection for hepatocellular carcinoma – Prognostic impact assessed from recurrence treatment

Journal:	*Annals of Surgical Oncology*
Manuscript ID	ASO-2021-02-0560.R2
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Minagawa, Masaaki; Juntendo University School of Medicine Graduate School of Medicine, Hepatobiliary-Pancreatic Surgery Mise, Yoshihiro; Juntendo University School of Medicine Graduate School of Medicine, Hepato-Biliary-Pancreatic Surgery Omichi, Kiyohiko; Cancer Institute Hospital, Japanese Foundation for Cancer Research, Hepato-Biliary-Pancreatic Surgery Ichida, Hirofumi; Juntendo University School of Medicine Graduate School of Medicine, Hepato-Biliary-Pancreatic Surgery Mizuno, Tomoya; Juntendo University School of Medicine Graduate School of Medicine, Hepato-Biliary-Pancreatic Surgery Yoshioka, Ryuji; Juntendo University School of Medicine Graduate School of Medicine, Hepato-Biliary-Pancreatic Surgery Imamura, Hiroshi; Juntendo University School of Medicine Graduate School of Medicine, Hepato-Biliary-Pancreatic Surgery Yanagisawa, Naotake; Juntendo University, Medical Technology Innovation Center Inoue, Yosuke; Cancer Institute Hospital, Japanese Foundation for Cancer Research, Hepatobiliary-Pancreatic Surgery Takahashi, Yu; Cancer Institute Hospital, Japanese Foundation for Cancer Research, Gastroenterological Surgery Saiura, Akio; Juntendo University School of Medicine Graduate School of Medicine, Hepatobiliary-Pancreatic Surgery; Cancer Institute Hospital, Japanese Foundation for Cancer Research, Hepatobiliary-Pancreatic Surgery

TITLE: Anatomic resection for hepatocellular carcinoma – Prognostic impact assessed from recurrence treatment

AUTHORS:

Masaaki Minagawa, MD[1]; Yoshihiro Mise, MD, PhD[1]; Kiyohiko Omichi, MD, PhD[2]; Hirohumi Ichida, MD, PhD[1]; Tomoya Mizuno, MD, PhD[1]; Ryuji Yoshioka, MD, PhD[1]; Hiroshi Imamura, MD, PhD[1]; Naotake Yanagisawa, PhD[3]; Yosuke Inoue, MD, PhD[2]; Yu Takahashi, MD, PhD[2]; Akio Saiura, MD, PhD[1, 2]*

INSTITUTION:

[1] Department of Hepatobiliary-Pancreatic Surgery, Juntendo University, Graduate School of Medicine, Tokyo, Japan.

[2] Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan.

[3] Medical Technology Innovation Center, Juntendo University, Tokyo, Japan.

***CORRESPONDENCE AND REPRINT REQUESTS TO:**

Akio Saiura, MD, PhD

Department of Hepatobiliary-Pancreatic Surgery, Juntendo University, Graduate School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo, 113-8421, Japan.

Tel, +81-3-3813-3111; Fax, +81-3-3812-7560;

E-mail, a-saiura@juntendo.ac.jp

RUNNING TITLE: Anatomic Resection for HCC

KEYWORDS: Hepatocellular carcinoma, Anatomic resection, Non-anatomic resection, Propensity score matching, segmentectomy, overall survival, recurrence-free survival

FUNDING:

There was no financial support for this study.

DISCLOSURE:

The authors declared no conflict of interest.

SYNOPSIS:

Anatomic resection (AR) for solitary hepatocellular carcinoma (HCC) decreases the recurrence after initial hepatectomy. However, curative-intent interventions for the recurrence compensate for the impaired recurrence-free survival (RFS) even in patients undergoing non-anatomic resection (NAR).

ABSTRACT

Background. The oncological advantage of anatomic resection (AR) for primary hepatocellular carcinoma (HCC) remains controversial. We aimed to evaluate the clinical advantages of AR for primary HCC by using propensity score matching (PSM) and assessing treatment strategies for recurrence after surgery.

Methods. Data of patients who underwent AR or non-anatomic resection (NAR) for solitary HCC (≤ 5cm) in two institutions between 2004 and 2017 were reviewed. Surgical outcomes were compared between the two groups in a propensity-score-adjusted cohort. The time-to-interventional failure (TIF), which was defined as the elapsed time from resection to unresectable/unablatable recurrence, was also evaluated.

Results. A total of 250 patients met the inclusion criteria, 77 (31%) with AR and 173 (69%) with NAR. In the propensity score-matched populations (AR, 67; NAR, 67), the 5-year recurrence-free survival (RFS) for AR was better than for NAR (62% vs 35%, $P = 0.005$). No differences, however, were found in the 5-year overall survival between the two groups (72% vs 78%, $P = 0.666$). The 5-year TIF rates of the NAR group (60%) was also similar to that in the AR group (66%, $P = 0.413$). Among the cohort of 67 patients, curative repeat resection or ablation therapy was performed more frequently in the NAR (42%) than in the AR group (10%, $P < 0.001$).

Conclusion. AR for solitary HCC decreases the recurrence after initial hepatectomy. However, aggressive curative-intent interventions for recurrence compensate for the impaired RFS, even in patients undergoing NAR.

