Algorithm for Resecting Hepatocellular Carcinoma in the Caudate Lobe

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Objective: To propose an algorithm for resecting hepatocellular carcinoma (HCC) in the caudate lobe.

Background: Owing to a deep location, resection of HCC originating in the caudate lobe is challenging, but a plausible guideline enabling safe, curable resection remains unknown.

Methods: We developed an algorithm based on sublocation or size of the tumor and liver function to guide the optimal procedure for resecting HCC in the caudate lobe, consisting of 3 portions (*Spiegel*, *process,* and *caval)*. Partial resection was prioritized to remove *Spiegel* or *process* HCC, while total resection was aimed to remove *caval* HCC depending on liver function.

Results: According to the algorithm, we performed total (n = 43) or partial (n = 158) resections of the caudate lobe for HCC in 174 of 201 patients (compliance rate, 86.6%), with a median blood loss of 400 (10–4530) mL. Postoperative morbidity (Clavien grade ≥III b) and mortality rates were 3.0% and 0%, respectively. After a median follow-up of 2.6 years (range, 0.5–14.3), the 5-year overall and recurrence-free survival rates were 57.3% and 15.3%, respectively. Total and partial resection showed no significant difference in overall survival (71.2% vs 54.0% at 5 yr; $P = 0.213$), but a significant factor in survival was surgical margin (58.0% vs 45.6%, $P = 0.034$). The major determinant for survival was vascular invasion (hazard ratio 1.7, 95% CI 1.0–3.1, $P = 0.026$).

Conclusions: Our algorithm-oriented strategy is appropriate for the resection of HCC originating in the caudate lobe because of the acceptable surgical safety and curability.

Keywords: caudate lobe, hepatocellular carcinoma, liver anatomy, liver surgery

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Despite recent advances in liver surgery, resection of hepatocellular carcinoma (HCC) originating in the caudate lobe remains most demanding. After Couinaud serial definitions,[1,2] the caudate lobe of the liver is now well defined anatomically as the territory that is behind both the right and left hemilivers and is surrounded by the 3 components, such as the hepatic veins, hepatic hilum, and inferior vena cava (IVC), and subdivided into 3 portions.[3] The caudate lobe is supplied by, and drains into the proper vascular systems independently from those of both hemilivers.[4,5] Such a specific anatomical characteristic makes it difficult to resect HCC in the caudate lobe.[6]

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The strategy for safer liver resection is the priority,[7] because a caudate lobe HCC is located deeply and is close to the major vessels. Complete resection with a sufficient surgical margin seems tough to achieve, and combined resection with the adjacent hemi-liver or other segment is recommended in patients with good liver function.[8-10] On the other hand, most HCC patients have chronic hepatitis or cirrhosis, making limited resection of the caudate lobe an alternative procedure of choice.[11–13] However, even for such patients with diseased liver, small but ‘‘anatomic’’ resection for HCC is of clinical value to improve patients' survival.[14,15]

Based on the background, we previously developed 2 procedures for anatomic total resection of the caudate lobe, designed to systematically remove HCC: *high dorsal resection*[16,17] and *splitting anterior resection*.[18] Although such operations are safe and potentially curative,[15] complete resection of the caudate lobe alone remains technically challenging and thus applied infrequently.[6,16] To date, there is no consensus on how to standardize the procedure,[19] and plausible guidelines are therefore required to plan such a specific liver resection, based on characteristics of HCC or the patient's liver function.

In this study, we propose an algorithm for resecting HCC originating in the caudate lobe, considering the unique anatomy and diverse surgical options, to guarantee acceptable outcomes for patients.

METHODS

Patients

Between April 2001 and December 2017, the study group consisted of 1621 consecutive patients who underwent resection of HCC at 3 hospitals affiliated with Nihon University School of Medicine in Tokyo. A total of 201 patients were the target cohort to clarify the prognostic impact of resection for HCC originating in the caudate lobe. Informed consent was obtained from the patients, and analyses were performed in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies proposed by the committee of Nihon University Hospitals.

Anatomy

We have defined the caudate lobe of the liver as an independent domain with a unique configuration, which is located in the centro-dorsal region of the liver, under part of segments II, III, IV, V, and VIII, and at the left side of segment VII, resembling a joining pin of a fan.[4-6] In the 1950s, Couinaud first defined the caudate lobe (classified as segment I) as only the left protuberant dorsal part from Arantius' ligament (corresponding to Spiegel lobe),[1] and therefore it is of note that the ‘‘original'' Couinaud segment I is obviously smaller than the caudate lobe according to the current understanding.[3-6,16]

In accordance with Kumon classification by cast analyses,[3] we surgically classified the caudate lobe into 3 portions with the prominent landmarks: 1) *Spiegel* portion (left protruding part from Arantius' ligament), 2) *process* portion (right protruding part caudal to the right portal pedicle), and 3) *caval* portion (para-caval part like a "hidden portion" covered by the right and middle hepatic vein and bordered on the dorsal side by the right portal pedicle)[6,8,16] (Fig. 1). To date, no researcher has described the intrahepatic right border of the caudate lobe, but we propose here to define its border as the posterior surface of the right hepatic vein in situ, which can clearly discriminate segments VII and VI from the caudate lobe. Actually, we have used the counterstaining technique[20] in which blue-dye is injected into the posterior portal vein to identify the otherwise undefined right border of the caudate lobe during isolated total caudate lobectomy.[16,17]

