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BRIEF ARTICLE

Propensity score analysis demonstrated the prognostic advantage of anatomical liver resection in hepatocellular carcinoma

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Abstract

AIM: To compare the prognoses of hepatocellular carcinoma (HCC) patients that underwent anatomic liver resection (AR) or non-anatomic liver resection (NAR) using propensity score-matched populations.

METHODS: Between January 2002 and December 2010, 268 consecutive HCC patients, including 110 and 158 patients that underwent AR and NAR, respectively, were retrospectively enrolled in this study. Forty-four patients from each group were selected and matched using logistic multivariate analysis followed by propensity score analysis.

RESULTS: In the whole analysis set, the histological background of the liver, liver function, and tumor marker levels differed significantly among the groups. Although the overall survival (OS) and recurrence-free survival rates of the two groups did not differ significantly in the whole analysis set, the OS of the AR group was significantly longer than that of the NAR group after propensity matching (76.2 ± 6.3 mo *vs* 58.9 ± 6.3 mo; $P = 0.0039$). Although AR (HR = 0.456, $P = 0.039$) was found to be a prognostic factor in the univariate analysis, only vascular invasion (HR = 0.228, $P = 0.002$) and the hepatocyte growth factor level (HR = 52.366, $P = 0.035$) were subsequently found to be independent prognostic factors.

CONCLUSION: AR conveys a survival advantage over NAR in specific subpopulations of HCC patients with tumors of less than 5 cm in diameter, single tumor, and good liver function.

Key words: Anatomical liver resection; Propensity score analysis; Hepatocellular carcinoma

Core tip: The aim of this study was to compare the prognostic advantage of hepatocellular carcinoma (HCC) patients that underwent anatomic liver resection (AR) or non-anatomic liver resection (NAR) using propensity score-matched populations. Consecutive 268 HCC patients were enrolled and 44 patients from each group were matched using logistic multivariate analysis followed by propensity score analysis. The overall survival of the AR group was significantly longer than that of the NAR group after propensity matching. Vascular invasion and the hepatocyte growth factor level were subsequently found to be independent prognostic fac-

tors. AR conveys a survival advantage over NAR in specific subpopulations of HCC patients.

INTRODUCTION

Liver resection is one of the curative approaches employed for hepatocellular carcinoma (HCC), which is the sixth most prevalent cancer worldwide[1-3]. The optimal strategy for HCC management depends on the balance between the characteristics of the tumor and host liver function[4-6]. Although the indications for liver resection for HCC recommend that only patients that retain good liver function should undergo the procedure[7,8], the liver function of these patients can deteriorate due to chronic liver disease, including cirrhosis associated with viral hepatitis[2,3].

The optimal type of liver resection for HCC has been debated and is divided into anatomic resection (AR) and non-anatomic resection (NAR)[9-12]. Basically, AR is recommended for HCC patients who maintain good liver function[11,13,14]. On the other hand, the clinical prognosis of cirrhotic patients that undergo NAR is comparable to that of cirrhotic patients that undergo AR[15-17]. Meta-analysis of AR *vs* NAR has demonstrated the superiority of AR in specific subgroups[18,19]. However, none of these reports were randomized control studies. Therefore, it is very difficult to compare the outcomes of the two surgical procedures due to the different tumor status and liver function backgrounds of the patients that undergo them, and so no conclusion about the matter has ever been reached.

To overcome the effects of patient background, performing multivariate analysis followed by propensity score-matched analysis makes it possible to compare elective groups whilst minimizing confounding factors in non-randomized retrospective studies[20-22]. The aim of this study is to elucidate the prognostic differences among AR and NAR for HCC after matching gender, tumor characteristics, and liver function using propensity score analysis.