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death and is estimated to be the fourth most common cause of death worldwide.[1] Liver resection is now accepted as an initial treatment for small HCC in patients with preserved hepatic function.[2] Percutaneous ablation is also a curative treatment for single and multinodular HCC (up to three lesions smaller than 3cm in diameter).[3]

Advances in surgical techniques and perioperative management have transformed the resection of HCC into a relatively safe operation with a low mortality rate.[4] Since HCC has a high propensity to invade intrahepatic vascular structures and spreads mainly via the closest portal veins,[5] anatomic resection (AR), including systemic removal of the tumor-bearing portal territories, was proposed in the 1980s as a theoretically curative procedure for HCC to eradicate potential micrometastases surrounding tumors.[6]

The prognostic superiority of AR to non-anatomic resection (NAR) has long been controversial. Recently, several authors published comparative studies using propensity score-matched (PSM) analysis,[7-13] however, the conclusions of these studies lacked consensus. Some studies found AR improved survival in patients with HCC,[7-11] while others did not show any prognostic benefit of AR compared with NAR.[12,13]

The major limitation of the previous PSM studies is that they did not consider treatment for tumor recurrence after initial hepatectomy in their analyses. The cumulative 5-year recurrence rate remains as high as 70% to 80%, even after radical surgery, and curative-intent repeat hepatectomy or radiofrequency ablation (RFA) significantly affects survival in patients having recurrence after surgery for HCC.[14]

In the present study, we aimed to evaluate the potential prognostic superiority of AR to NAR in patients with solitary HCC using PSM analysis. Recurrence pattern and recurrence treatment were also reviewed to assess the impact of initial AR or NAR on survival.

METHODS

Study population

We identified patients who underwent initial hepatectomy for HCC between January 2004 and December 2017 at two Japanese institutions (the Department of Hepato-biliary Pancreatic Surgery, Juntendo University Hospital [JUH], and the Department of Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research [CIH]). This study was approved by the ethics committees of the two institutions (JHS 18-060 for JUH and 2019-1028 for CIH).

The study population was composed of Asian patients who underwent AR of Couinaud's segment and NAR for solitary HCC (≤ 5cm). Exclusion criteria were as follows; history of previous treatment for HCC, other malignancy, and AR larger than Couinaud's segmentectomy (sectionectomy, right or left hepatectomy).

Surgical procedures

The detailed surgical procedures for HCC at JUH and CIH have been described previously.[15,16] Segmentectomy was defined as complete resection of one Couinaud's segment identified by dye staining. Segmental staining was conducted by indocyanine green (ICG) fluorescence and Sonazoid to indicate the segmental section. At CIH, the indication of whether to perform AR or NAR was based on an algorithm that included the presence/absence of ascites, the serum total bilirubin level, and the results of the ICG retention at 15 minutes (ICGR15) test (i.e., Makuuchi's criteria).[17] All patients at JUH underwent NAR which was defined as incomplete resection of the portal tributaries of the tumor-bearing segment, and included partial resection or enucleation of the liver.[15]

Patient follow-up

Perioperative/postoperative complications or death were recorded to assess the morbidity and mortality of the procedures. Major complication was defined as ≥ grade IIIa at Clavien-Dindo classification.[18] In-hospital and 90-day mortality were also assessed.[19] Patients were routinely followed by checking tumor markers, such as alpha-fetoprotein concentration (AFP) and prothrombin induced by vitamin K (PIVKA-II), and computed tomography or magnetic resonance imaging every three months. Recurrence was defined as the appearance of a new lesion having radiologic features compatible with HCC. When a recurrence was detected, the patient was treated further by repeat hepatectomy, ablation therapies (including RFA or transcatheter arterial chemoembolization [TACE]), or other treatment modalities (including systemic therapy). In both institutions, the resectability and ablatability of the recurrent lesions were initially determined based on the indication criteria for surgery in a multidisciplinary discussion by physicians, including hepatobiliary surgeons. Then, a treatment plan was discussed that considered the resectability/ablatability of tumors, recommended treatments from the multidisciplinary discussion, physical status of the patient, patient's preference of treatment, and other socioeconomic factors.

In the present study, the following survival outcomes were recorded. Recurrence-free survival (RFS) was defined as the interval between the date of operation and the date of diagnosis of the first recurrence or death. Overall survival (OS) was defined as the interval between the date of operation and the date of death due to any cause. Local recurrence was defined as any recurrence observed in the residual part of the tumor-bearing third-order portal branches or recurrence adjacent to the cut surface of the liver.

The time-to-interventional failure (TIF), which was defined as the elapsed time from resection to unresectable/unablatable recurrence, was also evaluated to assess the prognostic impact of interventional treatment for recurrent HCC.

Propensity score analysis

To avoid confounding differences due to baseline variation between AR and NAR groups, we established a propensity score-matched subset of the original data. The propensity scores were generated using a logistic regression model, and the following perioperative characteristics were included in the model: sex; age; underlying liver disease (hepatitis B surface antigen [HBsAg] and anti-hepatitis C virus antibody [HCV Ab] positivity); preoperative serum total bilirubin concentration; aspartate aminotransferase (AST); alanine aminotransferase (ALT) concentration; albumin concentration; platelet count; ICGR15; serum AFP; serum PIVKA-II concentration; image of maximum tumor size; and image of macroscopic vascular invasion in the portal and/or hepatic veins. After calculation of propensity scores, a matched subset of patients was extracted by one-to-one greedy nearest matching algorithm without replacement, with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score.