The caudate lobe exhibits a distinct segmentation with the portal fissure that is indicated internally by the *Spiegel* portion hepatic vein and externally by Kogure's notch,[4] which is a vestige of the portal segmentation of the caudate lobe, as demonstrated in animal livers (Fig. 1). The lobe is fed by the proper portal vein branches (median 4; range 2–7), fanning out in the posterior direction from the portal confluence and left and right portal pedicles, and is drained by the proper hepatic vein branches (3; 2–4) and many short hepatic veins directly to the IVC.[4] The hepatic vein draining the *caval* portion runs between the posterior segment and *caval* portion, which corresponds to a short hepatic vein or inferior right hepatic vein.[5]

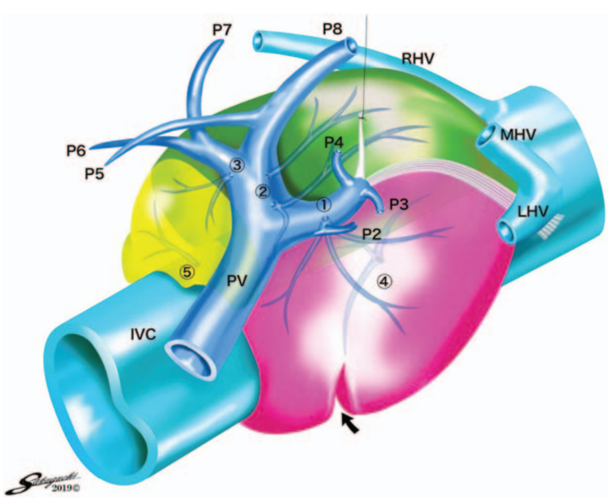

FIGURE 1. Caudate Lobe of Liver. The caudate lobe is dorsally located just behind the middle and right hepatic veins, and subdivided into the *Spiegel* portion (pink), *process* portion (yellow), and *caval* portion (green). The border between the *Spiegel* portion and *caval* portion is Arantius' ligament, and that between the *process* portion and *caval* portion is the right portal pedicle. The caudate lobe proper portal veins (median 4) arise from the left and right portal pedicles, and the hepatic veins (median 2) with many short hepatic veins drain directly into the IVC. PV indicates portal vein; P2-8, portal venous branch to segment II-VIII; ① P*s*, portal venous branch to *Spiegel* portion; ② P*c*, portal venous branches to *caval* portion; ③ P*p*, portal venous branch to *process* portion; ④ sHV, *Spiegel* portion hepatic vein; ⑤ *p*HV, *process* portion hepatic vein. Arrow indicates Kogure's notch.[4]

Indications

We published in 1998 a preliminary policy for resecting HCC in the caudate lobe,[8] and determined in 2001 an algorithm to propose the procedure, based on the tumor sublocation, tumor size, and the indocyanine green retention rate at 15 minutes (ICG-R$_{15}$). Because the algorithm has not appeared in an official journal, this study has been done retrospectively. In this series, liver resection was indicated only for patients with less than 3 nodules of HCC; the biggest nodule should exist in the caudate lobe, and others were presumed to be metastases or multicentric HCC.[21]

Basically, the acceptable hepatic volume to be resected was defined according to the Makuuchi criteria.[22] Removal of about two-thirds of the liver was permitted when ICG-R$_{15}$ was $<$10% (indicating normal liver), removal of one-third when ICG-R$_{15}$ was $<$20% (chronic hepatitis), and removal of one-sixth when ICG-R$_{15}$ was $<$30% (cirrhosis), respectively. In the hospital where the ICG test is unavailable, background liver status will be assessed on the basis of gross findings or biopsy on laparotomy.

In patients with HCC ($<$3 cm) localized in the *Spiegel* or *process* portion (Fig. 2), "partial resection" (PR) of each portion was indicated, while in those with large HCC ($\geqq$3 cm) and good ICG-R$_{15}$ ($<$10%) left hemihepatectomy (LH) for *Spiegel*-HCC or right hemihepatectomy (RH) for *process*-HCC was the first procedure of choice, and in those with ICG-R$_{15}$$\geqq$10% PR or ventral resection (VR)[23] was the first option. On the other hand, in patients with HCC ($\geqq$3 cm) in the *caval* portion, "total resection" by RH was the first procedure of choice in those with ICG-R$_{15}$$<$10%, but when cirrhosis was confirmed on laparotomy we have preferred VR to hemihepatectomy to avoid a risk of liver failure. Irrespective of tumor size, VR was the first procedure in patients with ICG-R$_{15}$ between 10% and 20%, and dorsal resection (DR)[16] was the choice in those with ICG-R$_{15}$$\geqq$20%, indicating cirrhosis.[22]

For multiple tumors, we performed independent resection for other segment (s), or *en-bloc* resection of the caudate lobe extending to other segment (s).

Operation

In this series, "total resection" (equivalent to anatomic resection) of the caudate lobe was defined as removing completely the entire caudate lobe consisting of 3 portions *en-bloc*, and other procedures were considered "partial resection" (nonanatomic resection) of the lobe. Hepatic parenchymal transection was performed under ultrasonographic guidance by the clamp-crushing method with Pringle maneuver.[24–26] Postoperative management and follow-up were done as described elsewhere.[27,28]

Two consultant liver surgeons (T.T. and T.H.) performed operations in 165 patients. The first surgeon had done approximately 3500 liver resections and 200 living liver transplantations, and the second had performed 1000 resections. Nine resident surgeons (who had done or assisted with at least 100 liver resections) did the operations in 36 patients while being assisted by the consultant.

