ABSTRACT

Objective: The aim of the present study was to evaluate the value of anatomical resection for HCC with micro-portal vascular invasion (vp1) between 2000 and 2010. **Summary of Background:** Vascular invasion has been reported as a prognostic factor of liver resection for hepatocellular carcinoma (HCC). Anatomical resection for HCC has resulted in optimum outcomes of eradicating intrahepatic micrometastases through the portal vein, but opposite results have also been reported.

Methods: A clinical chart review was performed for 546 HCC patients with vp1. We retrospectively evaluated the recurrence-free survival (RFS) between anatomical (AR) and non-anatomical resection (NAR). The site of recurrence was also compared between these groups. The influence of AR on the overall survival (OS) and RFS rates was analyzed in patients selected by propensity score matching, and the prognostic factors were identified.

Results: A total of 546 patients were enrolled, including 422 in the AR group and 124 in the NAR group. There was no difference in the 5-year OS and RFS rates between the two groups. Local recurrence was significantly more frequent in the NAR group than in the AR group. In a multivariate analysis, hepatitis C (HCV), PIVKAII $\geq$380 mAU/ml, tumor diameter $\geq$5 cm and $\geq$70 years of age were significant predictors of a poor RFS after liver

resection. There were no significant differences in the OS or RFS between the AR and

NAR groups by a propensity score-matched analysis.

Conclusion: Although local recurrence around the resection site was suppressed by AR,

AR for HCC with vp1 did not influence the RFS or OS rates after hepatectomy in the

modern era.

1 **Impact of anatomical resection for hepatocellular carcinoma with micro-portal invasion**

2 **(vp1): A Multi-Institutional Study by the Kyushu Study Group of Liver Surgery**

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17 **Abbreviations**

18 HCC: hepatocellular carcinoma, HCV: hepatitis C virus, LR: liver resection, ICG-R15:

19 indocyanine green retention at 15 minutes, LHL 15: liver to heart uptake ratio at 15 minutes,

1   AR: anatomical resection, NAR: non-anatomical resection, AFP: alpha-fetoprotein, PIVKAII:

2   serum protein induced by vitamin K absence II, LCSGJ: Liver Cancer Study Group of Japan,

3   vp1: micro-portal invasion,

4   Key words: hepatocellular carcinoma, liver resection, portal venous invasion, propensity score

5   matching

6   There is no financial support in this study.

7   Short running head: Anatomical resection for HCC with vp1

8

9

1 **INTRODUCTION**

2 Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide (1).

3 Although the safety of liver resection for HCC has been established in recent years, the

4 optimum types of liver resection differ by institute, size and location of HCC and the underlying

5 liver function. Several tumor-related prognostic factors after liver resection for HCC have been

6 reported, including the tumor size, number, biological tumor marker levels, histological

7 differentiation and micro-vascular invasion, along with the background liver function, such as

8 portal hypertension, hepatitis C virus (HCV), inflammation of the liver and liver fibrosis. To

9 improve the outcome after liver resection, several studies have reported that anatomical

10 resection (AR) significantly contributed to the overall survival (OS) and recurrence-free

11 survival (RFS) after liver resection, as this procedure suppressed tumor spread through portal

12 vein invasion compared with non-anatomical resection (NAR) (2-9). However, other studies

13 have reported no marked differences in the OS or RFS rates between these methods (10-15).

14 In Japan, a nationwide survey reported that there was no marked difference in the OS or RFS

15 rates after liver resection (LR) for solitary HCC between the AR and NAR groups. In a

16 subgroup analysis, the recurrence rates in the AR group were significantly better than in the

17 NAR group, even with a tumor diameter of 2 to 5 cm (16). Clinical and pathological

18 characteristics of HCC tend to include spread along the portal vein branches. Theoretically, the

19 AR approach should suppress tumor spread via portal invasion in primary HCC (2). However,

1   the efficacy and benefits of AR for HCC with micro-vascular invasion remain unclear and

2   controversial (6, 8, 9, 13).

3   The aim of the present study was to clarify whether or not AR influences the OS or RFS

4   rates of HCC with histological vascular invasion after LR according to a multicenter analysis.

5

1 **PATIENTS AND METHODS**

2 All patients with solitary HCC who initially underwent hepatic resection and were diagnosed

3 with micro-portal invasion of HCC by a pathological examination between January 2000 and

4 December 2010 at the 13 institutions belonging to the Kyushu Study Group of Liver Surgery

5 (Department of Surgery, Nagasaki University; Kurume University; Kumamoto University;

6 Kyushu University; Miyazaki University; National Hospital Organization Kyushu Medical

7 Center; Oita University; Ryukyu University; Kagoshima University; Fukuoka University;

8 Department of Surgical Oncology, Nagasaki University; National Hospital Organization

9 Nagasaki Medical Center; Saga University and Kagoshima Prefectural Oshima Hospital) were

10 enrolled in this study. This study was approved by the Institutional Review Board of each

11 institution.

12 Of the 546 HCC patients who underwent curative resection and were diagnosed with

13 histological portal vein invasion by the pathologist at each institution, we excluded those with

14 multiple HCC and repeated hepatic resection. Micro-portal invasion (vp1) was defined as

15 tumor cells invading the micro portal vessels around HCC, which was diagnosed by an expert

16 pathologist in each center, according to the criteria defined by the Liver Cancer Study Group

17 of Japan (LCSGJ) (17), which did not include micro-hepatic vein invasion. The selection of

18 hepatic resection was based on preoperative tumor staging and liver function tests by each

19 institution. AR was defined as anatomical resection including sub-segmentectomy. NAR was

20 defined as partial resection containing the tumor located between two segments. Tumor staging

1   was determined by preoperative ultrasonography (US), multidetector computed tomography

2   (MDCT) and magnetic resonance imaging (MRI). The preoperative liver function was assessed

3   by liver function tests, indocyanine green retention for 15 minutes (ICG-R15), Child-Pugh

4   classification and the liver damage classification, defined by the LCSGJ (17).