Statistical analysis

To summarize patient characteristics, medians and 25th-75th percentiles were used for continuous variables, while frequencies and proportions were calculated for categorical variables. Clinical characteristics of the two groups were compared by either the χ^2 test or Fisher's exact test for categorical variables, and the Wilcoxon rank-sum test for continuous variables. The RFS, OS and TIF rates after hepatectomy were calculated by the Kaplan–Meier product-limit method and compared by the log-rank test. PSM and statistical analysis were performed using SAS (Version 9.4, SAS institute, Cary, NC). Statistical analyses other than PSM were performed with IBM SPSS software (version 26.0 SPSS Inc., IL, USA).

RESULTS

During the study interval, a total of 1217 patients underwent initial hepatic resection for HCC at the two institutions. Patients with multiple tumors (n = 397), with a tumor larger than 5 cm (n = 296), with another malignancy, and with unknown follow-up (n = 211) were excluded, which left 313 patients. Of these, 63 patients were excluded who underwent sectionectomy, right or left hepatectomy. This left 77 patients who underwent AR of Couinaud's segment and 173 patients who underwent NAR enrolled in the study. After PSM, 134 patients were divided into the AR group (n = 67) and the NAR group (n= 67). Figure 1 outlines patient selection. Table 1 summarizes the characteristics of both groups before and after PSM.

Before PSM, platelet count, albumin level, prothrombin time, and PIVKA-II level were lower in the NAR group than in the AR group. All baseline characteristics except for platelet count were matched after PSM.

Surgical outcomes

Table 2 summarizes the surgical outcomes of the two groups before and after PSM. The amount of blood loss was lower in the NAR group compared with the AR group. No differences were found in pathological findings between the two groups after PSM.

Long-term outcomes

The median follow-up period was 53 (i.q.r. 27-79) months in the AR group and 75 (i.q.r. 45-110) months in the NAR group. Figure 2 shows survival curves of the two groups before PSM. The 5-year RFS in the AR group was better than that in the NAR group (63% vs 42%, P = 0.023). However, no difference was found in the 5-year OS between the two groups (74% vs 79%, P = 0.61).

After PSM, the 5-year RFS in the AR group was better than that in the NAR group (62% vs 35%, P = 0.005, Figure 3a). However, no difference was found in the 5-year OS between the two groups (72% vs 78%, P = 0.666, Figure 3b).

Recurrence after initial hepatectomy

Table 3 summarizes the recurrence mode and treatment for recurrence after initial hepatectomy. Among PSM patients, intrahepatic recurrence after initial hepatectomy was observed in 17 (25.3%) patients in the AR group and 41 (61.2%) patients in the NAR group.

The incidence of recurrence at the same segment after initial hepatectomy in the NAR was 15% (6/41). The rates of the recurrence within the adjacent portal veinous territories in the NAR and AR groups were 41% (17/41), and 29% (5/17, *P* = 0.389], respectively.

Although the incidence of curative-intent interventions for recurrence was similar between the two groups, among the cohort of 67 patients, repeat hepatectomy or RFA for recurrence was performed more frequently in the NAR group (n = 28 [42%]) than in the AR group (n = 7 [10%], $P < 0.001$). There was an institutional difference in the prevalence of curative-intent interventions for recurrence (43% [9/21] in CIH, and 70% [26/37] in JUH, respectively, *P* = 0.043).

The TIF of the two groups are shown in Figure 3c, which shows the TIF of the curative intent treatment, including repeat hepatectomy or RFA, were not significantly different from that of TACE (*P* = 0.413).

DISCUSSION

The present study investigated the prognostic impact of anatomic resection of Couinaud's segments by comparing surgical outcomes between patients who underwent AR and NAR for a solitary HCC ≤ 5cm. We found AR decreased recurrence after initial hepatectomy, however, OS was not different between the AR and NAR groups. Assessment of recurrence mode and treatment for the recurrence revealed that aggressive curative-intent interventions for the intrahepatic recurrence was performed more frequently in the NAR than in the AR group, which led to the comparable TIF and OS between the two groups.

The current PSM analysis demonstrated that curability of AR as an initial treatment outweighs NAR in patients with solitary HCC by showing better RFS in the AR group than in the NAR group. Previous PSM studies analyzing the prognostic impact of AR for HCC failed to reach robust conclusions.[7-9] The major cause of the incoherence is that most of the studies included hepatectomies larger than Couinaud's segmentectomy, which may have introduced bias in selecting surgical procedures influenced by tumor characteristics, such as size, location, or vascular infiltration. In addition, including large hepatectomies, such as sectionectomy or hemihepatectomy, bears a risk to overestimate the prognostic impact of AR as large hepatectomy removes a greater amount of 'at-risk' liver parenchyma in which future recurrences may occur. To minimize these biases, two PSM studies previously limited the procedure to Couinaud's segmentectomy when comparing AR with NAR.[10,11] These two studies and our present study agree that RFS is better in the AR group compared with the NAR group, which reinforces the theory that AR improves local control of the disease by eradicating potential micrometastases via the portal veins.[10,11] In addition, tumor exposure at the surgical margin was found in 6% of the NAR group. On the other hand, no patients in the AR group had positive surgical margin. This result indicates that NAR bears a risk to expose the tumor during resection. However, in the current analysis, the incidence of early recurrence that the tumor exposure might have caused was not different between the AR and NAR groups. In our clinical practice, surgical procedures need to be selected considering the radicality and the hepatic functional reserve as well because the parenchymal-sparing NAR can be the only choice for surgical treatment in patients with impaired liver function.

