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

<table>
<thead>
<tr>
<th>Journal:</th>
<th>Annals of Surgical Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>ASO-2021-02-0560.R2</td>
</tr>
<tr>
<td>Manuscript Type:</td>
<td>Original Article</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>n/a</td>
</tr>
</tbody>
</table>
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TITLE: Anatomic resection for hepatocellular carcinoma – Prognostic impact assessed from recurrence treatment

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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. Liver resection is now accepted as an initial treatment for small HCC in patients with preserved hepatic function. Percutaneous ablation is also a curative treatment for single and multinodular HCC (up to three lesions smaller than 3cm in diameter).

Advances in surgical techniques and perioperative management have transformed the resection of HCC into a relatively safe operation with a low mortality rate. Since HCC has a high propensity to invade intrahepatic vascular structures and spreads mainly via the closest portal veins, 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.

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, however, the conclusions of these studies lacked consensus. Some studies found AR improved survival in patients with HCC, while others did not show any prognostic benefit of AR compared with NAR.

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.
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. 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). 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.

**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. In-hospital and 90-day mortality were also assessed. 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 $\chi^2$ 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 \( \leq 5 \text{cm} \). 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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], \( P = 0.159 \)). 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. 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.

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.
1 REFERENCES


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.

<table>
<thead>
<tr>
<th>Background characteristics</th>
<th>Before PSM</th>
<th>After PSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR (n = 77)</td>
<td>NAR (n = 173)</td>
<td>P-value</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>59(77%)</td>
<td>127(73%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69(58-73)</td>
<td>69(63-74)</td>
</tr>
<tr>
<td>HBsAg, +, n (%)</td>
<td>9(12%)</td>
<td>27(16%)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.8(0.6-1.0)</td>
<td>0.8(0.6-1.0)</td>
</tr>
<tr>
<td>Platelet count (×10,000/ml)</td>
<td>16.0(12.0-18.0)</td>
<td>13.6(9.7-17.4)</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>36.0(24.5-48.5)</td>
<td>36.0(28.0-52.0)</td>
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<tr>
<td>ALT (U/l)</td>
<td>33.0(23.5-58.0)</td>
<td>32.0(20.5-50.0)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.2(3.9-4.5)</td>
<td>4.0(3.7-4.3)</td>
</tr>
<tr>
<td>PT(%)</td>
<td>90.0(85.0-98.0)</td>
<td>88.0(81.0-95.5)</td>
</tr>
<tr>
<td>Child–Pugh class (A/B)</td>
<td>76(99%)/1(1%)</td>
<td>168(97%)/5(3%)</td>
</tr>
<tr>
<td>Image vascular invasion in portal vein</td>
<td>6(8%)</td>
<td>9(5%)</td>
</tr>
<tr>
<td>Maximum tumor size (cm)</td>
<td>2.7(2.0-3.4)</td>
<td>2.7(2.0-3.6)</td>
</tr>
</tbody>
</table>

Bold value indicates statistical significance.

Continuous data were expressed as median (25th-75th percentiles).

Values in table are number of patients (percentage).

AR indicates anatomic resection; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HCV Ab, 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>
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<tr>
<th>Surgical factors</th>
<th>Before PSM</th>
<th>After PSM</th>
<th>$P$-value</th>
<th>Before PSM</th>
<th>After PSM</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating time (min)</td>
<td>257.0(218-327)</td>
<td>257.0(208-320)</td>
<td>0.7</td>
<td>256.0(207-330)</td>
<td>280.0(230-334)</td>
<td>0.5</td>
</tr>
<tr>
<td>Operative blood loss (mL)</td>
<td>360(260-630)</td>
<td>170(80-297)</td>
<td>$&lt;0.001$</td>
<td>360(260-650)</td>
<td>195(120-350)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Laparoscopic hepatectomy, +, n (%)</td>
<td>1(1%)</td>
<td>8(5%)</td>
<td>0.2</td>
<td>1(1%)</td>
<td>3(4%)</td>
<td>0.6</td>
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<tr>
<td>Major complications, +, n (%)</td>
<td>7(9%)</td>
<td>6(4%)</td>
<td>0.1</td>
<td>4(6%)</td>
<td>2(3%)</td>
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<tr>
<td>90-day mortality, n (%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</table>

<table>
<thead>
<tr>
<th>Pathological factors</th>
<th>Before PSM</th>
<th>After PSM</th>
<th>$P$-value</th>
<th>Before PSM</th>
<th>After PSM</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological tumor differentiation</td>
<td>74(96%)/3(4%)</td>
<td>160(93%)/13(7%)</td>
<td>0.2</td>
<td>65(97%)/2(3%)</td>
<td>61(91%)/6(9%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Surgical margin, +, n (%)</td>
<td>0(0%)</td>
<td>10(6%)</td>
<td>0</td>
<td>0(0%)</td>
<td>4(6%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Vascular invasion, +, n (%)</td>
<td>10(13%)</td>
<td>18(11%)</td>
<td>0.6</td>
<td>9(13%)</td>
<td>8(12%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Micro vascular invasion, +, n (%)</td>
<td>20(26%)</td>
<td>25(15%)</td>
<td>0.7</td>
<td>1(1%)</td>
<td>2(3%)</td>
<td>0.5</td>
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<tr>
<td>Associated liver disease</td>
<td>9(12%)/31(40%)/37(48%)</td>
<td>18(10%)/59(34%)/96(56%)</td>
<td>0.6</td>
<td>8(12%)/26(39%)/33(48%)</td>
<td>6(9%)/27(40%)/34(51%)</td>
<td>0.9</td>
</tr>
<tr>
<td>The UICC/AJCC 8th Staging System</td>
<td>16(21%)/36(47%)/25(32%)</td>
<td>41(24%)/94(54%)/38(22%)</td>
<td>0.2</td>
<td>14(21%)/31(46%)/22(33%)</td>
<td>11(16%)/40(60%)/16(24%)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

| 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

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

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

Initial hepatectomy for HCC (2004–2017)
\( n = 1217 \)

- Multiple: \( n = 397 \)
- Solitary: \( n = 820 \)
  - > 50mm: \( n = 296 \)
  - Lost to Follow-Up: \( n = 211 \)
  - \( \leq 50\text{mm} \):
    - NAR \( n = 173 \)
    - AR (Coutinaud’s segmentectomy) \( n = 77 \)

- Right hepatectomy: \( n = 5 \)
- Left hepatectomy: \( n = 20 \)
- Left lateral sectionectomy: \( n = 21 \)
- Left medial sectionectomy: \( n = 1 \)
- Right anterior sectionectomy: \( n = 1 \)
- Right posterior sectionectomy: \( n = 12 \)
- Central bisegmentectomy: \( n = 3 \)

338x190mm (150 x 150 DPI)
Figure 2

940x529mm (72 x 72 DPI)
Figure 3

940x529mm (72 x 72 DPI)
Anatomic resection for hepatocellular carcinoma
Prognostic impact assessed from recurrence treatment

Propensity-score matched analysis
of patients undergoing initial hepatectomy
for solitary, ≤ 50mm HCC

Anatomic resection (AR)   Non-anatomic resection (NAR)

Recurrence-free survival
Overall survival

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

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Visual Abstract

940x529mm (72 x 72 DPI)