Research Article

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# Complete removal of the tumor-bearing portal territory decreases local tumor recurrence and improves disease-specific survival of patients with hepatocellular carcinoma

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**Background & Aims**: Anatomic resection (AR) of the tumor-bearing portal territory has been reported to be associated with a decreased recurrence of hepatocellular carcinoma (HCC). However, because of the heterogeneity of the study populations, its oncologic advantage remains controversial. The objective of the present study was to determine the clinical advantage of AR for primary HCC, based on the data from a large prospective cohort treated under a constant surgical policy.

**Methods**: In 209 Child-Pugh class A patients with primary, solitary HCC measuring ⩽5.0 cm in diameter, which was resectable either by AR or limited resection (non-AR), the overall survival (OS) and disease-free survival (DFS) were compared with patients in whom complete AR was achieved and those who eventually ended up with non-AR after adjustment for the propensity scores to select AR. Advantages of AR in disease-specific survival and local recurrence were also evaluated by competing-risks regression to clarify the true oncologic impact of AR.

**Results**: The AR group showed better DFS than the non-AR group (HR, 0.67; 95% CI, 0.45–0.99; $p = 0.046$), while no significant difference was observed in OS (hazard ratio [HR], 0.82; 95% CI, 0.46–1.48; $p = 0.511$). Competing-risks regression revealed that AR significantly decreases local recurrence (HR, 0.12; 95% CI, 0.05–0.30; $p < 0.001$) and improves disease-specific survival (HR, 0.50; 95% CI, 0.28–0.90; $p = 0.020$), while the other cause of death was highly influenced by patient age (>65 years) (HR, 7.51; 95% CI, 2.16–26.04; $p = 0.002$) and not associated with AR.

**Conclusion**: Complete removal of tumor-bearing portal territory decreases the risk of local recurrence and death from HCC.



Keywords: Hepatocellular carcinoma; Anatomic resection; Surgery; Propensity score.

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*Abbreviations:* AR, anatomic resection; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; OS, overall survival; DFS, disease-free survival; PS, propensity score; IPTW, inverse probability of treatment weighting.

## Introduction

Liver resection is now accepted as the first line treatment for hepatocellular carcinoma (HCC) in patients with preserved hepatic function [1,2]. A recent retrospective study has reported that surgical resection may have a prognostic advantage over the radiofrequency ablation (RFA) especially in patients with solitary HCC [3]. However, the high incidence of postoperative recurrence remains a major issue even after curative resection of HCC [4–9].

Because HCC has a high propensity to invade the intrahepatic vascular structures and spreads mainly via the closest portal veins [10,11], systematic removal of the tumor-bearing portal territories, so called "anatomic resection (AR)", was proposed in the 1980s as a theoretically curative surgical procedure for HCC to eradicate potential micrometastases surrounding tumors [11]. To date, a number of retrospective studies and meta-analyses have reported that AR may reduce the risk of tumor recurrence and probably improve the survival [6,12–18], showing an evident correlation with decreased local tumor recurrence rate [14,16,19]. However, AR is usually indicated for patients with a relatively low degree of liver damage, and those with poor hepatic functional reserve tend to be treated by the reduced extent non-anatomic resection of the liver (non-AR). Therefore, a simple prognostic comparison between patients treated by AR and non-AR would necessarily entail selection bias, and the true prognostic advantage of AR remains controversial.

The objective of this study was to clarify the prognostic advantage of complete removal of the tumor-bearing 3rd-order portal territories using a propensity score (PS) analysis method, focusing on patients with primary, solitary HCC treatable either by AR or non-AR, selected from a large prospective cohort treated under a constant surgical policy.

## Patients and methods

### *Study population*

The subject pool consisted of 1298 consecutive patients who underwent curative liver resection for HCC between January 1994 and December 2011 at the

University of Tokyo Hospital. To clarify the pure prognostic impact of AR among patients who were treatable by either AR or non-AR, 1089 patients were excluded from the initial cohort due to following reasons: 1) recurrent tumor (n = 468); 2) multiple tumors (n = 455); 3) tumor greater than 5 cm (n = 293); 4) Child-Pugh class B (n = 142); 5) indocyanine green retention rate of ⩾30% (n = 117); 6) presence of macroscopic vascular invasion (n = 145); 7) tumor requiring resection of two or more Couinaud's segments (n = 266); 8) history of other malignancy within 5 years prior to surgery (n = 41); and 9) missing clinicopathologic data (n = 11). Data of the remaining 209 patients were analyzed in detail. Informed consent for clinical analysis was obtained from each patient and all the analyses were performed in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies of the University of Tokyo Hospital.

*Definition and indications of anatomic resection*

AR was defined as complete removal of one Couinaud's segment (i.e., Segment I through VIII) or a combination of contiguous territories of the "3rd-order" subsegmental portal venous branches smaller than one Couinaud's segment [11]. The indication for surgery was constantly based on an algorithm including the presence/absence of ascites, the serum total bilirubin level, and the results of the indocyanine green retention test as previously described [20]. All of the patients fulfilled the safety criteria for resection of at least one Couinaud's segment. However, a reduced extent of resection (i.e., non-AR) was eventually performed in some patients according to surgeon's intraoperative decision based on the surgical findings and/or physical status of patients.

*Technical details and quality control of the surgery*

First, the target territories of the tumor-bearing portal branches were stained using a blue dye (indigocarmine, Daiichi Sankyo Co., Ltd. Tokyo, Japan) by ultrasonically guided puncture of the corresponding portal branches (Supplementary Fig. 1A, B). Hepatic parenchymal transection was started along the segmental border confirmed on the liver surface. To secure complete removal of the target part of the liver, the landmark veins were exposed on the cut surface of the liver and the corresponding portal branches were ligated at the root of the segment (Supplementary Fig. 1C).