1) Dorsal resection

Through a dorsal approach, this is an isolated total caudate lobectomy for *caval* HCC in cirrhosis (Fig. 3A, B). High dorsal resection' (Takayama procedure)[16,17,29] enables removal of 3 portions of the caudate lobe *en-bloc* without sacrificing any other part of the liver. In brief, the counterstaining technique[20] was used to identify the right-side border of the caudate lobe. Liver transection initiated from the stained border proceeded cranially toward the posterior surface of right and middle hepatic veins, and reached "dorsally" as "high" as the root of the veins. On the resected plane, both posterior surfaces of the right and middle hepatic veins were exposed completely.

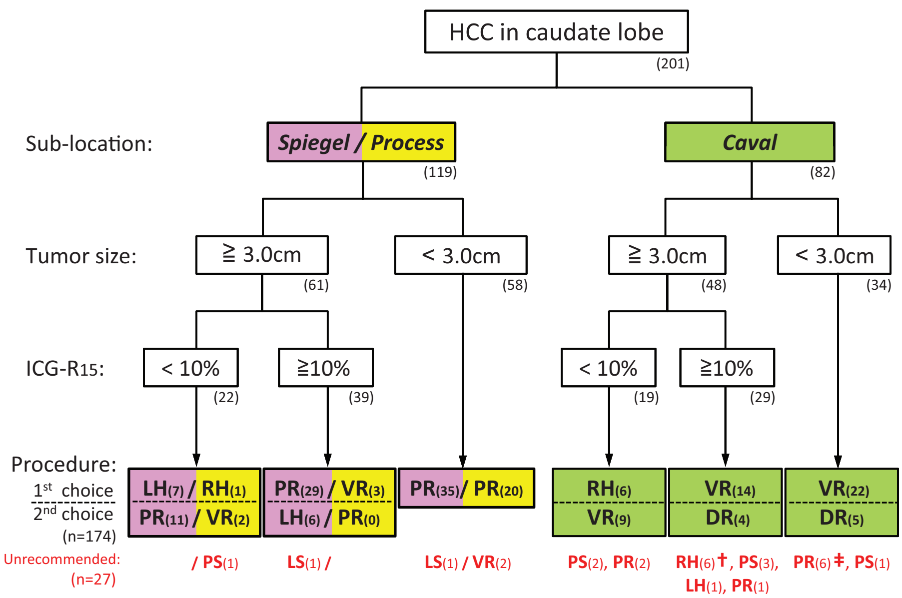

FIGURE 2. Algorithm for Resecting Caudate Lobe HCC. For *Spiegel* or *process* HCC (n = 119), the 1st (n = 95) and 2nd (n = 19) or unrecommended (n = 5) procedures were performed, respectively. For *caval* HCC (n = 82), the 1st (n = 42) and 2nd (n = 18) or unrecommended (n = 22) procedures were performed, respectively. Our recommendation was the first procedure of choice in the first row, the second procedure in the second row, and unrecommended procedure (in red) in the bottom row. †Right hemi-hepatectomy was performed (n = 6) because of confirming left hemi-liver hypertrophy (43%–55% in volume). ‡Partial resection was performed (n = 6) due to identifying a superficial tumor on the dorsal surface of the liver. PS indicates posterior segmentectomy; LS, lateral segmentectomy; VR, ventral resection; DR, dorsal resection. The parentheses indicate the number of patients.