While there was a difference in RFS, our study found no difference in the 5-year OS between the two groups. This paradoxical result may be due to specific characteristics of HCC treatment. Similar to colorectal liver metastases, survival outcomes in patients with HCC can be improved by optimal repeated interventions for recurrence.[20-24] A major strength of the current study was the detailed analysis of recurrence treatment, which revealed that aggressive curative-intent interventions for recurrence compensate for the impaired RFS even in patients undergoing NAR. Shindoh et al. found that treatment choice for recurrence significantly affects the survival outcomes in patients with resectable/ablatable HCC recurrence.[14] In their report which first introduced the concept of TIF, the survival of patients undergoing curative-intent treatment (repeat resection or RFA) for recurrence was better compared with those who had non-curative-intent treatment (TACE, radiotherapy, chemotherapy, etc.).

The current study found that optimal treatment for recurrence can salvage the impaired RFS of the NAR group. Conversely however, repeated interventions are needed to achieve comparable OS in patients who underwent NAR as an initial treatment. In our analysis, as many as 42% of patients in the NAR group underwent interventional treatment for recurrence, compared with 10% in the AR group. Although the institutional difference in treatment approach to the recurrence cannot be ignored, the parenchymal-sparing nature of NAR may have improved salvageability for the recurrence by saving room for future aggressive treatment even in patients with well-preserved liver function.[25] In addition, necessity to expose the Glissonean sheath and major hepatic veins during AR may have made surgeons reluctant to perform repeat resection because the exposure of the major vessels is reportedly a risk to increase the complexity of repeat hepatectomy.[26]

The necessity of frequent interventions raises two concerns in choosing NAR as an initial surgical procedure. First, repeated surgery or RFA can compromise physical and mental quality of life (QOL) during the entire course of treatment. Previous studies have demonstrated temporary deterioration of QOL following hepatectomy, as well as RFA in patients having an initial treatment for HCC.[27-30] Although no evidence is available regarding QOL change after repeated surgery or RFA, the recurrence treatment must affect the patient's mental and emotional well-being due to the anxiety associated with the tumor still being present. Further investigations are needed to confirm the clinical benefits of AR from a viewpoint of QOL in HCC patients who need to undergo repetitive treatments.

Second, institutional differences in aggressiveness in performing repeated interventions may directly affect the survival outcomes in patients undergoing NAR. Although several studies have demonstrated its feasibility, repeated hepatectomy is reportedly technically demanding in terms of the increased operation time or the higher incidence of bile leakage, compared with initial hepatectomy.[26,31-36] Additionally, repeated RFA after hepatic resection raises the possibility of several complications. Bowel damage is more likely after initial hepatic resection compared with the first initial treatment of HCC due to fibrotic adhesions between the liver and bowel.[37] Abscess formation is another potential complication in patients who undergo repeat RFA after hepatic resection. RFA makes connections between the biliary duct and the ablations zones through a thermal injury to the bile ducts, which causes enteric bacterial contamination around the ablation zones when combined with hepatic resection.[38,39] Conflicting results of OS in previous comparative studies may well be explained by the institutional differences in treatment policies for recurrence.

There are a couple of limitations in the present study, mainly associated with the retrospective data derived from two different institutions. Selection bias could not be completely eliminated even after PSM analysis as the treatment policies for primary and recurrent HCC differed between the two institutions. Particularly, as discussed above, differences in aggressiveness in performing repeated interventions for the recurrence must have strongly affected OS outcomes.

A previous comparative PSM study of 54 institutions demonstrated a better OS in the AR group than in the NAR group, which may be attributable to the comparable rates of repeated interventions for recurrence between the two groups (AR: 31% [35/114], NAR: 28% [33/114], $P = 0.159$).[11] In addition, platelet count was lower in patients in the NAR than in those in the AR group even after PSM, which indicates baseline liver function may be worse in patients of the NAR group. On the other hand, the institutional difference in the treatment policy for recurrence in the current study revealed that impaired RFS following NAR can be compensated by aggressive curative-intent interventions for recurrence. Another limitation is that de novo HCC derived from the injured underlying liver was discriminated from recurrence of residual HCC, which confounds the interpretation of the survival outcomes.[40] However, the superiority of AR to NAR as an initial procedure to reduce the recurrence, indicated by its improvement to RFS, is a consistent result across PMS studies.[10,11]

In conclusion, AR for solitary HCC decreases tumor recurrence after initial hepatectomy. However, aggressive curative-intent interventions for tumor recurrence can compensate for the impaired RFS, even in patients undergoing NAR.

ACKNOWLEDGEMENT:

Not applicable.

REFERENCES

1. Fitzmaurice C, Allen C, Barber RM, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA oncology.* Apr 1 2017;3(4):524-548.

2. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology (Baltimore, Md.).* Mar 2011;53(3):1020-1022.

3. Makuuchi M, Kokudo N, Arii S, et al. Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan. *Hepatol Res.* Jan 2008;38(1):37-51.

4. Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma: toward zero hospital deaths. *Annals of surgery.* Mar 1999;229(3):322-330.

5. Nakashima T, Kojiro M. Pathologic characteristics of hepatocellular carcinoma. *Seminars in liver disease.* Aug 1986;6(3):259-266.

6. Makuuchi M, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. *Surg Gynecol Obstet.* Oct 1985;161(4):346-350.

7. Ishii M, Mizuguchi T, Kawamoto M, et al. Propensity score analysis demonstrated the prognostic advantage of anatomical liver resection in hepatocellular carcinoma. *World journal of gastroenterology.* Mar 28 2014;20(12):3335-3342.