5   Patient data collected before surgery included the age, sex, virus status, serum alpha-

6   fetoprotein (AFP) and serum protein induced by vitamin K absence II (PIVKA-II) levels,

7   Child-Pugh class, liver damage defined by the LCSGJ, tumor diameter (cm) and type of

8   hepatectomy (3).

9   Postoperative follow-up included assessments of the AFP and PIVKA-II levels and US,

10   CT or MRI every three months. If indicated, chest CT or bone scintigraphy was performed.

11   Regarding the definition of local recurrence, each center requested that each radiologist define

12   local recurrence based on imaging findings of the branch of the portal vessels on CT. Local

13   recurrence was defined the same subsegment of resected region in NAR group.

14   If tumor recurrence was found, the optimum treatment (transarterial chemoembolization

15   for intrahepatic multiple recurrence, radio frequency ablation for single small recurrence,

16   repeat hepatectomy for single intrahepatic recurrence) was selected for patients with a

17   preserved liver function.

18   This study was conducted as a multi-institutional survey by the Kyushu Study Group of

19   Liver Surgery.

1

2 *Analyses and statistics*

3 Preoperative clinical data in the AR and NAR groups were compared, including the age, sex,

4 virus status, Child-Pugh classification, liver damage, ICG R15, LHL15, AFP (ng/ml), PIVKA-

5 II (mAU/ml), operative data, pathological data (tumor number and diameter), arterial and

6 venous invasion, bile duct invasion and liver fibrosis. Clinical and pathological factors between

7 the NAR and AR groups were compared by Mann-Whitney U test and chi-squared tests. To

8 overcome the selection bias produced by an imbalance in the preoperative factors between the

9 two groups, propensity score matching (PSM) was carried out to compare the OS and RFS

10 rates. The propensity score was calculated using a logistic regression model. Preoperative

11 variables were entered to PSM except for surgical related factors (operation time, blood loss,

12 and blood transfusion). PSM was performed by a 1:1 matching method with a caliper width of

13 0.01 using the SPSS software package, Version 24.0 (Tokyo, Japan).

14 The survival was analyzed from the day of surgery to the most recent follow-up.

15 Recurrence after surgery was determined by imaging findings. The OS and RFS rates between

16 the NAR and AR groups were assessed with the Kaplan-Meier method using the log-rank test.

17 Regarding the prognostic factors for the OS and RFS, 14 clinical and pathological variables

18 were determined. Univariate and multivariate analyses of the prognostic factors were

19 performed using a Cox proportional hazard model. The recurrence sites after liver resection

1   were compared by imaging findings between the AR and NAR groups. Differences were

2   considered statistically significant when the p-values were < 0.05. Statistical analyses were

3   performed using the SPSS software package, Version 24.0.

4

1 **RESULTS**

2 *Patient characteristics and differences between the AR and NAR groups*

3 Five hundred and forty-six patients were enrolled in this study, including 422 patients with AR

4 and 124 with NAR. AR included subsegmentectmy in 74 patients, lateral segmentectomy

5 (S2+3) in 46, median (S4) in 8, anterior (S5+8) in 36, posterior (S6+7) in 72, right lobectomy

6 (S5,6,7,8) in 97, left lobectomy (S2,3,4) in 49, right tri-segmentectomy (S4,5,6,7,8) in 8 and

7 bi-segmentctomy (S4,5,8) in 32.

8 The characteristics of patients with AR and NAR were compared between these two

9 groups, as shown in Table 1. Patients with AR had a lower platelet count, lower proportion of

10 HCV-positivity, higher proportion of non-B- and non-C-related HCC, higher CP class, higher

11 liver damage class, lower ICG R15, higher PIVKAII level, lower AFP level and larger tumor

12 diameter than those in the NAR group. Regarding the operative findings the AR group had a

13 longer operation time, more blood loss and higher rate of blood transfusion than the NAR group.

14 There were no marked differences in the rate of postoperative complications between these

15 groups.

16

17 *OS and RFS rates in HCC vp1 patients with AR and NAR after hepatectomy*

18 The median follow-up of all patients was 49.9 months (0.2-183) for the OS. Two hundred and

19 forty-three patients died after liver resection. A total of 51 (41.1%) patients in the NAR group

1　and 192 (45.4%) in the AR group died after liver resection during the follow-up. The 1-, 3- and

2　5-year OS rates in the AR group (n=422) were 90.9%, 73.9% and 62.3%, respectively. The 1-,

3　3- and 5-year OS rates in the NAR group (n=124) were 91.8%, 75.7% and 66.7%, respectively.

4　There were no marked differences in the OS rates between the NAR and AR groups in Figure

5　1A.

6　　　The median follow-up of all patients was 20.7 months (0.2-183) for the RFS. Recurrence

7　after resection developed in 315 patients, including 241 (57.1%) patients in the AR group and

8　74 (59.6%) in the NAR group. The 1-, 3- and 5-year RFS rates in the AR group (n=422) were

9　68.8%, 45.8% and 38.2%, respectively. The 1-, 3- and 5-year RFS in the NAR group (n=124)

10　were 75.4%, 43.1% and 36.6%, respectively. There were no marked differences in the RFS

11　rates between the NAR and AR groups in Figure 1B.

12

13　*Initial recurrence pattern of HCC measuring <5 cm between NAR and AR*

14　The initial recurrence site of the liver in patients with HCC <5 cm with vp1 after liver resection

15　in NAR was as follows: same segment in 14 (13.6%), same lobe in 18 (17.5%), opposite lobe

16　in 11 (10.7%) and bi-lobar in 10 (9.7%). The initial recurrence site in the subsegmentectomy

17　group was same the segment in 1 (2.2%), same lobe in 7 (15.6%), opposite lobe in 6 (13.3%)

18　and bi-lobar in 4 (8.9%).