All the resections were performed exclusively by the attending hepatobiliary surgeons. All the surgical records and intraoperative photographs were reviewed and approved at a departmental meeting. In this study, only those surgical maneuvers in which all of the following four principal steps were completed were classified as AR: i) confirmation and marking of the segmental border by a segmental staining method; ii) parenchymal transection from the segmental border to the landmark veins; iii) full exposure of the land mark veins on the cut surface of the liver; and iv) ligation of the segmental portal pedicle near the root of the segment. Other surgical maneuvers, including incomplete removal of the tumor-bearing 3rd-order portal regions were classified as non-AR (Fig. 1).

*Patient follow-up*

All the patients were regularly screened for recurrences through monitoring of the plasma levels of the HCC-specific tumor markers every 1–2 months, ultrasonography every 2 months, and dynamic computed tomography every 4 months [21]. Recurrence was defined as the appearance of a new lesion having radiologic features compatible with HCC, as confirmed using at least two imaging modalities. When a recurrence was detected, the patient was aggressively treated further by repeat hepatectomy, locoregional ablation therapies including RFA or transcatheter arterial chemoembolization, or other treatment modalities, including systemic therapy, as appropriate.

In the present study, the following survival outcomes were recorded: 1) disease-free survival (DFS), defined as the interval between the operation and the date of diagnosis of the first recurrence or death; and 2) overall survival (OS), defined as the interval between the operation and the date of any cause of death. All the cases without specific events for each prognostic outcome were censored at the date of the last follow-up.

Cause of death was recorded for every patient. In addition, the types of recurrence were also recorded and compared between the groups. Local recurrence was defined as any recurrence observed in the residual part of the tumor-bearing 3rd-order portal branches after non-AR (Fig. 1B) or recurrence adjacent to the cut surface of the liver at the time of the initial tumor recurrence, irrespective of the presence of additional recurrences in other parts of the liver.

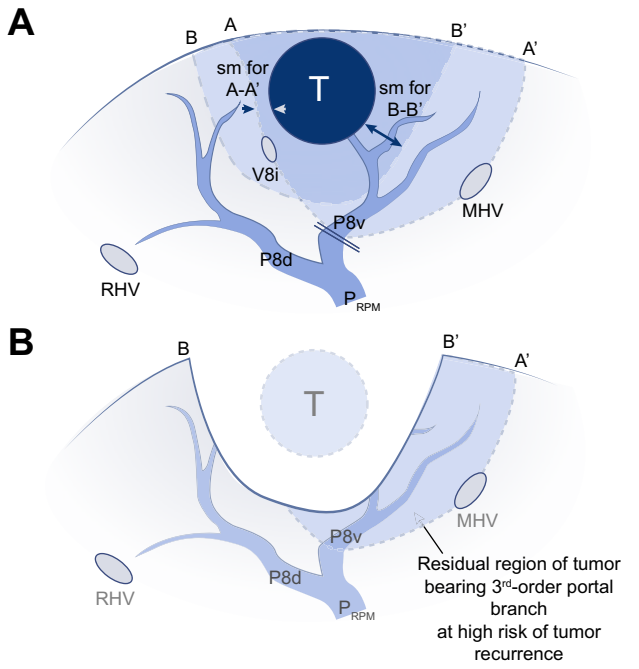


**Fig. 1. Anatomic resection and non-anatomic resection of the liver.** (A) Anatomic resection (A-A′) removes entire feeding part of the tumor-bearing portal branch bordered by the landmark veins, while non-anatomic resection (B-B′) is any other types of resection in which the tumor-bearing 3rd-order portal region is not fully removed. (B) After non-anatomic limited resection of liver tumor some part of the tumor-bearing portal region is left, which is at high risk of tumor recurrence. RHV, right hepatic vein; MHV, middle hepatic vein; V8i, intermediate vein for segment VIII; $P_{PRM}$, right paramedian pedicle; P8v, ventral branch of P8; P8d, dorsal branch of P8.

*Data analysis*

Statistical analysis was performed using the SAS 9.4 software (SAS institute inc., NC, USA). The medians and ranges of continuous data were compared using the Mann-Whitney *U* test. Categorical data were compared using Pearson's chi-squared test or Fisher's exact test, as appropriate. *p* values of <0.05 were considered to indicate statistical significance.

This study was designed to investigate the risk of leaving the tumor-bearing portal territories after non-AR, and to clarify the clinical impact of complete removal of such regions for primary HCC. To account for potential selection bias, PS to receive AR was adjusted by a stabilized inverse probability of treatment weighting (IPTW) method [22,23]. In stabilized IPTW, every patient was weighted by the inverse of the probability of receiving the treatment of interest (i.e., the PS in the treated patients and 1-PS in the untreated patients), and these weights were stabilized by the marginal overall prevalence of the treatment actually received. OS and DFS were then compared using the PS-adjusted pseudo-population created by this statistical procedure. Weighted survival curves were generated using the Kaplan-Meier method and compared by univariate Cox regression for the effect of AR.

Second, to further clarify the oncological impact of AR for primary HCC, efficacy of AR for disease-specific survival and local recurrence was also evaluated by a competing-risks regression model using the Fine & Gray method [24] in the original population. The other cause of death (i.e., non-HCC-related death) or the other patterns of recurrence (i.e., non-local recurrence) was treated as a competing event in the proportional subdistribution hazards models for the disease-specific survival or local recurrence, respectively.