8. Cucchetti A, Qiao GL, Cescon M, et al. Anatomic versus nonanatomic resection in cirrhotic patients with early hepatocellular carcinoma. *Surgery.* Mar 2014;155(3):512-521.

9. Kaibori M, Kon M, Kitawaki T, et al. Comparison of anatomic and non-anatomic hepatic resection for hepatocellular carcinoma. *Journal of hepato-biliary-pancreatic sciences.* Nov 2017;24(11):616-626.

10. Shindoh J, Makuuchi M, Matsuyama Y, et al. Complete removal of the tumor-bearing portal territory decreases local tumor recurrence and improves disease-specific survival of patients with hepatocellular carcinoma. *J Hepatol.* Mar 2016;64(3):594-600.

11. Kaibori M, Yoshii K, Hasegawa K, et al. Impact of systematic segmentectomy for small hepatocellular carcinoma. *Journal of hepato-biliary-pancreatic sciences.* Jun 2020;27(6):331-341.

12. Okamura Y, Ito T, Sugiura T, Mori K, Uesaka K. Anatomic versus nonanatomic hepatectomy for a solitary hepatocellular carcinoma : a case-controlled study with propensity score matching. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract.* Nov 2014;18(11):1994-2002.

13. Marubashi S, Gotoh K, Akita H, et al. Anatomical versus non-anatomical resection for hepatocellular carcinoma. *The British journal of surgery.* Jun 2015;102(7):776-784.

14. Shindoh J, Kawamura Y, Kobayashi Y, et al. Time-to-Interventional Failure as a New Surrogate Measure for Survival Outcomes after Resection of Hepatocellular

Carcinoma. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract.* Jun 12 2019.

15. Oguro S, Yoshimoto J, Imamura H, Ishizaki Y, Kawasaki S. Clinical significance of macroscopic no-margin hepatectomy for hepatocellular carcinoma. *HPB : the official journal of the International Hepato Pancreato Biliary Association.* Sep 2018;20(9):872-880.

16. Kishi Y, Saiura A, Yamamoto J, et al. Significance of anatomic resection for early and advanced hepatocellular carcinoma. *Langenbeck's archives of surgery.* Jan 2012;397(1):85-92.

17. Makuuchi M, Kosuge T, Takayama T, et al. Surgery for small liver cancers. *Seminars in surgical oncology.* Jul-Aug 1993;9(4):298-304.

18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of surgery.* Aug 2004;240(2):205-213.

19. Mise Y, Vauthey JN, Zimmitti G, et al. Ninety-day Postoperative Mortality Is a Legitimate Measure of Hepatopancreatobiliary Surgical Quality. *Annals of surgery.* Dec 2015;262(6):1071-1078.

20. Xing H, Sun LY, Yan WT, et al. Repeat hepatectomy for patients with early and late recurrence of hepatocellular carcinoma: A multicenter propensity score matching analysis. *Surgery.* Dec 23 2019.

21. Erridge S, Pucher PH, Markar SR, et al. Meta-analysis of determinants of survival following treatment of recurrent hepatocellular carcinoma. *The British journal of surgery.* Oct 2017;104(11):1433-1442.

22. Zhou Y, Sui C, Li B, et al. Repeat hepatectomy for recurrent hepatocellular carcinoma: a local experience and a systematic review. *World J Surg Oncol.* Jul 1 2010;8:55.

23. Chan DL, Morris DL, Chua TC. Clinical efficacy and predictors of outcomes of repeat hepatectomy for recurrent hepatocellular carcinoma - a systematic review. *Surg Oncol.* Jun 2013;22(2):e23-30.

24. Feng Y, Wu H, Huang DQ, et al. Radiofrequency ablation versus repeat resection for recurrent hepatocellular carcinoma (≤ 5 cm) after initial curative resection. *Eur Radiol.* Nov 2020;30(11):6357-6368.

25. Mise Y, Aloia TA, Brudvik KW, Schwarz L, Vauthey JN, Conrad C. Parenchymal-sparing Hepatectomy in Colorectal Liver Metastasis Improves Salvageability and Survival. *Annals of surgery.* Jan 2016;263(1):146-152.

26. Mise Y, Hasegawa K, Shindoh J, et al. The Feasibility of Third or More Repeat Hepatectomy for Recurrent Hepatocellular Carcinoma. *Annals of surgery.* Aug 2015;262(2):347-357.

27. Toro A, Pulvirenti E, Palermo F, Di Carlo I. Health-related quality of life in patients with hepatocellular carcinoma after hepatic resection, transcatheter arterial chemoembolization, radiofrequency ablation or no treatment. *Surg Oncol.* Mar 2012;21(1):e23-30.

28. Huang G, Chen X, Lau WY, et al. Quality of life after surgical resection compared with radiofrequency ablation for small hepatocellular carcinomas. *The British journal of surgery.* Jul 2014;101(8):1006-1015.

29. Chie WC, Yu F, Li M, et al. Quality of life changes in patients undergoing treatment for hepatocellular carcinoma. *Qual Life Res.* Oct 2015;24(10):2499-2506.

30. Mise Y, Satou S, Ishizawa T, et al. Impact of surgery on quality of life in patients with hepatocellular carcinoma. *World J Surg.* Apr 2014;38(4):958-967.

31. Yamashita Y, Hamatsu T, Rikimaru T, et al. Bile leakage after hepatic resection. *Annals of surgery.* Jan 2001;233(1):45-50.