19　　　A comparison of the recurrence rate between these groups showed that the recurrence

1   rate in the NAR group occurred in the same segment significantly more frequently than in the

2   subsegmentectomy group (p=0.035). There were no significant differences in the rates of other

3   recurrence sites between these groups (Table 2). A comparison of the recurrence rate between

4   the NAR and segmentectomy groups showed no significant difference in the recurrence sites.

5   The recurrence rate of opposite site in the hemi-hepatectomy group was significantly higher

6   than in the NAR group. There was no significant difference in the recurrence rate between the

7   NAR and central liver resection groups.

8

9   *OS and RFS rates in HCC vp1 patients with AR and NAR after hepatectomy regarding to*

10   *various size in HCC <2 cm, 2-5 cm and >5 cm*

11   Regarding the tumor size, the 1-, 3- and 5-year OS rates in patients with vp1 HCC <2 cm in

12   the AR group (n=26) were 100%, 84.0% and 70.9%, respectively. The 1-, 3- and 5-year OS

13   rates in the NAR group (n=27) were 92.6%, 80.9% and 70.4%, respectively. There were no

14   marked differences in the survival rates between the NAR and AR groups . The 1-, 3- and 5-

15   year OS rates in patients with vp1 HCC between 2-5 cm in the AR group (n=187) were 95.2%,

16   84.4% and 72.3%, respectively. The 1-, 3- and 5-year OS rates in the NAR group (n=78) were

17   94.7%, 80.2% and 72.9%, respectively. There were no marked difference in the survival rates

18   between the NAR and AR groups. The 1-, 3- and 5-year OS rates in patients with vp1 HCC >5

19   cm in the AR group (n=209) were 85.9%, 63.3% and 51.4%, respectively. The 1-, 3- and 5-

year OS rates in the NAR group (n=19) were 78.9%, 50.5% and 37.0%, respectively. There

were no marked differences in the survival rates between the NAR and AR groups.

Regarding the tumor size, the 1-, 3- and 5-year RFS rates in patients with vp1 HCC <2

cm in the AR group (n=26) were 84.6%, 72.5% and 54.0%, respectively. The 1-, 3- and 5-year

RFS rates in the NAR group (n=27) were 81.2%, 60.9% and 49.8%, respectively. There were

no marked difference in the RFS rates between the NAR and AR groups (Figure 2A). The 1-,

3- and 5-year RFS rates in patients with vp1 HCC between 2-5 cm in the AR group (n=187)

were 73.6%, 52.5% and 42.6%, respectively. The 1-, 3- and 5-year RFS rates in the NAR group

(n=78) were 78.2%, 40.8% and 36.8%, respectively. There were no marked difference in the

RFS rates between the NAR and AR groups (Figure 2B). The 1-, 3- and 5-year RFS rates in

patients with vp1 HCC >5 cm in the AR group (n=209) were 62.4%, 39.6% and 32.2%,

respectively. The 1-, 3- and 5-year RFS rates of the NAR group (n=19) were 55.6%, 25.9% and

19.4%, respectively. There were no marked differences in the RFS rates between the NAR and

AR groups (Figure 2C).

The OS and RFS based on the viral status

The 1-, 3- and 5-year OS rates in the HBV group (n=155) were 88.4%, 72.9% and 68.4%,

respectively. The 1-, 3- and 5-year OS rates in the HCV group (n=249) were 92.3%, 74.2% and

60.3%, respectively. The 1-, 3- and 5-year OS rates in the non-HBV, non-HCV group (n=142)

1   were 90.9%, 75.1% and 62.4%, respectively. There were no significant differences in the OS

2   between these groups (p=0.064).

3   The 1-, 3- and 5-year RFS rates in the HBV group (n=155) were 67.1%, 47.5% and 42.7%,

4   respectively. The 1-, 3- and 5-year RFS rates in the HCV group (n=249) were 68.8%, 38.2%

5   and 29,3%, respectively. The 1-, 3- and 5-year RFS rates in the non-HBV, non-HCV group

6   (n=142) were 75.0%, 53.8% and 46.9%, respectively. The RFS in the HCV group was

7   significantly worse than in the other groups (p=0.01). No benefit of AR was significantly

8   observed for any virus status group.

9

10 *Prognostic factors for the RFS*

11 A univariate analysis identified seven significant prognostic factors for the RFS in patients with

12 micro-vascular invasion. The presence of HCV, tumor diameter $\geq$5 cm, PIVKAII $\geq$380

13 mAU/ml, age $\geq$70 years, Child-Pugh class B, liver damage class B and blood transfusion were

14 significant prognostic factors for a poor RFS. A multivariable analysis was performed for the

15 RFS based on the variables identified as significant in the univariate analysis. The presence of

16 HCV, a tumor diameter $\geq$5 cm, PIVKAII $\geq$380 mAU/ml and age $\geq$70 years were identified as

17 independent prognostic indicators for recurrence (Table 3).

18

19 *Patient characteristics and long-term outcomes after PSM between the AR and NAR groups*

1   After1:1 PSM, 172 patients were classified into the propensity-matched anatomical resection

2   (PSM-AR) (n=86) and propensity-matched non-anatomical resection (PSM-NAR) groups

3   (n=86). The characteristics of clinical and operation factors are summarized in Table 4. After

4   PSM, there were no significant differences in the background characteristics between the PSM-

5   AR and PSM-NAR groups. However, the operation time was still significantly longer in the

6   PSM-AR group than in the PSM-NAR group. The 1-, 3- and 5-year OS rates were 89.3%,

7   76.0% and 64.5% in the PSM-AR group and 92.9%, 73.5% and 65.3% in the PSM-NAR group,

8   respectively. The 1-, 3- and 5-year RFS rates were 68.6%, 44.6% and 37.0% in the PSM-AR

9   group and 74.3%, 46.2% and 42.2% in the PSM-NAR group, respectively. There were no

10   marked differences in the OS and RFS rates between the PSM-NAR and PSM-AR groups

11   (Figure 3).

