

## Choice of approach for hepatectomy for hepatocellular carcinoma located in the caudate lobe: Isolated or combined lobectomy?

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### Abstract

**AIM:** To investigate the significance of the surgical approaches in the prognosis of hepatocellular carcinoma (HCC) located in the caudate lobe with a multivariate regression analysis using a Cox proportional hazard model.

**METHODS:** Thirty-six patients with HCC underwent caudate lobectomy at a single tertiary referral center between January 1995 and June 2010. In this series, left-sided, right-sided and bilateral approaches were used. The outcomes of patients who underwent isolated caudate lobectomy or caudate lobectomy combined with an additional partial hepatectomy were compared. The survival curves of the isolated and combined resection groups were generated by the Kaplan-Meier method and compared by a log-rank test.

**RESULTS:** Sixteen (44.4%) of 36 patients underwent isolated total or partial caudate lobectomy whereas 20

(55.6%) received a total or partial caudate lobectomy combined with an additional partial hepatectomy. The median diameter of the tumor was 6.7 cm (range, 2.1-15.8 cm). Patients who underwent an isolated caudate lobectomy had significantly longer operative time (240 min *vs* 170 min), longer length of hospital stay (18 d *vs* 13 d) and more blood loss (780 mL *vs* 270 mL) than patients who underwent a combined caudate lobectomy ( $P < 0.05$ ). There were no perioperative deaths in both groups of patients. The complication rate was higher in the patients who underwent an isolated caudate lobectomy than in those who underwent combined caudate lobectomy (31.3% *vs* 10.0%,  $P < 0.05$ ). The 1-, 3- and 5-year disease-free survival rates for the isolated caudate lobectomy and the combined caudate lobectomy groups were 54.5%, 6.5% and 0% and 85.8%, 37.6% and 0%, respectively ( $P < 0.05$ ). The corresponding overall survival rates were 73.8%, 18.5% and 0% and 93.1%, 43.6% and 6.7% ( $P < 0.05$ ).

**CONCLUSION:** The caudate lobectomy combined with an additional partial hepatectomy is preferred because this approach is technically less demanding and offers an adequate surgical margin.

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**Key words:** Hepatocellular carcinoma; Hepatectomy; Caudate lobectomy; Caudate lobe; Combined resection

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## INTRODUCTION

The caudate lobe is a segment of the liver that is surgically difficult to approach because of its deep location in the hepatic parenchyma<sup>[1-3]</sup>. The anatomic relationship of the caudate lobe to the hepatic vasculature was initially described by Couinaud. The caudate lobe is located anterior to the inferior vena cava (IVC), which may envelop this structure circumferentially. It extends to the hilum of the liver just posterior to the bifurcation of the portal vein. Cephalad, the caudate lobe lies posterior to the confluence of the left and middle veins as they enter the IVC on the left<sup>[4]</sup>.

The caudate lobe is generally divided into three regions: the left Spiegelian lobe, the process portion and the paracaval portion. As these regions are supplied by different vasculobiliary branches of the portal triad and they are drained separately by branches of the hepatic veins, each region can be resected independently, thus making partial caudate lobectomy possible<sup>[5]</sup>.

Caudate lobectomy is commonly indicated for hepatocellular carcinoma (HCC). It has been performed infrequently in the past, partly because of technical difficulties and the inadequate understanding of the anatomy<sup>[5-7]</sup>. Precise anatomic knowledge of the caudate lobe, and improvement in perioperative care and the surgical techniques have resulted in more performance of caudate lobectomies. However, caudate lobectomy remains a technical challenge, even for experienced hepatic surgeons. Caudate lobectomy is classified as total or partial lobectomy, and as isolated caudate lobectomy or caudate lobectomy combined with an additional partial hepatectomy. This study aimed to evaluate the surgical outcomes of caudate lobectomy and the optimal surgical approach for HCC in the caudate lobe.

## MATERIALS AND METHODS

### Study subjects

Thirty-six patients with HCC underwent caudate lobectomy at the Department of Hepatobiliary Surgery and Liver Transplantation Surgery, Navy General Hospital between January 1995 and June 2010. Informed consent was obtained from each patient. Surgical outcomes for patients who underwent isolated caudate lobectomy or caudate lobectomy combined with an additional partial hepatectomy were compared. The data were collected prospectively and analyzed retrospectively.