32. Nagano Y, Togo S, Tanaka K, et al. Risk factors and management of bile leakage after hepatic resection. *World J Surg.* Jun 2003;27(6):695-698.

33. Capussotti L, Ferrero A, Viganò L, Sgotto E, Muratore A, Polastri R. Bile leakage and liver resection: Where is the risk? *Arch Surg.* Jul 2006;141(7):690-694; discussion 695.

34. Morimura R, Saiura A, Koga R, et al. Impact of previous hepatectomy on short-term outcomes of repeat hepatectomy for liver tumors with a special concern of operative time. *Hepatogastroenterology.* May 2012;59(115):809-813.

35. Sadamori H, Yagi T, Matsuda H, Shinoura S, Umeda Y, Fujiwara T. Intractable bile leakage after hepatectomy for hepatocellular carcinoma in 359 recent cases. *Dig Surg.* 2012;29(2):149-156.

36. Sadamori H, Yagi T, Shinoura S, et al. Risk factors for major morbidity after liver resection for hepatocellular carcinoma. *The British journal of surgery.* Jan 2013;100(1):122-129.

37. Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. *Radiology.* Feb 2003;226(2):441-451.

38. Choi D, Lim HK, Rhim H, et al. Percutaneous radiofrequency ablation for recurrent hepatocellular carcinoma after hepatectomy: long-term results and prognostic factors. *Ann Surg Oncol.* Aug 2007;14(8):2319-2329.

39. Choi D, Lim HK, Kim MJ, et al. Liver abscess after percutaneous radiofrequency ablation for hepatocellular carcinomas: frequency and risk factors. *AJR Am J Roentgenol.* Jun 2005;184(6):1860-1867.

40. Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol.* Feb 2003;38(2):200-207.

FIGURE LEGENDS

Figure 1. Patient selection flow diagram.

Figure 2. Long-term survival outcomes after anatomic resection and non-anatomic resection before propensity score matching. (a) Recurrence-free survival. (b) Overall survival. (c) Time-to-interventional failure (TIF).

Figure 3. Long-term survival outcomes after anatomic resection and non-anatomic resection after propensity score matching. (a) Recurrence-free survival. (b) Overall survival. (c) Time-to-interventional failure (TIF).

Table 1: Baseline characteristics of AR and NAR groups before and after PSM.

	Before PSM			After PSM		
	AR (n = 77)	NAR (n = 173)	*P*-value	AR (n = 67)	NAR (n = 67)	*P*-value
Background characteristics						
Sex, male, n (%)	59(77%)	127(73%)	0.591	50(75%)	56(84%)	0.202
Age (years)	69(58-73)	69(63-74)	0.132	67(62-73)	66(60-73)	0.248
HBsAg, +, n (%)	9(12%)	27(16%)	0.415	8(12%)	12(18%)	0.332
HCV Ab, +, n (%)	33(43%)	78(45%)	0.743	28(42%)	25(37%)	0.596
Total bilirubin (mg/dl)	0.8(0.6-1.0)	0.8(0.6-1.0)	0.137	0.8(0.6-1.0)	0.8(0.7-1.0)	0.389
Platelet count (×10,000/ml)	**16.0(12.0-18.0)**	**13.6(9.7-17.4)**	**0.01**	**16.0(11.7-17.9)**	**13.4(10.2-15.6)**	**0.018**
AST (U/l)	36.0(24.5-48.5)	36.0(28.0-52.0)	0.366	35.0(24.0-45.0)	32.0(25.0-49.0)	0.788
ALT (U/l)	33.0(23.5-58.0)	32.0(20.5-50.0)	0.588	30.0(23.0-52.0)	35.0(22.0-60.0)	0.331
Albumin (g/dl)	**4.2(3.9-4.5)**	**4.0(3.7-4.3)**	**0.001**	4.2(3.9-4.4)	4.1(3.8-4.4)	0.572
PT(%)	**90.0(85.0-98.0)**	**88.0(81.0-95.5)**	**0.03**	90.0(85.0-98.0)	88.0(81.0-95.5)	0.323
Child–Pugh class (A/B)	76(99%)/1(1%)	168(97%)/5(3%)	0.401	66(99%)/1(1%)	67(100%)/0(0%)	0.5
ICGR15 (%)	13.3(10.8-18.0)	15.5(10.4-21.2)	0.084	13.4(10.9-18.5)	13.4(9.4-20.2)	0.982
AFP (ng/ml)	11.6(4.9-210.5)	9.0(5.0-34.5)	0.171	11.6(5.0-223.0)	9.7(5.0-54.0)	0.555
PIVKA-II (mAU/ml)	**46.0(24.0-137.5)**	**27.0(17.0-128.0)**	**0.04**	42.0(23.0-142.0)	28.0(18.0-147.0)	0.306
Image vascular invasion in portal vein and/or hepatic vein, +, n (%)	6(8%)	9(5%)	0.298	6(9%)	6(9%)	1
Maximum tumor size (cm)	2.7(2.0-3.4)	2.7(2.0-3.6)	0.588	2.7(2.0-3.3)	2.9(2.1-3.6)	0.246

Bold value indicates statistical significance.
Values in table are number of patients (percentage).
Continuous data were expressed as median (25th-75th percentiles).
AR indicates anatomic resection; AFP, alpha-fetoprotein; ALT, alanine aminotransferase;
HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody;
ICGR15, indocyanine green retention rate at 15 min; NAR, non-anatomic resection;
PIVKA-II, protein induced by vitamin K absence or antagonist-II; PSM, propensity score matching.