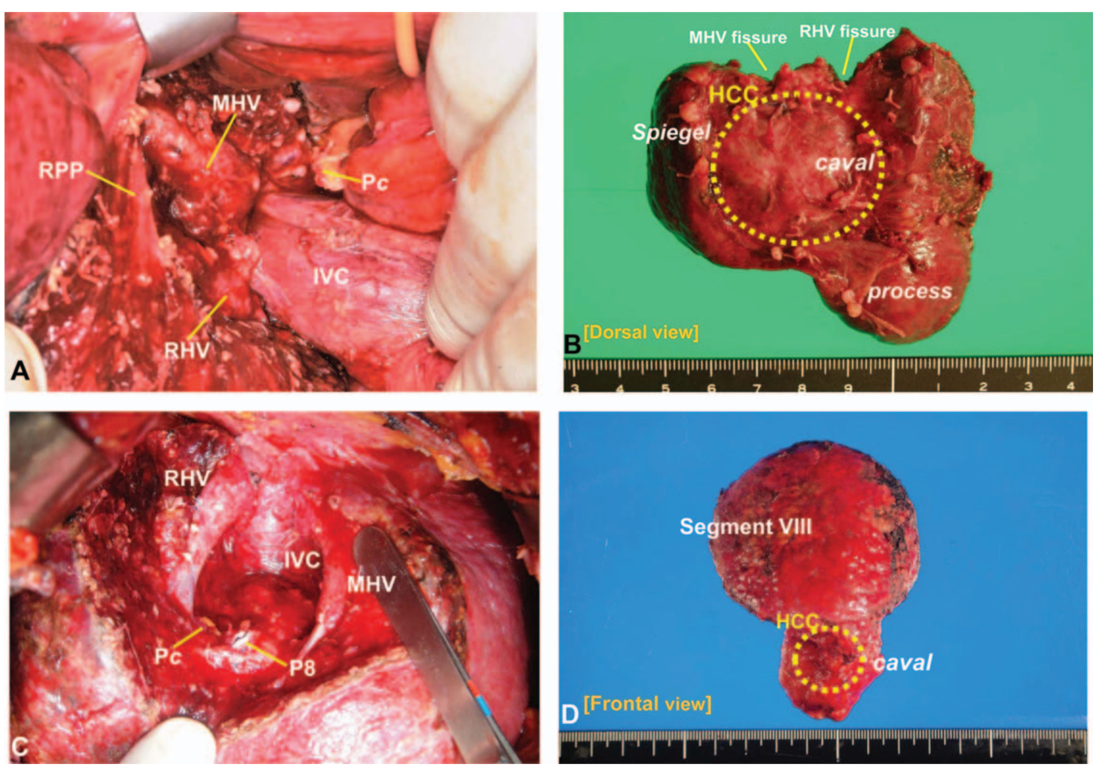

FIGURE 3. Dorsal and Ventral Resection of Caudate Lobe. After high dorsal resection (A), middle hepatic vein (MHV), right hepatic vein (RHV), inferior vena cava (IVC), right portal pedicle (RPP), and a stump of the portal venous branch to *caval* portion (P*c*) are exposed on the resected surface, and the resected specimen (B) shows 3 portions of the caudate lobe *en-bloc* (*Spiegel*, *process*, and *caval*) including *caval* HCC (4.2 cm in diameter) [Dorsal view]. Note the fissures for MHV and RHV seen just above the HCC, indicating that dorsal resection can reach as ''high'' as the root of both hepatic veins. After ventral resection with segment VIII (C), MHV, RHV, IVC, and the stumps of portal venous branch to segment VIII (P8) and *caval* portion (P*c*) are exposed, and the specimen (D) shows segment VIII extended to include *caval* HCC (2.2 cm in diameter) [Frontal view].

2) Ventral resection

Through a ventral approach, we developed an extended segmentectomy to the caudate lobe involving a neighboring segment, such as segments VIII to IV (Fig. 3C, D).[23] One segment most closely located to an HCC was selected, and the segmentectomy was advanced deeply to 1 or 2 portions of the caudate lobe. Representatively, extended segment VIII resection based on Makuuchi procedure[30] was initiated along the segmental border identified by the staining technique, proceeded along the trunks of middle and right hepatic veins to be exposed, and reached most deeply to the dorsal surface of the *caval* portion to remove HCC *en-bloc* with segment VIII.

According to the modified Clavien–Dindo classification,[31] postoperative complications were categorized into 7 grades, and morbidities were defined as complications with a score of grade IIIb or higher. Complications specific to liver surgery were defined as described previously.[27,28]

Analysis

Data collected from the 2 groups of total and partial resection were statistically analyzed with Fisher exact test and the Wilcoxon rank-sum test. Survival curves were generated using the Kaplan–Meier method and compared by the log-rank test. Prognostic factors for patients' survival and the recurrence of HCC were identified with the Cox proportional hazards regression model, and a P value of less than 0.10 was set as the cut-off value for elimination. The 17 variables were examined as potential confounders to define independent prognostic variables. In all analyses, P values of < 0.05 were considered to indicate statistical significance.

RESULTS

Characteristics

Among the 1621 patients who underwent resection of HCC, 201 (12.4%) had HCC originating in the caudate lobe. We performed total (anatomic) resection of the lobe (3 portions *en-bloc*) in 43 patients (21.4%) and partial (nonanatomic) resection in 158 patients (78.6%) (Table 1). Between the groups, 7 of the patients' characteristics differed significantly. As compared with the partial resection group, the total resection group had a more platelet, lower ICG-R_{15} level, and higher DCP level.

Algorithm

Among 9 procedures for liver resection (Table 2), 43 patients underwent total resection of the caudate lobe by extended LH or RH, high DR, and extended posterior segmentectomy, while the 158 patients underwent partial resection of the *Spiegel* portion, *process* portion, *caval* portion, or VR combined with segment VIII to IV, and extended lateral segmentectomy, respectively.

According to the algorithm (Fig. 2), we performed the recommended procedure in 174 patients of the 6 subgroups (compliance rate, 86.6%). For *Spiegel/process* HCC ($\geqq$3 cm) (n = 61), we first performed LH for *Spiegel* HCC (n = 7) or RH for *process* HCC (n = 1) in patients with ICG-R_{15}<10%, and did PR (n = 29) or VR (n = 3) in those with ICG-$R_{15}\geqq$10%. As the second choice, LH was done in 6 patients because the HCC was too large (median 6.3 cm, range 4.0–15.0) to enucleate and their ICG-R_{15} (less than 20%) permitted the selection. For the small (<3 cm) HCC (n = 58), PR of *Spiegel* portion (n = 35) or *process* portion (n = 20) was a single option.

For *caval* HCC ($\geqq$3 cm) (n = 48), we first performed RH (n = 6) and secondarily did VR (n = 9) in patients with ICG-R_{15}<10%, while VR (n = 14) or DR (n = 4) was the option in those with ICG-$R_{15}\geqq$10%. For small (<3 cm) HCC (n = 34), VR (n = 22) or DR (n = 5) was also the procedure.

By contrast, unrecommended procedures were performed in 27 patients (13.4%) because of severe cirrhosis (n = 17), right portal embolization (n = 6), and the surgeons' preference (n = 4) (Fig. 2). For example, 6 patients with *caval* HCC ($\geqq$3 cm, ICG-$R_{15}\geqq$10%) underwent RH because the tumors were large (median 10.0 cm, range 4.5–15.0) enough to attach to the biliaro-vascular connections at the hepatic hilum, after confirming hypertrophy of the left hemiliver caused by embolization (n = 3) or tumor thrombi (n = 3) of the right portal vein.

For 50 patients with multiple tumors, independent resection for other segment (s) underwent in 40 patients, and *en-bloc* resection with hemi-liver (n = 3) or other segment (s) (n = 7) in 10 patients.