12

1 **DISCUSSION**

2 Over the past several decades, arguments about the effectiveness of AR for preventing the

3 dissemination of HCC in the liver after liver resection have progressed. Regarding the

4 pathological progression of HCC, AR might be suitable for preventing the portal spread of

5 HCC (2). However, the multi-centric occurrence of HCC in the liver persists, even though AR

6 prevents the pathological spread of HCC (18).

7 Hasegawa et al. reported that AR improved the OS and RFS after liver resection and was

8 an independent factor, just like the absence of microvascular invasion in HCC (3). A Japanese

9 nationwide survey showed that AR was an independent factor influencing the disease-free

10 survival (DFS) for HCC measuring from 2-5 cm in size. Regarding the liver function, no

11 significant differences in DFS between the AR and NAR groups according to the liver function

12 were noted (16). A meta-analysis showed that AR provided a better patient survival and DFS

13 than NAR. However, a meta-regression analysis showed that different proportions of liver

14 cirrhosis in the NAR group significantly affected the patient survival and DFS (20).

15 Shi et al. suggested that micro-metastases were present in the margin with 1.0-2.0 cm

16 around HCC as same as margin less than 1.0 cm (20). This suggested that a wide margin would

17 be needed in order to maintain the liver function. The present study focused on the recurrence

18 of HCC after liver resection in patients with pathological portal invasion of HCC, defined based

19 on the findings of a resected specimen, as other authors have reported several benefits of AR

1 in cases of HCC without micro vascular invasion (8, 9). We noted significant differences in the

2 viral status, Child-Pugh grade, liver damage, ICG-R15, AFP, PIVKAII, tumor diameter,

3 operation time, blood loss and blood transfusion rate between the AR and NAR groups, after

4 excluding patients with macrovascular invasion and multiple tumors.

5 Despite this bias, AR was not superior to NAR in providing a better OS and RFS. With

6 regard to the tumor size, as the type of liver resection has been shown not to affect the outcome

7 in small HCC (16), our study showed no difference in the OS or RFS between the two groups.

8 For tumors about 2-5 cm in size, AR failed to produce a better OS or RFS than NAR. Several

9 reports have described the superiority of AR to NAR in the RFS or OS. In the present study,

10 the NAR group had greater proportions of HCV, Child-Pugh class B and liver damage class B

11 and worse ICGR15 test findings than the AR group for 2-5 cm vp1 HCC; however, there were

12 no marked differences in the AFP, PIVKAII or tumor diameter between these groups.

13 Regarding tumors >5 cm in size, the NAR group had 19 patients with such tumors, while

14 the AR group had 209 patients with such tumors. This affected the RFS of the groups, although

15 there was no marked difference between the AR and NAR group in the number of patients with

16 tumors >5 cm in size.

17 A multivariate analysis showed that HCV, elevated PIVKAII, tumor diameter >5 cm and

18 age $\geq$70 years were independent prognostic factors for the RFS in patients with vp1. These

19 findings suggest that the recurrence pattern might be associated with the background liver

1 status. Indeed, a meta-analysis suggested that a poor liver function led to a worse outcome after

2 LR (19).

3   Regarding the recurrence pattern, 20% of initial recurrences occurred in the opposite lobe

4 and bilobar in the liver, which might reflect the multi-centric recurrence of HCC. Compared to

5 NAR, the subsegmentectomy procedure significantly suppressed the incidence of recurrence

6 in the same segment (subsegmentectomy 2.2% vs. NAR 13.6%). However, the rate of

7 recurrence in the same lobe was similar between these two groups, suggesting that wide

8 resection might be better than NAR if the remnant liver function preserved. Recurrence at the

9 opposite site was more frequent in the hemi-hepatectomy group than in the NAR group.

10 However, this result indicated that there were no marked differences in recurrence rate between

11 the hemi-hepatectomy and NAR groups, as the total recurrence rates in these groups were

12 roughly 40%-50% after resection.

13   Shindoh et al. reported that the incidence of local recurrence in the AR group was lower

14 than in the NAR group, and that AR significantly suppressed the recurrence of HCC with

15 micro-metastasis after resection (6, 7).

16   A few previous studies reported that AR showed a better outcome than NAR in

17 propensity-matched analyses of procedure efficacy (8, 12-14). In cases of HCC with micro-

18 vascular invasion in particular, AR significantly suppressed the RFS after LR (8). However,

19 there were no marked differences in the RFS or OS between the AR and NAR groups in another

1 three studies (12-14). Zhao et al. suggested that these conflicting findings were due to

2 differences in the background vital status and the proportion of patients with liver cirrhosis

3 between the groups. In addition, the marginal recurrence rate in the NAR group with PSM was

4 significantly higher than that in the AR group in their study, a finding that resembled our own

5 pathological examination finding of more invaded microvessels in the AR group with PSM

6 than in the NAR group (8). Our results showed that AR did not affect the OS or RFS in patients

7 with vp1, even though the clinical factors were similar between the AR and NAR groups on

8 PSM. We hypothesize that AR suppressed the tumor spread from HCC, especially HCC with

9 microscopic portal vein invasion, as AR can remove HCC and the surrounding liver

10 parenchyma supplied by tumor-bearing portal tributaries. Interestingly, Shi et al. reported that

11 partial hepatectomy with a wide margin (>2 cm) had a significantly better RFS and OS than

12 that with a narrow margin (<1 cm) according to a randomized control trial (21). However, Lee

13 et al. found that AR itself and not the width of the margin influenced the OS and RFS (22). In

14 our study, the surgical margin in the NAR group may have been adequate, even when surgeons

15 performed partial resection for HCC.