MATERIALS AND METHODS

Patients

Between January 2002 and December 2010, 268 consecutive HCC patients who underwent hepatectomy were recruited for this study after providing informed consent. Among the 268 patients, 110 underwent AR and 158

underwent NAR. The patients' tumors were evaluated by both ethoxybenzyl-enhanced magnetic resonance imaging and contrast-enhanced computed tomography scans were performed prior to surgery in order to assess tumor number and size. Clinical laboratory tests were carried out before surgery under stable conditions without inflammation. Histological evaluations of the tumor and liver parenchyma were carried out using surgical or biopsy specimens. Operative variables were recorded by the operating staff including the anesthesiologists. The design of this retrospective study conformed to the ethical guidelines of the Declaration of Helsinki, and all the patients gave their informed consent with individual signatures.

Surgical procedure

AR was defined as the complete removal of at least one Couinaud segment and exposure of the hepatic veins on the resected liver surface at the segment border. NAR was defined as the removal of the tumor regardless of the tumor margin or Couinaud segment without exposing the hepatic veins on the cut liver surface. All cases attempted to select AR, but some patients did not qualify for AR after liver resection due to unexposure of any segmental landmark or poor liver function. Indication of liver resection is based on same criteria[23] during entire study period with same team. During surgery, a Cavitron ultrasonic sound aspirator and saline-linked electric cautery were used for the parenchymal dissection. When necessary, the pedicle of the hepatic hilum was intermittently clamped in cycles involving 10 min of clamping and 5 min of reperfusion.

Statistical analysis

For the statistical analyses, demographic data and perioperative laboratory test results were extracted from the clinical database, and the differences among the groups were compared using the χ^2 test followed by the post-hoc 2×2 Fisher's exact test, when necessary. Continuous variables were compared using the Mann-Whitney U test. The factors affecting overall survival were assessed using the Kaplan-Meier method, with comparisons performed using the Log-rank test and univariate or multivariate analyses performed using the Cox proportional hazards regression model. Multivariate analyses were performed by backward selection of covariates with cut-off univariate P value of 0.05. To adjust for the different covariate distributions of the two groups (the AR and NAR groups), one-to-one matches were performed using propensity score analysis. The variables entered into the propensity model were gender, age, albumin level, bilirubin concentration, prothrombin time, tumor size, tumor number, operation time, and intraoperative blood loss. The model was then used to obtain one-to-one matches using the nearest-neighbor matching method. All calculations were performed using the StatView 5.0 software package (Abacus Concepts Inc., Berkeley, CA), NCSS (NCSS, Kaysville, UT), or SPSS 16.0 (SPSS Inc., Chicago,

Table 1 Clinicopathological characteristics of hepatocellular carcinoma patients who underwent initial hepatectomy in the full analysis set and one-to-one propensity score-matched pairs