Table 2: Surgical and pathological characteristics of AR and NAR groups before and after PSM

	Before PSM			After PSM		
	AR (n = 77)	NAR (n = 173)	*P*-value	AR (n = 67)	NAR (n = 67)	*P*-value
Surgical factors						
Operating time (min)	257.0(218-327)	257.0(208-320)	0.7	256.0(207-330)	280.0(230-334)	0.5
Operative blood loss (mL)	**360(260-630)**	**170(80-297)**	**<0.001**	**360(260-650)**	**195(120-350)**	**<0.001**
Laparoscopic hepatectomy, +, n (%)	1(1%)	8(5%)	0.2	1(1%)	3(4%)	0.6
Major complications, +, n (%)	7(9%)	6(4%)	0.1	4(6%)	2(3%)	0.3
90-day mortality, n (%)	NA	NA		NA	NA	NA
Pathological factors						
Histological tumor differentiation well+mod/por, n (%)	74(96%)/3(4%)	160(93%)/13(7%)	0.2	65(97%)/2(3%)	61(91%)/6(9%)	0.1
Surgical margin, +, n (%)	**0(0%)**	**10(6%)**	**0**	0(0%)	4(6%)	0.1
vp, +, n (%)	**20(26%)**	**25(15%)**	**0**	17(25%)	10(15%)	0.1
vv, +, n (%)	10(13%)	18(11%)	0.6	9(13%)	8(12%)	0.8
bv, +, n (%)	1(1%)	2(1%)	0.7	1(1%)	2(3%)	0.5
micro vascular invasion, +, n (%)	**26(34%)**	**37(21%)**	**0**	22(33%)	15(22%)	0.2
Associated liver disease (normal liver/chronic hepatitis or liver fibrosis/cirrhosis)	9(12%)/31(40%)/37(48%)	18(10%)/59(34%)/96(56%)	0.6	8(12%)/26(39%)/33(48%)	6(9%)/27(40%)/34(51%)	0.9
The UICC/AJCC 8th Staging System (Ia/Ib/II)	16(21%)/36(47%)/25(32%)	41(24%)/94(54%)/38(22%)	0.2	14(21%)/31(46%)/22(33%)	11(16%)/40(60%)/16(24%)	0.3

Bold value indicates statistical significance.
Values in table are number of patients (percentage).
Continuous data were expressed as median (interquartile range).
Complication classified as Clavien-Dindo class IIIa or higher.
AR indicates anatomic resection; NA, not available; NAR, non-anatomic resection; PSM, propensity score matching.

Table 3: Clinical characteristics of patients with recurrent tumors in the AR and NAR groups

	After PSM		
	AR (n = 67)	NAR (n = 67)	*P*-value
Variables			
Number of patients with HCC recurrence, n (%)	**20(30)**	**42(63)**	**<0.001**
Intrahepatic recurrence (±)	**17/50**	**41/26**	**<0.001**
Number of intrahepatic recurrences, n			
1	6	20	**<0.001**
2	1	9	
3	0	5	
≥4	10	7	
Treatment for intrahepatic recurrence			
Repeat hepatectomy or percutaneous ablation, n (%)	**7(10)**	**28(42)**	**<0.001**
TACE or others, n (%)	10(15)	13(19)	0.492
Time to recurrence			
Recurrence within 1 yr after hepatectomy, n (%)	6(9)	10(15)	0.287
Number of deceased patients, n (%)	14(21)	19(28)	0.316
Cause of death			
HCC-related	10	16	0.351
Liver-related	2	0	
Others	2	3	

Values in table are number of patients (percentage).
AR indicates anatomic resection; NAR, non-anatomic resection;
PSM, propensity score matching;
TACE, transcatheter arterial chemoembolization.

Figure 1

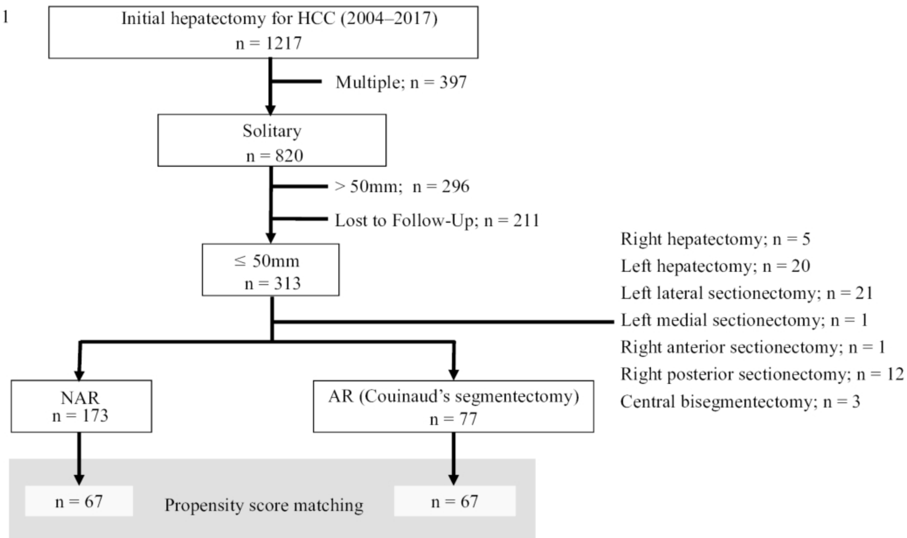
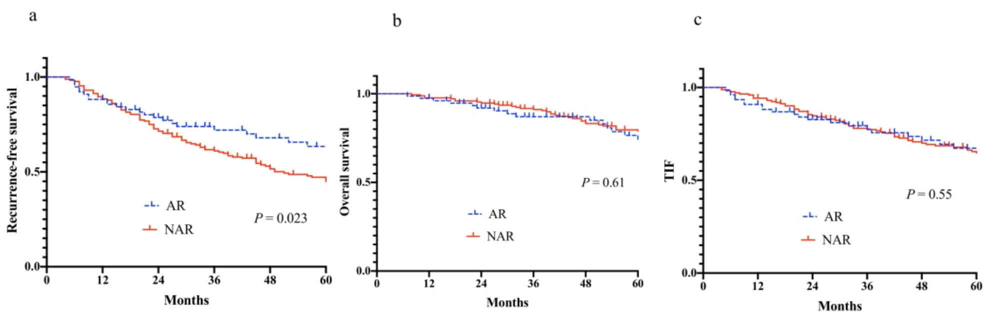