TABLE 1. Patient Characteristics

Characteristic	Overall (n = 201)	Total Resection (n = 43)	Partial Resection (n = 158)	P^*
Age, yr	69 (32–85)	65 (44–82)	68 (32–85)	0.045
Male, n (%)	156 (77.6)	33 (76.7)	123 (77.8)	0.839
Body mass index, kg/m^2	23.3 (15.5–36.9)	22.2 (18.3–34.9)	23.2 (15.5–36.9)	0.291
Hepatitis B, n (%)†	36 (17.9)	6 (14.0)	30 (19.0)	0.509
Hepatitis C, n (%)	101 (50.2)	12 (27.9)	89 (56.3)	0.001
Bilirubin, mg/dL	0.6 (0.2–1.6)	0.6 (0.3–1.1)	0.6 (0.2–1.6)	0.626
AST, U/L	35 (11–265)	34 (11–157)	35 (13–265)	0.728
ALT, U/L	32 (7–296)	29 (10–107)	34 (7–296)	0.976
Prothrombin time, %	100 (53–100)	100 (70–100)	98 (53–100)	0.605
Albumin, g/L	4.0 (2.6–5.0)	4.1 (3.2–4.9)	4.0 (2.6–5.0)	0.478
Platelet, 10^5/L	14.5 (1.6–66.5)	18.4 (5.6–66.5)	13.9 (1.6–41.3)	<0.001
Child-Pugh A, n (%)	175 (87.1)	41 (95.3)	134 (84.8)	0.076
ICG-R_{15} (%)	11.6 (2.3–82.3)	10.0 (2.3–25.0)	13.3 (4.3–82.3)	<0.001
Cirrhosis, n (%)	77 (38.3)	9 (20.9)	68 (43.0)	0.008
α-fetoprotein, ng/mL	12 (1–42,030)	17 (1–42,030)	11 (1–9578)	0.580
DCP, AU/mL	65 (8–75,000)	238 (10–75,000)	49 (8–68,283)	0.001
Esophageal varices, n (%)	36 (17.9)	2 (4.7)	34 (21.5)	0.012
Diabetes mellitus, n (%)	58 (28.6)	14 (32.6)	44 (27.8)	0.571

Data were presented as median (range), if not specified.
*P value was calculated between total resection and partial resection groups.
†Three patients had both hepatitis B and C infection.
AST indicates aspartate transaminase; ALT, alanine transaminase; ICG-R_{15}, indocyanine green clearance rate at 15 minutes; DCP, des-gamma-carboxy prothrombin.

TABLE 2. Operative Outcomes

Outcome	Overall (n = 201)	Total Resection (n = 43)	Partial Resection (n = 158)	P^*
Procedure				–
Left hemihepatectomy†	14 (7.0)	14 (32.6)	–	
Right hemihepatectomy†,‡	13 (6.5)	13 (30.2)	–	
High dorsal resection§	9 (4.5)	9 (20.9)	–	
Posterior segmentectomy†	7 (3.5)	7 (16.3)	–	
Spiegel resection	66 (32.8)	–	66 (41.8)	
Ventral resection¶	52 (25.9)	–	52 (32.9)	
Process resection	29 (14.4)	–	29 (18.4)	
Caval resection	9 (4.5)	–	9 (5.7)	
Lateral segmentectomy†	2 (1.0)	–	2 (1.3)	
Operation				
Blood loss, mL	400 (10–4530)	590 (65–4530)	356 (10–2688)	0.002
Blood transfusion, n (%)	16 (8.0)	5 (11.6)	11 (7.0)	0.227
Operation time, min	406 (113–1004)	504 (320–903)	385 (113–1004)	<0.001
Thoracotomy, n (%)	110 (54.7)	31 (72.1)	79 (50.0)	<0.001
Margin positive,‖n (%)	32 (15.9)	5 (11.6)	27 (17.1)	0.485
Complication, n%				
Overall	76 (37.8)	15 (34.9)	61 (38.6)	0.724
Morbidity**	6 (3.0)	1 (2.3)	5 (3.2)	0.774
Mortality	0	0	0	1
Reoperation	4 (2.0)	0	4 (2.5)	0.579
Bile leakage	13 (6.5)	3 (7.0)	10 (6.3)	0.878
Bleeding	1 (0.5)	0	1 (0.6)	1
Abdominal infection	14 (7.0)	5 (11.6)	9 (5.7)	0.184
Portal vein thrombus	2 (1.0)	1 (2.3)	1 (0.6)	0.382
Hepatic insufficiency	2 (1.0)	1 (2.3)	1 (0.6)	0.382
Ascites	11 (5.5)	2 (4.7)	9 (5.7)	0.789
Pleural effusion	23 (11.4)	4 (9.3)	19 (12.0)	0.789
Atelectasis	11 (5.5)	2 (4.7)	9 (5.7)	0.789
Heart failure	1 (0.5)	1 (2.3)	0	0.213
Wound infection	9 (4.5)	1 (2.3)	8 (5.1)	0.687
Others	8 (4.0)	0	8 (5.1)	0.206
Hospital stay, day	13 (6–99)	13 (7–93)	13 (6–99)	0.679
Pathology				
Size, cm	3.0 (0.7–15.0)	5.3 (1.8–15.0)	2.8 (0.7–12.5)	<0.001
Multiple, †† n (%)	50 (24.9)	6 (14.0)	44 (27.8)	0.073
Vascular invasion,‡‡n (%)	54 (26.9)	20 (46.5)	34 (21.5)	0.001
Tumor exposure,§§n (%)	10 (5.0)	0	10 (6.3)	0.123