16   Although the recurrence rates in the same segment after liver resection were higher in

17 the NAR group than in the AR group, the RFS rates between the two groups were similar. This

18 may suggest that the treatment for HCC recurrence after hepatectomy was more important than

19 the initial type of surgical procedures. Issues remained with regard to the recurrence rates after

1   resection between the subsegment and NAR group. This discrepancy may have been due to

2   differences in the area of liver, as the segment remnant was smaller in the subsegment group

3   than in the NAR group, potentially resulting in significant differences in the recurrence rates

4   between these two groups. There was also a significant difference in the recurrence rate

5   between the hemihepatectomy and NAR groups. However the remaining liver after

6   hemihepatectomy was only the opposite liver. This result should be carefully evaluated, as

7   NAR might not be better than hemihepatectomy with respect to recurrence rates. Overall, the

8   cases of recurrence in the NAR group accounted for 50.4% of all site of recurrence in the

9   remaining liver.

10   In our study, patients with HCV accounted for more than half of the total patients, similar

11   to other studies in Japan (12-14). This indicated that the multi-centric occurrence of HCC did

12   not affect the effectiveness of AR in achieving suppression of tumor spread, as HCV was an

13   independent prognostic factor for recurrence after liver resection in this study. Maintaining the

14   remnant liver function might be more important if recurrence occurs in the remnant liver after

15   hepatectomy.

16   One limitation associated with this study is its retrospective design. Another is that there

17   was a difference in the sample size between the AR and NAR groups. A selection bias therefore

18   remained between the two groups despite PSM to adjust for background factors, as the

19   procedures of liver resection were selected by each center at each surgeon's preference. This

1   might have affected the conclusion about the lower efficacy of AR with regard to the RFS after

2   LR.

3

4   **Conclusion**

5   AR for HCC with vp1 did not improve the RFS or OS after hepatectomy, although local

6   recurrence around the resection site was suppressed by AR.

7

11

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2

1 **Figure legends**

2 **Figure 1.** A comparison of the overall survival (1A) and the recurrence-free survival (1B) in

3 vp1 HCC patients with AR or NAR after hepatectomy (N.S.).

4

5 **Figure 2.** A comparison of recurrence-free survival in patients with vp1 HCC less than 2 cm

6 (2A), 2-5 cm (2B) and more than 5 cm measuring less than 2 cm with AR and NAR after

7 hepatectomy (N.S.).

8

9 **Figure 3.** A comparison of the overall survival (3A) and recurrence-free survival (3B) in

10 patients with vp1 HCC with PSM-AR and PSM-NAR after hepatectomy (N.S.).

11

1   **Table 1. Clinical characteristics of patients with AR or NAR which had histological vp1**

2   **HCC**

Variables	AR group (n=422)	NAR group (n=124)	p-value
Ages (years)	69 (32-87)	67 (35-86)	N.S.
Gender (M/F)	331/91	95/29	N.S.
Etiology			
Hepatitis B	122 (28.9%)	33 (26.6%)	N.S.
Hepatitis C	175 (41.5%)	74 (59.7%)	0.001
Negative	125 (29.6%)	17 (13.7%)	0.001
Child Pugh classification			
Class A	404 (95.7%)	108 (86.3%)	0.001
Class B	18 (4.3%)	16 (13.7%)	
Liver damage			
Class A	360 (85.3%)	82 (66.1%)	0.001
Class B	51 (12.1%)	29 (23.3%)	
ICG R15 (%)	12.9 (1.0-64.9)	20.0 (4.5-73)	0.001
AFP (ng/ml)	18.9 (0.8-930,900)	61.5 (1.0-29,285)	N.S.
PIVKAII (mAU/ml)	535 (2.4-672,900)	131 (9-61,755)	0.001

Tumor diameter (cm)	4.9 (1.0-25.0)	3.0 (0.5-19.0)	0.001
Operation time (min)	385 (105-1,175)	315 (81-855)	0.001
Blood loss (ml)	640 (5-11,720)	475 (0-2840)	0.001
Blood transfusion	113 (26.8%)	20 (16.1%)	0.028

1 AR, anatomical resection; NAR, non-anatomical resection; HCC, hepatocellular carcinoma.

2 AFP, alpha-fetoprotein; ICG R15, indocyanine green retention test at 15 minutes; PIVKA II,

3 protein induced by vitamin K absence II

4

1   **Table 2.** A comparison of the initial recurrence site in patients with histological vp1 HCC

2   measuring <5 cm with AR or NAR

	NAR (n=105)	Sub-segmentectomy (n=45)	p-value
Same segment	14 (13.3%)	1 (2.2%)	0.035
Same lobe	18 (17.1%)	7 (15.6%)	0.774
Opposite lobe	11 (10.5%)	6 (13.3%)	0.641
Bi-lobar	10 (9.5%)	4 (8.9%)	0.74

	NAR (n=105)	Segmentectomy (n=105)	p-value
Same segment	14 (13.3%)		
Same lobe	18 (17.1%)	10 (9.7%)	0.104
Opposite lobe	11 (10.5%)	19 (17.7%)	0.115
Bi-lobar	10 (9.5%)	8 (7.5%)	0.662

	NAR (n=105)	Hemi-hepatectomy (n=45)	p-value
Same segment	14 (13.3%)		
Same lobe	18 (17.1%)		
Opposite lobe	11 (10.5%)	20 (44.4%)	0.001
Bi-lobar	10 (9.5%)		