Figure 1

338x190mm (150 x 150 DPI)

Figure 2



at risk	0	12	24	36	48	60
AR	77	66	51	36	31	26
NAR	173	150	116	94	69	59

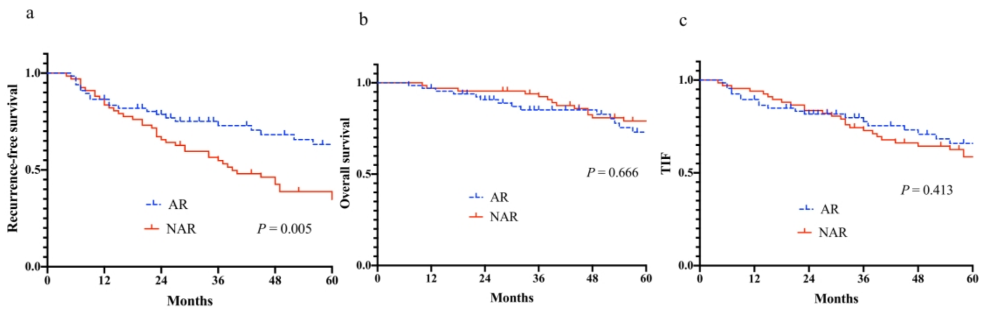
at risk	0	12	24	36	48	60
AR	77	72	61	45	42	34
NAR	173	168	159	145	119	105

at risk	0	12	24	36	48	60
AR	77	68	54	40	34	29
NAR	17	161	141	121	96	83

Figure 2

940x529mm (72 x 72 DPI)

Figure 3



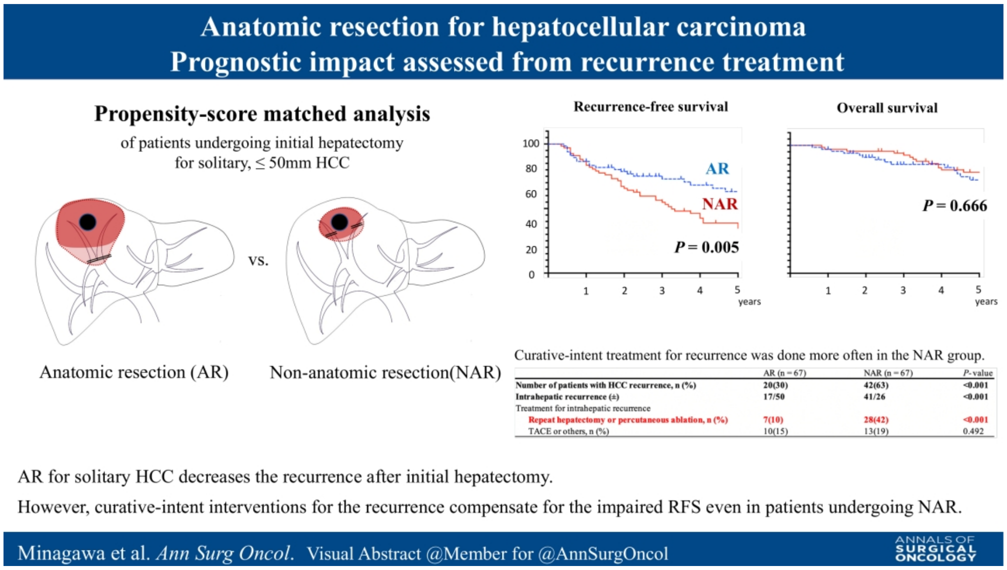
at risk	0	12	24	36	48	60
AR	67	56	44	32	28	24
NAR	67	55	43	33	23	17

at risk	0	12	24	36	48	60
AR	67	63	52	39	35	29
NAR	67	64	64	59	48	43

at risk	0	12	24	36	48	60
AR	67	55	46	35	30	25
NAR	67	57	52	41	31	26

Figure 3

940x529mm (72 x 72 DPI)



	AR (n = 67)	NAR (n = 67)	P-value
Number of patients with HCC recurrence, n (%)	**20(30)**	**42(63)**	**<0.001**
Intrahepatic recurrence (±)	**17/50**	**41/26**	**<0.001**
Treatment for intrahepatic recurrence			
Repeat hepatectomy or percutaneous ablation, n (%)	**7(10)**	**28(42)**	**<0.001**
TACE or others, n (%)	10(15)	13(19)	0.492

Visual Abstract

940x529mm (72 x 72 DPI)