Data were presented as median (range), if not specified.
**P* value was calculated between total resection and partial resection groups.
†Extended form of original procedure was applied.
‡Three patients underwent a partial resection of inferior vena cava followed by primary closure.
§Anatomic isolated total caudate lobectomy.[16]
¶Extended segmentectomy to caudate lobe.[23]
‖Defined as an exposure of tumor (R1) at the shallowest surgical margin macroscopically.[32]
**Defined as a complication with a Clavien's grade of IIIb or greater.
††50 patients had multiple tumors (37 had 2 HCCs, 8 had 3, and 5 had 4 or more).
‡‡Included microscopic tumor thrombi in the portal vein, hepatic vein, or bile duct.
§§Defined as an exposure of tumor cells at the surgical margin microscopically.[32]

Morbidities

In the study group as a whole, the median blood loss was 400 mL (10–4530), and blood transfusion was required in 16 patients (8.0%) (Table 2). As compared with partial resection, total resection required a significantly larger blood loss (590 vs 356 mL, $P = 0.002$) and longer operation time (504 vs 385 min, $P < 0.001$).

Between the 2 groups, there was no significant difference in the overall morbidity (34.9% vs 38.6%), or major morbidity (grade≧IIIb) (2.3% vs 3.2%). There was no operative mortality in either group. Reoperation was required because of bile leakage, bleeding, or abdominal infection in 4 patients who underwent partial resection. Portal vein thrombus or hepatic insufficiency (grade IVa) was seen in 1 patient in each group, who recovered within 30 days with medication. The median hospital stay was 13 days in both of the groups.

Pathologically, total resection was performed in the patients with significantly bigger tumors (5.3 vs 2.8 cm, $P < 0.001$), and was associated with more frequent vascular invasion in the resected specimen (46.5% vs 21.5%, $P = 0.001$) than was partial resection. After total resection there was no tumor exposure in the resected specimen.

Survival

After a median follow-up of 2.6 years (range, 0.5–14.3) in all of the 201 patients, the 5-year overall and recurrence-free survival rates were 57.3% and 15.3%, and the median survival periods were 6.3 years (95% CI 4.6–7.3) and 1.8 years (1.4–2.1), respectively. As for the operation procedure, total versus partial resection of the caudate lobe showed no significant difference in overall survival ($P = 0.213$; 71.2% vs 54.0% at 5 yrs) (Fig. 4A), or recurrence-free

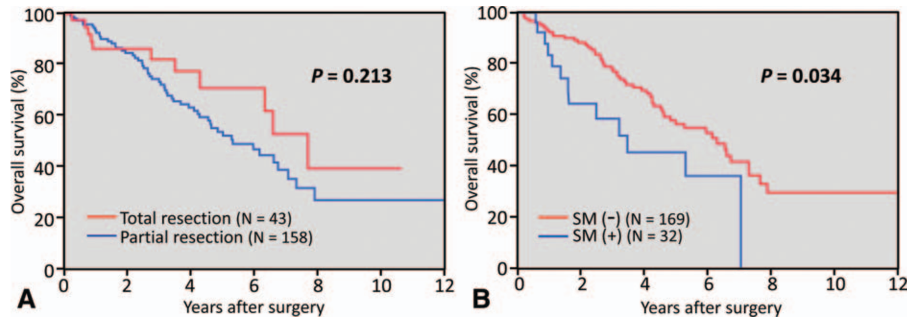

FIGURE 4. Survival after Resecting Caudate Lobe HCC. A, Kaplan–Meier estimates of overall survival after total (n = 43) or partial resection (n = 158). There was no significant between-group difference ($P = 0.213$). The 5-year survival rates were 71.2% versus 54.0%, respectively. B, The overall survival after resection with surgical margin (SM) negative (n = 169) or that with SM positive (n = 32) shows a significant difference ($P = 0.034$) with the 5-year survival rates of 58.0% versus 45.6%, respectively.

survival ($P = 0.897$; 6.1% vs 17.1%), respectively. In the subgroup analysis, surgical margin (negative vs positive) showed a significant difference ($P = 0.034$; 58.0% vs 45.6%) (Fig. 4B), but tumor location (*Spiegel/process* portion vs *caval* portion) showed a borderline significance ($P = 0.054$; 63.4% vs 49.1%).

On analysis with a Cox model (Table 3), the major determinants for survival were esophageal varices (hazard ratio 2.0; 95% CI 1.1–3.4, $P = 0.008$) and vascular invasion (1.7; 1.0–3.1, $P = 0.026$), and those for recurrence of HCC were multiple tumor (2.2; 1.4–3.4, $P < 0.001$) and alcohol (1.5; 1.0–2.2, $P = 0.035$).

DISCUSSION

According to our algorithm, we have resected the caudate lobe harboring HCC in 201 patients through an either partial or total maneuver in the 2 decades, resulting in favorable operative safety (major morbidity 3.0%, mortality 0%) and patients' survival (median 6.3 [95% CI 4.6–7.3] years, 57.3% after 5 yrs), indicating that our surgical strategy is recommended as a standard option of choice.