	NAR (n=105)	Central liver resection (n=8)	p-value
Same segment	14 (13.3%)		
Same lobe	18 (17.1%)	2 (3.2%)	0.575
Opposite lobe	11 (10.5%)	1 (17.7%)	0.858
Bi-lobar	10 (9.5%)	1 (7.5%)	0.784

1   AR, anatomical resection; NAR, non-anatomical resection

2

1 **Table 3.** Results of univariate and multivariate analyses of prognostic factors regarding the

2 recurrence-free survival in patients with histological vp1 HCC after hepatectomy

Variables	Category	Univariate analysis			Multivariate analysis		
		Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
HCV	+	1.33	1.06-1.66	0.012	1.86	1.37-2.53	0.001
PIVKA II	≥ 380	1.61	1.28-2.02	0.001	1.48	1.12-1.96	0.001
Tumor diameter (cm)	≥ 5	1.86	1.27-2.72	0.001	1.41	1.04-1.90	0.001
Age	≥ 70	1.38	1.10-1.73	0.005	1.37	1.03-1.82	0.03
Child Pugh	B	1.66	1.10-2.51	0.015	1.47	0.83-2.60	0.19
Liver damage	B	1.49	1.10-2.01	0.009	1.06	0.67-1.66	0.8
Blood transfusion	+	1.33	1.03-1.72	0.029	1.13	0.82-1.68	0.36

			0.97-	
AFP (ng/ml)	≥ 24	1.22	1.54	0.084
			0.97-	
ICG R15 (%)	≥ 15	1.22	1.54	0.089
Anatomical			0.77-	
resection	+	1	1.30	0.976
			0.95-	
Blood loss(ml)	≥ 600	1.19	1..50	0.119
Operation			0.83-	
time(min)	≥ 370	1.04	1.31	0.772
			0.85-	
Fibrosis	+	1.09	1.41	0.468
			0.68-	
HBV	+	0.87	1.13	0.297

1   AFP, alpha-fetoprotein; ICG R15, indocyanine green retention test at 15 minutes; PIVKA II,

2   protein induced by vitamin K absence II

1 **Table 4.** Clinical characteristics of patients with AR or NAR which had histological vp1 HCC

2 after propensity score matching

Variables	PSM-AR group (n=86)	PSM-NAR group (n=86)	p-value
Ages (years)	69.5 (42-84)	68.5 (39-86)	N.S.
Gender (M/F)	65/21	67/19	N.S.
Etiology			
Hepatitis B	19 (22.1%)	22 (25.6%)	N.S.
Hepatitis C	52 (60.5%)	49 (57.0%)	N.S.
Negative	15 (17.4%)	15 (17.4%)	N.S.
Child Pugh classification			
Class A	82 (95.3%)	80 (93.0%)	N.S.
Class B	4 (4.7%)	6 (7.0%)	
Liver damage			
Class A	71 (82.6%)	72 (83.7%)	N.S.
Class B	15 (17.4%)	14 (16.3%)	
ICG R15 (%)	16.6 (2.5-50.3)	16.8 (4.5-73.0)	N.S.
AFP (ng/ml)	38.0 (1.9-48,119)	31.5 (1.0-29,285)	N.S.
PIVKAII (mAU/ml)	127.5 (12-84,300)	92.5 (9-38,385)	N.S.

Tumor diameter (cm)	3.1 (1.1-9.5)	3.0 (0.5-19.0)	N.S.
Operation time (min)	370 (135-693)	320 (81-855)	0.03
Blood loss (ml)	460 (50-3,553)	520 (0-2,840)	N.S.
Blood transfusion	12 (13.9%)	12 (13.9%)	N.S.

1   AR, anatomical resection; NAR, non-anatomical resection; HCC, hepatocellular carcinoma;

2   PSM, propensity score matching; AFP, alpha-fetoprotein; ICG R15, indocyanine green

3   retention test at 15 minutes; PIVKA II, protein induced by vitamin K absence II