Variables	Full analysis set			Propensity score-matched pairs		
	A (*n* = 110)	NA (*n* = 158)	*P* value	A (*n* = 44)	NA (*n* = 44)	*P* value
Gender (M:F)	97:13	133:25	0.455	38:6	38:6	NA
Age (yr)	68 (64-70)	66 (64-68)	0.862	64.9 ± 10.2	64.5 ± 9.5	0.838
Etiology						
(B:C:BC:NBNC)	50:32:1:27	70:61:6:21	0.035	19:18:1:6	24:12:1:7	0.602
Background (N:CH:L)	16:56:38	9:49:100	< 0.001	4:20:20	5:14:25	0.422
Histology (W:M:P)	50:32:1:27	29:94:35	0.138	6:30:8	8:28:8	0.836
Albumin (mg/dL)	3.91 ± 0.42	3.86 ± 0.47	0.321	3.99 ± 0.34	3.92 ± 0.41	0.379
Bilirubin (mg/dL)	0.6 (0.6-0.6)	0.8 (0.7-0.9)	< 0.001	0.68 ± 0.26	0.72 ± 0.39	0.545
PT (%)	93.3 ± 12.2	90.6 ± 13.6	0.106	92.4 ± 11.5	92.5 ± 12.4	0.948
ICGR15 (%)	8.5 (7.4-9.9)	13 (10.8-15)	< 0.001	10.4 ± 5.6	13.5 ± 8.8	0.053
Child-Pugh score (A:B)	109:1	153:5	0.419	44:0	44:0	NA
MELD score	7.68 ± 2.73	7.58 ± 1.39	0.674	7.78 ± 3.21	7.37 ± 1.29	0.448
Tumor size (cm)	4.2 (3.5-5.5)	2.5 (2.2-3.0)	< 0.001	3 (2.5-3.5)	3 (2.3-3.5)	0.904
No. of tumors	1 (1-1)	1 (1-1)	0.761	1 (1-1)	1 (1-1)	0.554
VI (-:+:++)	75:18:17	124:25:9	0.027	34:7:3	31:10:3	0.716
OT (min)	400 (364-439)	280 (260-300)	< 0.001	340.1 ± 105.8	322.7 ± 96.8	0.441
Blood loss (mL)	435 (380-600)	300 (230-390)	< 0.001	400 (310-482)	355 (270-560)	0.926
Blood transfusion (U)	1.3 ± 3.6	0.5 ± 2.3	0.049	0.4 ± 1.4	0.5 ± 1.6	0.833
BMI	23.19 ± 3.27	23.61 ± 3.38	0.313	23.57 ± 3.01	22.83 ± 3.13	0.263
Platelets	15.6 (13.3-17.1)	12.6 (11.7-14.2)	0.504	13.45 ± 4.71	16.41 ± 13.69	0.178
AST (IU/L)	36 (31-41)	36 (31-45)	0.206	40 (33-46)	33 (30-48)	0.439
ALT (IU/L)	34 (29-38)	32 (28-37)	0.413	38 (32-43)	29 (27-39)	0.103
MELD	7.03 (6.87-7.19)	7.12 (6.87-7.42)	0.674	7.10 (6.87-7.39)	7.03 (6.43-7.29)	0.396
BTR	6.07 (5.60-6.59)	5.42 (5.07-5.84)	< 0.001	5.89 (4.99-6.50)	5.73 (5.06-6.02)	0.277
Hyaluronate (ng/mL)	98 (76-132)	155 (128-196)	< 0.001	103 (66-139)	137 (104-187)	0.204
HGF (ng/mL)	0.32 (0.29-0.36)	0.36 (0.32-0.39)	0.069	0.33 ± 0.14	0.39 ± 0.15	0.066
AFP (ng/mL)	21.2 (11.2-80.9)	13.7 (8-29.5)	0.178	11.7 (6.5-38.4)	14.5 (5.8-46.4)	0.902
PIVKA (mAU/mL)	228 (90-639)	35 (27-53)	0.015	38 (24-158)	30 (23-66)	0.721

Median (95%CI of median) for skewed distribution and mean ± SD for normal distribution. A: Anatomical resection; NA: Non-anatomical resection; M: Male; F: Female; B: Hepatitis B; C: Hepatitis C; NBNC: Non-B and non-C hepatitis; N: Normal; CH: Chronic hepatitis; L: Liver cirrhosis; W: Well differentiated hepatocellular carcinoma; M: Moderately differentiated hepatocellular carcinoma; P: Poorly differentiated hepatocellular carcinoma; PT: Prothrombin time; ICGR15: Indocyanine green retention rate at 15 min; VI: Vascular invasion; OT: Operative time; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; MELD: Model for end-stage liver disease; BTR: Branched chain amino acids to tyrosine ratio; HGF: Hepatocyte growth factor; AFP: Alpha-fetoprotein; PIVKA: Protein induced by vitamin K absence or antagonist.

II). All results are expressed as mean ± SD values. *P* values of < 0.05 were considered to be significant.