The surgical anatomy of the caudate lobe of the liver has remained confusing, mainly because Couinaud's definition had changed over the years.[1,2] Historically, in the 1950s Couinaud 1) first defined the caudate lobe (Segment I) as only the left protruding part from Arantius' ligament (corresponding to Spiegel's lobe); 2) redefined the lobe in 1989 as the "dorsal liver" including a territory dorsal to the hepatic veins, with division into 2 subsegments (Segment I *right* and *left*); 3) designated Segment I *right* in 1994 as Segment IX with no clear definition of its border; 4) expanded the definition of Segment IX in 1998 to include the periphery of the IVC, which was further subdivided to *d* and *b*; but finally 5) abandoned his own concept of Segment IX in 2002.[2] Such rapid changes in nomenclature made it difficult for the surgical community to maintain consistency of the definition for the caudate lobe.[6] Independently, however, Kumon[3] first classified by using 23 corrosion liver casts the caudate lobe into 3 portions in 1985, which has been the prototype definition for our surgical series (Fig. 1),[6,8,16,17,23] and Kogure et al detailed by examining 88 human livers in 2000 the structure of portal and hepatic veins proper to the caudate lobe.[4,5] Through an era of confusion, the anatomy of the caudate lobe is now well defined mainly by 2 Japanese surgeons, Kumon[3] and Kogure et al[4] (*double Ks*), to optimize indications and interventions for liver surgery.

Resection of HCC in the caudate lobe remains difficult to achieve owing to its deep location and adjacent major vessels, especially in patients with chronic liver disease. To guarantee safety

TABLE 3. Prognostic Variables

	Survival				Recurrence			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (≥75 vs <75 yr)	2.0 (1.1–3.5)	0.017	1.9 (1.0–3.5)	0.028	1.4 (0.9–2.0)	0.121		
Alcohol	0.9 (0.5–1.5)	0.697			1.4 (0.9–2.1)	0.059	1.5 (1.0–2.2)	0.035
Diabetes mellitus	1.9 (1.1–3.2)	0.011	1.6 (0.9–2.8)	0.060	1.3 (0.8–1.9)	0.184		
Child-Pugh class (A vs B)	1.4 (0.6–2.5)	0.350			1.4 (0.8–2.2)	0.131		
ICG-R_{15} (≥15 vs <15%)	1.3 (0.7–2.1)	0.283			1.1 (0.7–1.5)	0.568		
α-fetoprotein (≥100 vs <100 ng)	1.3 (0.7–2.2)	0.264			1.3 (0.8–1.9)	0.159		
DCP (≥100 vs <100 ng)	1.1 (0.7–1.8)	0.540			1.3 (0.9–1.9)	0.079	1.2 (0.8–1.8)	0.186
Esophageal varices	2.0 (1.2–3.4)	0.008	2.0 (1.1–3.4)	0.008	1.4 (0.9–2.1)	0.105		
Tumor location*	1.5 (0.9–2.5)	0.055			1.0 (0.7–1.4)	0.928		
Resection (total vs partial)	0.7 (0.4–1.3)	0.206			0.9 (0.6–1.4)	0.897		
Operation time (≥6 vs <6 h)	1.1 (0.7–1.8)	0.534			1.0 (0.7–1.5)	0.775		
Blood loss (≥600 vs <600 mL)	1.2 (0.7–2.0)	0.374			1.3 (0.9–2.0)	0.106		
Blood transfusion	1.5 (0.6–3.0)	0.291			1.2 (0.6–2.1)	0.458		
Tumor size (≥3 vs <3 cm)	1.0 (0.5–1.7)	0.983			1.2 (0.7–1.8)	0.382		
Multiple tumor	1.7 (1.0–2.8)	0.046	1.1 (0.6–2.1)	0.588	2.3 (1.5–3.3)	<0.001	2.2 (1.4–3.4)	<0.001
Vascular invasion	1.6 (1.0–2.6)	0.043	1.7 (1.0–3.1)	0.026	1.3 (0.9–1.9)	0.073	1.0 (0.7–1.5)	0.700
Surgical margin†	1.9 (1.0–3.4)	0.051			1.3 (0.8–2.0)	0.227		

*Spiegel/process portion vs caval portion.
†Margin positive vs negative microscopically.
HR indicates hazard ratio; 95% CI, 95% confidence interval; ICG-R_{15}, indocyanine green clearance rate at 15 minutes; DCP, des-gamma-carboxy prothrombin.

and curability, a decision-making system for surgery is crucial,[7,8,22] but no guidelines have emerged for resection of caudate lobe HCC. Recently, a proposal for novel hepatectomy[32] can be advisable for such marginally resectable tumors as caudate lobe HCC from a parenchyma-sparing perspective.[16,23] On the basis of our surgical experience, we have first proposed an algorithm consisting of 3 clinical factors (tumor sublocation, size, and ICG-R_{15}) to recommend the hepatectomy procedure of choice for patients with various background livers. In this series, the 201 patients underwent a liver resection that was selected among 9 procedures, including 4 types for total (anatomic) resection and 5 for partial (nonanatomic) resection. As a result, 27 patients (13.4%) did not undergo a recommended procedure based on the 3 reasons described before, and therefore our compliance rate (86.6%) with the algorithm was satisfactory. Importantly, our surgical policy is simple and feasible for selecting the optimal procedure for removing caudate lobe HCC.

Our algorithm recommends the 1st and 2nd best types of procedures for each of the 6 subgroups (Fig. 2). Accordingly, we prioritized ''partial resection'' for removing HCC arising in the *Spiegel* or *process* portion (n = 119), which is a ''semiexposed portion'' located independently from other segments. Actually, partial resection was performed predominantly in the 3 subgroups for HCC in the *Spiegel* and *process* portion (n = 95), while LH (n = 13) was indicated only when the HCC was larger than 4.0 cm. On the other hand, ''total resection'' combined with adjacent hemi-liver or segment was prioritized for removing HCC arising in the *caval* portion (n = 82), which exists as a ''hidden portion'' just behind both hemi-livers. Eventually, we performed RH (n = 6) or DR[16] (n = 9). In the other patients, VR[23] (n = 45) was performed through combined resection of segments VIII to VI.