4

Overall survival
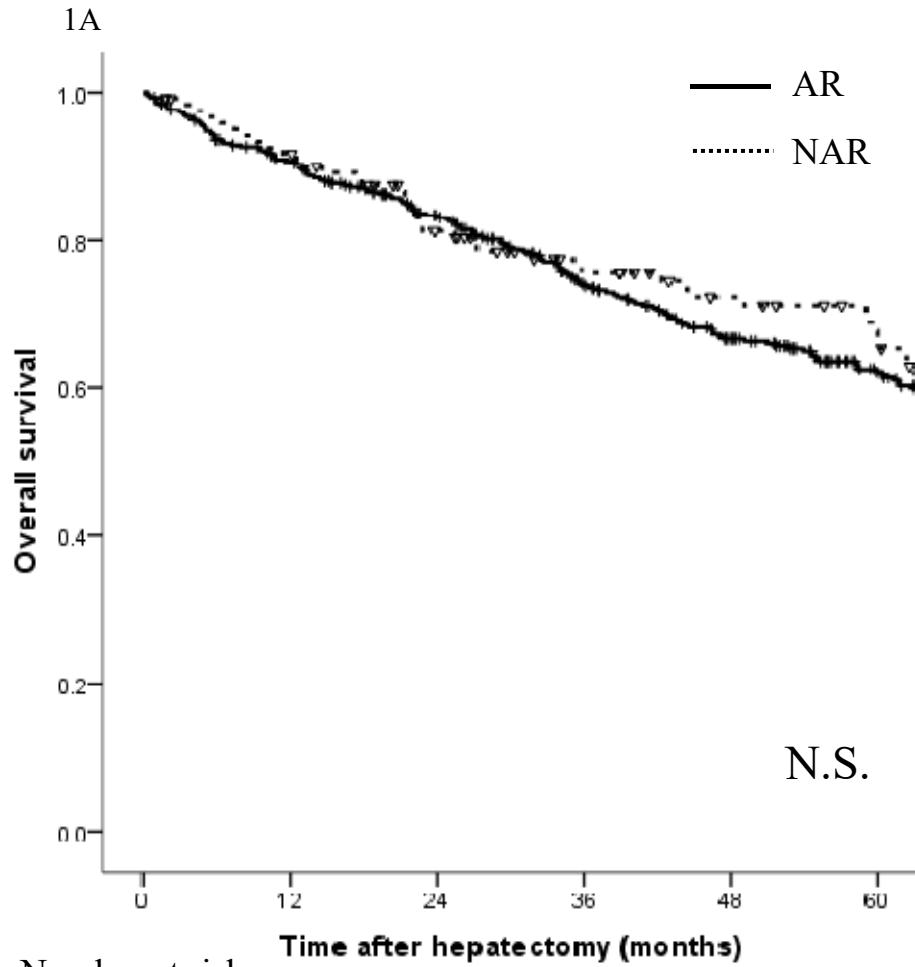
1A

Recurrence-free survival

1B
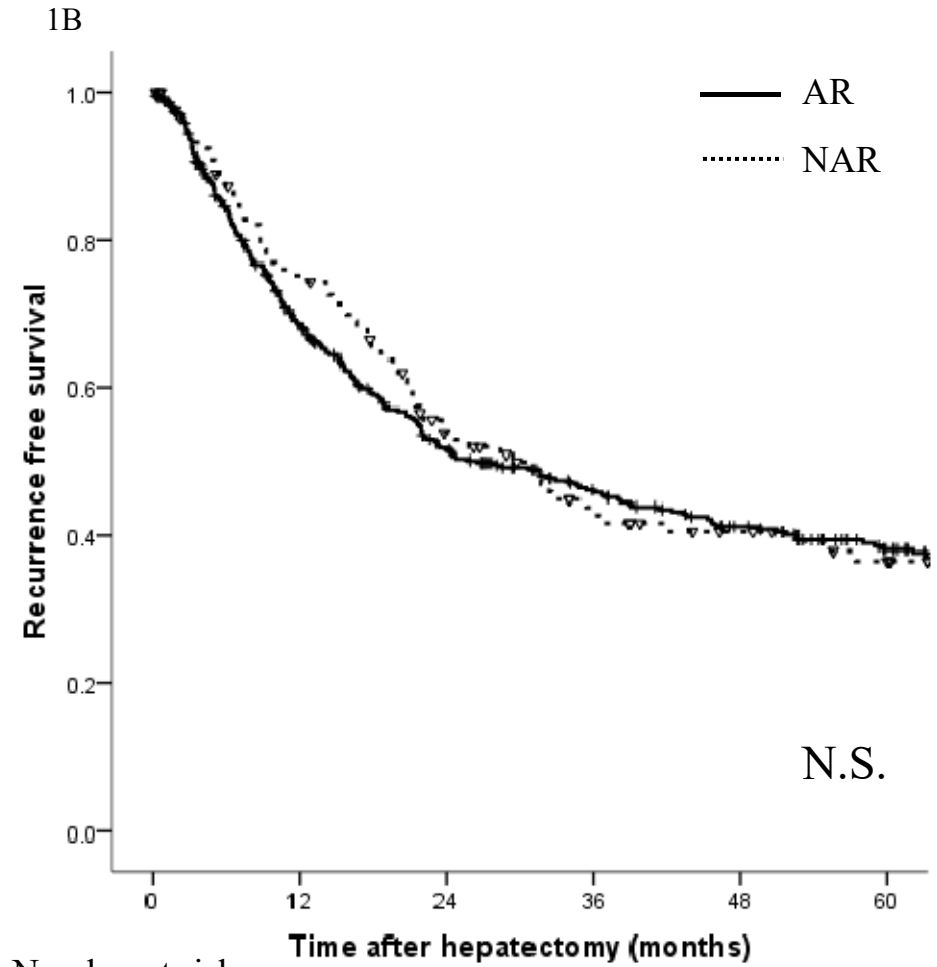
Figure 1. A comparison of the overall survival (1A) and the recurrence-free survival (1B) in vp1 HCC patients with AR or NAR after hepatectomy (N.S.).
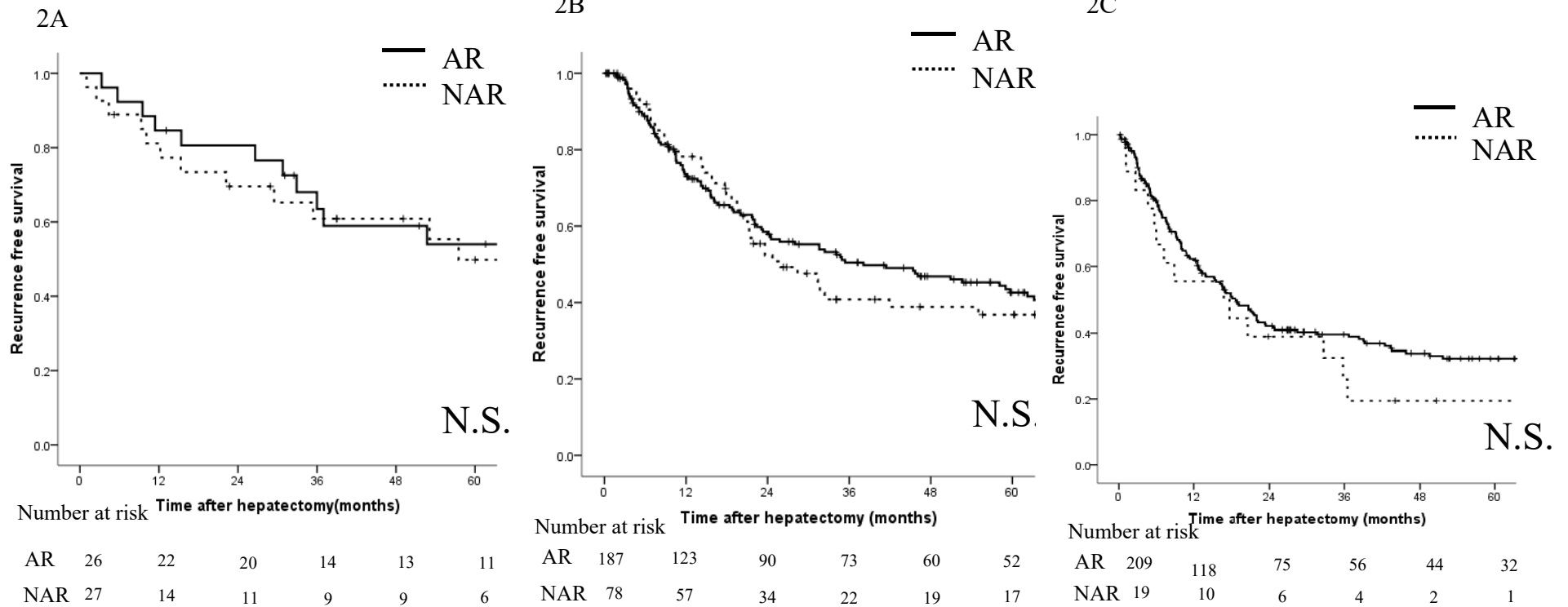
Recurrence-free survival