RESULTS

We retrospectively analyzed 268 HCC patients who initially underwent hepatectomy at our institute. Basically, AR was preferred, but some patients did not qualify for AR due to poor liver function and so were scheduled for NAR. In addition, no exposure of anatomical landmark after liver resection was also defined NAR. The full analysis set consisted of 110 and 158 patients that underwent AR and NAR, respectively (Table 1). After one-to-one matching using propensity score analysis, 44 pairs of patients were matched and compared. In the full analysis set, the histological background of the liver; indocyanine green retention rate at 15 min (ICGR15); vascular invasion; operative time; intraoperative blood loss; blood transfusion volume; branched-chain amino acid to tyrosine ratio; and serum bilirubin, hyaluronate, hepatocyte growth factor (HGF), and protein induced by vitamin K absence levels differed significantly among the groups (*P* < 0.05). Among the propensity score-matched pairs,

none of these factors differed between the groups, indicating that the clinical backgrounds of the two groups had been successfully matched.

In the full analysis set, recurrence free survival (RFS) and overall survival (OS) did not differ significantly among the groups (Figure 1); *i.e.*, the median RFS of the AR group was 48.1 ± 5.2 mo, and that of the NAR group was 47.2 ± 4.8 mo (*P* = 0.282). In addition, the OS of the AR group was 94.5 ± 8.2 mo, and that of the NAR group was 78.2 ± 5.1 mo (*P* = 0.293).

On the other hand, among the propensity score-matched pairs the OS of the AR group was significantly longer than that of the NAR group (76.2 ± 6.3 mo *vs* 58.9 ± 6.3 mo, *P* = 0.0039) (Figure 2), although there was no significant inter-group difference in RFS (43.9 ± 7.1 mo *vs* 36.8 ± 5.8 mo, *P* = 0.213).

Multivariate analysis of the variables that were found to be significant predictors of OS in the univariate analysis revealed that although AR (HR = 0.456, *P* = 0.039), ICGR15 (HR = 1.101, *P* < 0.001), tumor size (HR = 1.151, *P* = 0.001), vascular invasion (HR = 0.232, *P* < 0.001), blood loss (HR = 1.002, *P* = 0.001), serum aspartate transaminase level (HR = 1.024, *P* = 0.001), and serum HGF level
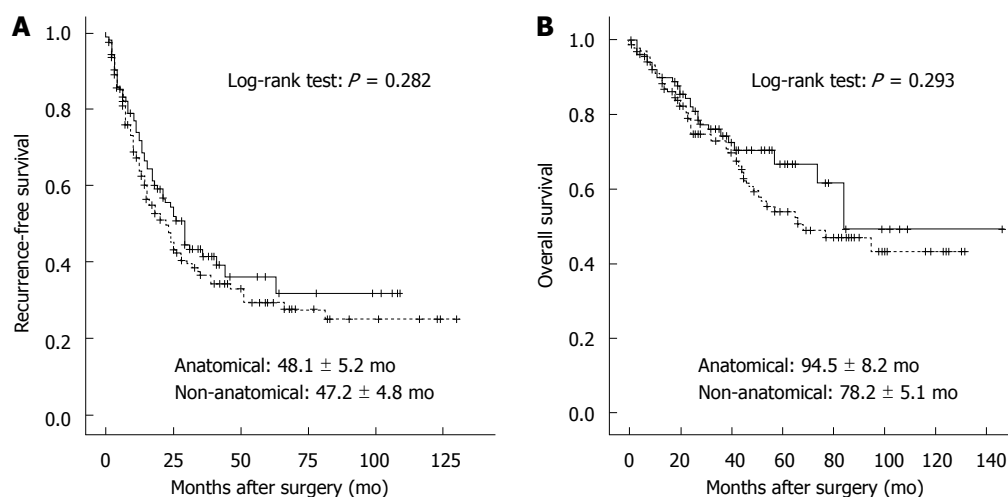
Figure 1 Recurrence-free survival (A) and overall survival (B) of hepatocellular carcinoma patients who underwent initial hepatectomy in the full analysis set. Anatomical resection (single line: *n* = 110); non-anatomical resection (dotted line: *n* = 158). *P* < 0.05 was considered to be significant.
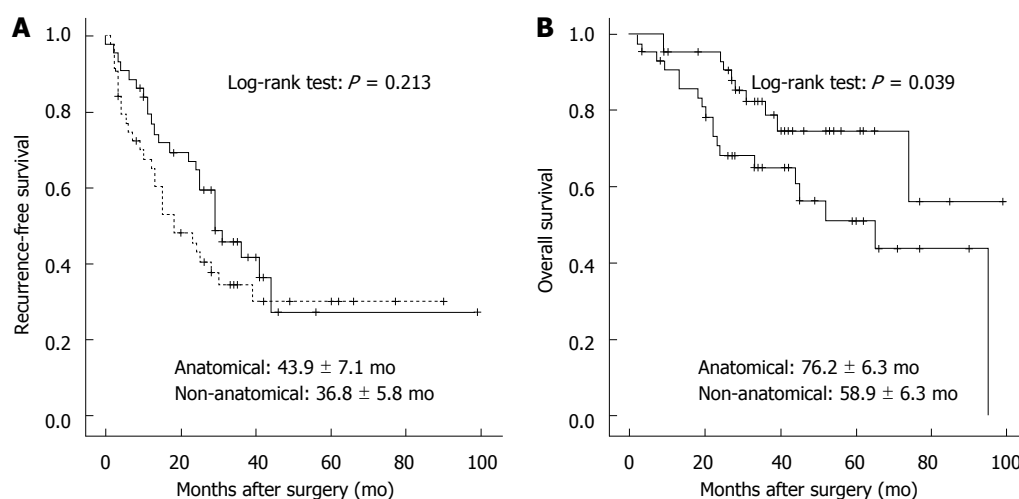