Unexpectedly (Fig. 2), in the *Spiegel/process* group (ICG-R_{15}<10%) the number of patients who underwent the 1st procedure (LH (7) plus RH (1)) was lower than those who underwent 2nd procedure (PR (11) plus VR (2)), and in the *caval* group (ICG-R_{15}<10%) the 1st procedure (RH (6)) was less applied than the second (VR (9)). This consequence suggests that we tended to select the 2nd procedure as a smaller type of partial or VR even if a good liver function would permit hemi-hepatectomy,[22] indicating a paradigm shift from standard major procedure toward a parenchyma-sparing approach.[33] Moreover, our conversion rate to unrecommended procedure was significantly higher in the *caval* group (22 of 82 patients, 26.8%) than that in the *Spiegel/process* group (5 of 119 patients, 4.2%) ($P < 0.0001$), suggesting that a resection for *caval* HCC is more demanding and multifactorial. A *caval* group (HCC ≧ 3.0 cm, ICG-R_{15} ≧ 10%) being the group with the highest unclassified patients included 11 patients of 29 (38%) who underwent unrecommended procedure because they were the group carrying the highest surgical risk. For example, we preferred to perform RH after embolization of the right portal vein, because HCCs were too large (median 10.0 cm) to undergo the recommended small procedure (VR or DR) on the standpoint to guarantee a safer surgery.[7] By adhering to the algorithm, we successfully selected and performed the optimal procedure in patients undergoing such specific liver resections.

The operative outcomes were compared between total and partial resection (Table 2). The results were related significantly to the aggressiveness of the operation; in total resection, blood loss, operative time, and thoracotomy were significantly higher. Total resection underwent for patients with larger tumor (median 5.3 vs 2.8 cm), and thus microvascular invasion was higher (46.5% vs 21.5%) than partial resection. In general, the postoperative complication is likely higher because caudate lobe resection is more complicated than other standard hepatectomies. In this study, however, our operative complications (37.8%), most of which were Clavien's classification I or II (Table 2), represented no more common than those reported in the recent 2 decades (25%–60%).[9,10,13,34,35] In fact, only 6 patients had morbidity (3.0%), and 4 patients required reoperation (2.0%). Although others reported operative mortality (8.3%[13] and 2.2%[34]) in 2 series, there was no operative death in either group in our series. Most of the Grade III a complications were bile leakage (6.5%), abdominal infection (7.0%), and pleural effusion (11.4%). Such a favorable outcome is attributed partly to limited blood loss (median, 400 mL) during operation, which would contribute to reduce the risk of postoperative complications, as we have demonstrated by spline regression analysis.[28] Thus, our algorithm-oriented surgery is appropriate for guaranteeing a safe perioperative outcome.

Survival outcomes remain contradictory after resection for caudate lobe HCC, because no earlier study has accumulated a sufficient number of patients (9–46 patients).[8-13,34-38] Up to now, only 3 studies have reported 5-year survival rates (26% [n = 20],[9] 41% [n = 30],[8] 76% [n = 46][34]) with a big difference, indicating an absence of consensus about patients' survival. In our study, performed in the largest cohort (n = 201), the 5-year survival rate (57.3%) is likely to be the best outcome among previously reported studies. The highest rate (76%) from Sakamoto's series[34] is overestimated because of using a subgroup analysis for the selected patients only with ''single'' caudate lobe HCC, which seems comparable to our rate (71.2%) undergoing total resection in this series (Fig. 4 A). Eventually, it is sufficiently reasonable that our results were as good as that (56.8%) derived from a Japanese mega-cohort (n = 20,866) including all the patients undergoing resection of HCC in every segment of the liver.[39]

As for the hepatectomy procedure, we prioritized total resection of the caudate lobe over local resection for the oncological point of tumor clearance.[14,15] Notably, we proved pathologically in this series (Table 2) that total resection completely avoided ''tumor exposure'' at the cut-stump in the resected specimens, although the target HCCs were larger than those in partial resection ($P < 0.001$), and significantly removed the clinically dormant ''vascular invasion'' ($P < 0.001$) within the specimens, that could minimize the risk of microscopic residual tumors or occult metastases.[40] Unfortunately, however, we failed to show a significantly better survival outcome after total resection due to a small sample size. About other factors, surgical margin represented a significance ($P = 0.034$) (Fig. 4B), to which surgeon should pay attention during operation. In fact, we performed radical resection with no microscopic tumor exposure especially in patients undergoing anatomic resection.[41] Prognostic factor analysis revealed that the powerful variables for overall survival were esophageal varices and vascular invasion (Table 3). Therefore, the surgical decision needs to be taken cautiously if a patient has such unfavorable factors. Taken together, our surgical policy for caudate lobe HCC is of value for achieving the reasonable patients' survival. In near future, laparoscopic resection may be useful in a selected cohort,[42] although precise orientation during liver transection and rigid control of massive bleeding are needed prior to active generalization.

CONCLUSIONS

Resection of HCC originating in the caudate lobe needs to be determined by ''Takayama algorithm'' which recommends the first and second best types of maneuver according to tumor characteristics and patients' liver function. Despite the hard-to-approach anatomic location, resection of the caudate lobe by adhering to the algorithm can be carried out with acceptable patients' safety and tumor curability. To our best knowledge, this study is the first to provide an easy-to-use guideline for performing such a specific liver resection for HCC.

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