Figure 2. A comparison of recurrence-free survival in patients with vp1 HCC less than 2 cm (2A), 2-5 cm (2B) and more than 5 cm measuring less than 2 cm with AR and NAR after hepatectomy (N.S.).
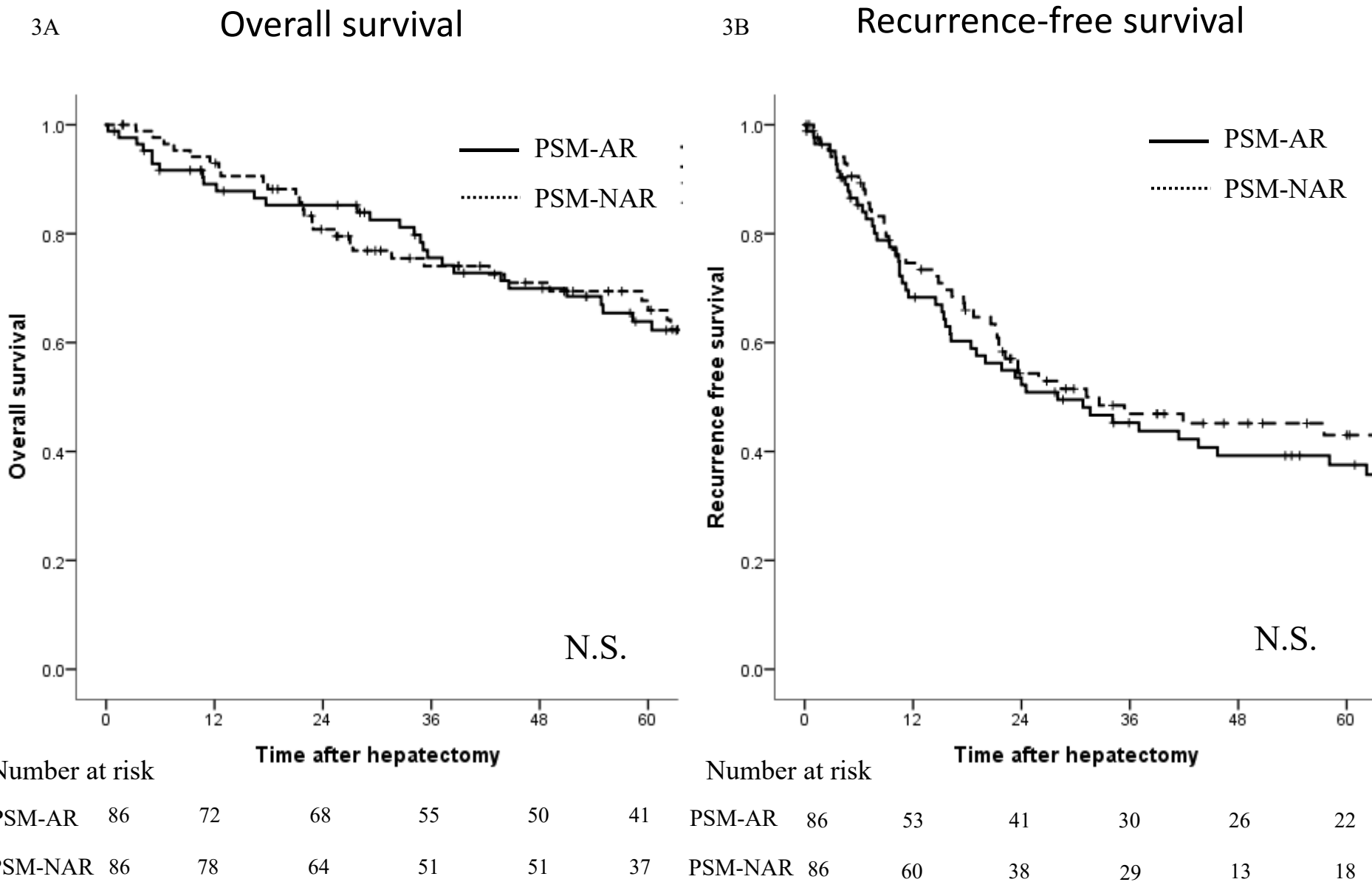
Figure 3. A comparison of the overall survival (3A) and recurrence-free survival (3B) in patients with vp1 HCC with PSM-AR and PSM-NAR after hepatectomy (N.S.).