Figure 2 Recurrence-free survival (A) and overall survival (B) of hepatocellular carcinoma patients who underwent initial hepatectomy among the one-to-one propensity score-matched pairs. Anatomical resection (single line: *n* = 44); non-anatomical resection (dotted line: *n* = 44). *P* < 0.05 was considered to be significant.

(HR = 43.179, *P* = 0.015) were identified as prognostic factors in the univariate analysis, only vascular invasion (HR = 0.228, *P* = 0.002) and the HGF level (HR = 52.366, *P* = 0.035) were subsequently confirmed as independent prognostic factors in the multivariate analysis (Table 2).

DISCUSSION

We have demonstrated the survival benefit of AR compared with NAR for HCC patients who initially elect to undergo surgery, although the type of liver resection was not found to be an independent prognostic factor in the multivariate analysis. We have also demonstrated that propensity score-matched analysis can be used to compare specific therapies among selected subgroups.

AR for initial hepatectomy was selected for patients who possessed good liver function and reasonably sized tumors[11,14,18,19,24]. Although the initial backgrounds of the AR and NAR groups were significantly different, we successfully matched 44 patients from each group to produce pair with very similar clinical variables. In this matched patients, all cases attempted to select AR initially. AR is only qualified by the exposure of anatomical landmark, otherwise the others were defined as NAR. First of all, we need to examine the selection bias in this matched patient group. All of the matched patients belonged to Child-Pugh class A, had a mean tumor size of less than 5 cm, a mean tumor number of less than 1.5, and a mean BMI of less than 24. Therefore, our results were obtained under particular circumstances; *i.e.*, among lean patients with good liver function, tumors measuring less than 5 cm in diameter, and a small number of tumors (most patients only had one).

The prognosis of HCC patients after hepatectomy is determined by the balance between their liver function[4,25,26] and the characteristics of their tumors, such

Table 2 Univariate and multivariate analysis of prognostic factors in the one-to-one propensity score-matched pairs

Overall survival	Univariate analysis			Multivariate analysis		
Prognostic factors	HR	95%CI	*P* value	HR	95%CI	*P* value
Anatomical resection	0.456	0.211-0.983	0.039	0.546	0.205-1.453	0.226
Female gender	0.673	0.157-2.877	0.572			
Age	0.994	0.955-1.033	0.747			
Background (N + CH)	0.867	0.412-1.825	0.707			
Histology (W + M)	0.442	0.194-1.005	0.068			
Albumin	0.536	0.187-1.534	0.249			
Bilirubin	1.247	0.375-4.145	0.721			
Prothrombin time	0.984	0.951-1.019	0.371			
ICGR15	1.101	1.047-1.158	< 0.001	1.059	0.990-1.134	0.097
Tumor size	1.151	1.069-1.241	0.001	1.165	0.977-1.389	0.089
No. of tumors	1.075	0.728-1.588	0.723			
Absence of VI	0.232	0.109-0.496	< 0.001	0.228	0.092-0.568	0.002
Operative Time	1.003	0.999-1.006	0.189			
Blood loss	1.002	1.001-1.002	0.001	1.001	1.000-1.002	0.179
Blood transfusion	1.117	0.914-1.364	0.316			
Body mass index	0.957	0.839-1.091	0.509			
Platelets	1.023	1.000-1.047	0.109			
AST	1.024	1.012-1.037	0.001	1.010	0.994-1.026	0.209
ALT	1.005	0.992-1.019	0.472			
MELD	1.067	0.966-1.179	0.278			
BTR	0.772	0.557-1.068	0.084			
Hyaluronate	1.001	0.999-1.003	0.234			
HGF	43.179	2.321-803.29	0.015	52.366	1.310-2094.1	0.035
Alpha-fetoprotein	1.000	1.000-1.000	0.138			
PIVKA	1.000	1.000-1.000	0.534			

P < 0.05 was considered to be significant. N: Normal; CH: Chronic hepatitis; W: Well differentiated hepatocellular carcinoma; M: Moderately differentiated hepatocellular carcinoma; ICGR15: Indocyanine green retention rate at 15 min; VI: Vascular invasion; CI: Confidence interval; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; MELD: Model for end-stage liver disease; BTR: Branched chain amino acids to tyrosine ratio; HGF: Hepatocyte growth factor; PIVKA: Protein induced by vitamin K absence or antagonist.

as tumor size, tumor number, and vascular invasion[27,28]. Our matched pairs exhibited similar liver function and tumor characteristics before hepatectomy. One possible reason why AR was associated with better OS than NAR in the matched pair analysis is that liver function was preserved better after AR than after NAR. The patients' tumor characteristics were matched by propensity score analysis, and the insignificant difference in RFS among the groups in the matched pair analysis demonstrates that this was successful. The AR procedure basically involves the resecting of the whole segmental area fed by portal blood flow; and hence, few or no necrotic non-functioning areas remain after the procedure[13]. On the other hand, NAR only involves the resecting of the tumor margin and regions of the tumor that cross into other liver segments[16]. Therefore, NAR might leave intact necrotic tissue or areas of hypo-perfusion in which liver function could deteriorate. If the resected liver volume had been similar in both groups, liver function might have been better after AR than after NAR due to the size of the ischemic area. However, we did not compare liver function or the total liver volume after liver resection between the AR and NAR groups. Most patients were discharged soon after hepatectomy without suffering any serious adverse events (data not shown). The above mentioned hypothesis should be examined in a future study.

AR eradicates putative intrahepatic occult metastases from HCC[13,24]. Therefore, the local recurrence rate af-

ter AR might be lower than that after NAR. Indeed, the RFS curve of the AR was superior to that of the NAR within 24 mo after operation (RFS rate at 24 mo of AR was 59.7% *vs* that of NAR was 48.3%). However, RFS curves between the groups were becoming closer after 24 months after operation and the RFS periods of the AR and NAR groups eventually overlapped. Therefore, recurrence-free expectation of AR might be limited to within the early period after the operation. In addition, most recurrence was observed away from the resected segment in the NAR group (data not shown). This supports the hypothesis that HCC recurrence mainly involves multicentric tumor development rather than intrahepatic metastasis[15-17]. Therefore, no apparent RFS difference was observed between the AR and NAR although the OS of the AR was significantly longer than that of the NAR.

Oncological behavior, such as the size and number of tumors, also plays an important role in the prognosis of HCC patients after initial hepatectomy[29,30]. The Milan criteria[31] represent the gold standard method for predicting prognosis not only after liver transplantation[32] but also after liver resection[33,34]. Most studies that found that AR was associated with favorable outcomes recruited patients with single tumors of less than 5 cm in diameter (who would meet the Milan criteria) who had maintained good liver function. Our results generally support the findings of these reports, but some patients in our study had more than one tumor. Hence, our results suggest that

the indications for AR for HCC should be extended from only patients with single tumors to include patients with two small tumors. Further study is needed to determine the exact number and size of tumors that predict a better clinical outcome after AR.

Although selection bias was inevitable in the matched pair analysis, we obtained an interesting result in our Cox proportional hazards model-based multivariate analysis; *i.e.*, we identified two independent prognostic factors among the matched pair cases. Vascular invasion had already been identified as a significant prognostic factor in HCC[2,35,36]. The biological activity of HGF promotes the proliferation of both native[37,38] and malignant cells[39,40]. Both the serum HGF level and the incidence of HCC development increase with the progression of hepatitis and cirrhosis[4,41,42]. This suggests that a relationship exists between tumor progression and HGF activity in HCC patients. Although this might be unique to the specific subgroup of patients examined in the present study, the blockade of this biological pathway might represent a target of molecular therapy for HCC.

We compared the post-hepatectomy prognosis of HCC patients between patients that underwent AR and those that underwent NAR. Propensity score analysis successfully matched subjects from each group with similar liver function levels and tumor characteristics. Although RFS did not differ significantly between the groups, the OS of the AR group was significantly longer than that of the NAR group. Therefore, AR for HCC conveys a survival advantage over NAR in patients with tumors of less than 5 cm in diameter, single tumor, and good liver function.

ACKNOWLEDGMENTS

COMMENTS

Background
The optimal type of liver resection for hepatocellular carcinoma (HCC) has been debated and is divided into anatomic resection (AR) and non-anatomic resection (NAR). Meta-analysis of AR *vs* NAR has demonstrated the superiority of AR in specific subgroups. However, none of these reports were randomized control studies. To overcome the effects of patient background, performing multivariate analysis followed by propensity score-matched analysis makes it possible to compare elective groups whilst minimizing confounding factors in non-randomized retrospective studies. The aim of this study is to elucidate the prognostic differences among AR and NAR for HCC after matching gender, tumor characteristics, and liver function using propensity score analysis.

Research frontiers
Propensity matched analysis could compare the groups who had similar background of the clinical factors and features. Although it allows us to compare specific subpopulations, it can be alternative for randomized control study. We could conclude our clinical interests in specific circumstances after propensity matched analysis if the number of recruiting patients were large enough to obtain statistical significance.

Innovations and breakthroughs
The authors compared the post-hepatectomy prognosis of HCC patients between patients that underwent AR and those that underwent NAR. Propensity score analysis successfully matched subjects from each group with similar liver function levels and tumor characteristics. Although recurrence free survival did not differ significantly between the groups, the overall survival of the AR group was significantly longer than that of the NAR group.

Applications
AR for HCC conveys a survival advantage over NAR in patients with tumors of less than 5 cm in diameter, single tumor, and good liver function.

Terminology
AR is a resection of one or more segment which is characterized by Glisson's anatomy. On the other hand, NAR is a resection of the liver parenchyma regardless anatomic structure. AR tends to lose more liver parenchyma with liver proper function than NAR. If the liver function was maintained, AR was preferred to select for HCC resection. On the contrary, NAR was preferred if the liver function was deteriorated to avoid postoperative liver failure.

Peer review
This paper describes the prognosis comparison of HCC patients between patients that underwent AR and NAR using propensity score-matched populations. Further two independent prognostic factors have been found from multivariate analysis. This study provides the information for the prognostic advantage of AR in HCC patients.

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