### Procedure

The surgeries of this series were completed over the past

15 years. The choice of approach mainly depended on the prevailing conditions and surgeon's experience. Surgery was performed through a bilateral subcostal incision in eight patients, while a Mercedes-Benz incision was used in 28 patients. After an exploratory laparotomy, the liver was fully mobilized from all its peritoneal attachments. The liver was then assessed with intraoperative ultrasound. We carefully searched the abdominal cavity for the extent of local disease, extrahepatic metastases and peritoneal seedings. In this series, three approaches were used<sup>[8,9]</sup>: (1) a left-sided approach for tumors situated mainly in the Spiegelian lobe, or when a caudate lobectomy was combined with a left hepatectomy; (2) a right-sided approach for tumors situated mainly in the caudate process or paracaval portion, or when a caudate lobectomy was combined with a right hepatectomy; and (3) a bilateral approach for tumors situated in the whole caudate lobe. Although we started with one particular surgical approach in most patients, we had to combine different approaches to facilitate the caudate lobectomy. The suprahepatic and infrahepatic IVC was slung with vascular loops. Resection began with a pringle maneuver in cycles of 15/5 min of clamp/unclamp times. Total vascular exclusion was used only when patients had excessive bleeding from a lacerated IVC or hepatic vein. Liver resection was carried out by a clamp crushing method.

### Statistical analysis

The survival curves of the isolated and combined resection groups were generated by the Kaplan-Meier method and compared with a log-rank test. To investigate the prognostic significance of the operative procedure, we performed a multivariate regression analysis with a Cox proportional hazard model, using a variable-selection method by a backward-elimination procedure.  $P < 0.15$  was set as the cutoff for elimination. In the multivariate analysis, we chose 12 factors as potential confounders, considering their clinical significance and the results of previous reports<sup>[10,11]</sup>. Because any factors that are of potential importance can be incorporated into a multivariate analysis, whether or not they are statistically significant<sup>[12]</sup>, we entered some nonsignificant factors in the univariate analysis into the model of the multivariate analysis in the present study. The 12 factors included: age (older *vs* younger than 65 years), sex, preoperative serum total bilirubin level (more *vs* less than 1 mg/dL), Child-Pugh class (A *vs* B), background liver status (cirrhosis *vs* noncirrhosis) as assessed histologically, tumor size (larger *vs* smaller than 30 mm), cancer spread (present or absent), tumor cell differentiation (well *vs* moderate or poor), serum-fetoprotein level (more *vs* less than 100 ng/mL), history of red blood cell transfusion (yes *vs* no), surgical margin (greater *vs* smaller than 5 mm) and tumor exposure (yes *vs* no). The Mann-Whitney  $U$  test and  $\chi^2$  test were used for the continuous and categorical data, respectively. All statistical analysis were performed using statistical software (SPSS 11.5 for Windows, SPSS, Inc., Chicago, IL).  $P < 0.05$  was considered to be statistically significant.

Table 1 Patient characteristics

	Isolated caudate lobectomy group ( <i>n</i> = 16)	Combined caudate lobectomy group ( <i>n</i> = 20)	<i>P</i> value
Age (yr)	51 ± 14	48 ± 17	NS
Gender			NS
Male	12	15	
Female	4	5	
Liver cirrhosis			NS
Present	10	14	
Absent	6	6	
Child-Pugh class			NS
A	14	17	
B	2	3	
Liver function			
Albumin (g/dL) <sup>1</sup>	2.9	3.5	0.03
ALT (IU/L) <sup>1</sup>	54	32	0.04
Total bilirubin (mg/dL) <sup>1</sup>	1.2	0.8	0.04
Prothrombin time (%) <sup>1</sup>	75	79	NS
Location of the tumor			NS
Spiegel	2	3	
Paracaval portion	2	3	
Caudate process	1	2	
Spiegel + paracaval portion	3	4	
Paracaval portion + caudate process	3	2	
Complete caudate lobe	5	6	
Surgical margin (mm)			0.04
< 5 mm	5	1	
≥ 5 mm	11	19	
α-Fetoprotein (ng/mL) <sup>1</sup>	23	25	
Cancer spread <sup>2</sup>			NS
Positive	3	5	
Negative	13	15	
Differentiation of tumor			NS
Edmondson I	1	1	
Edmondson II	5	4	
Edmondson III	10	14	
Edmondson IV	0	1	
Tumor size, median (range), cm	6.1 (2.1-13.4)	7.5 (2.3-15.8)	NS

<sup>1</sup>Median; <sup>2</sup>Cancer spread was defined by presence of microscopic vascular invasion and/or intrahepatic metastasis. ALT: Alanine aminotransferase; NS: Not significant.

## RESULTS

During the study period, 36 patients (28 males and 8 females) underwent caudate lobectomy for HCC. The median age was 49 years (range 31-74 years), and 66.7% of the patients had liver cirrhosis. The median diameter of the tumor was 6.7 cm (range 2.1-15.8 cm). Tumors were present in all three parts of the caudate lobe in 11 patients, in the Spiegel lobe in five patients, in the paracaval portion in five patients, in the caudate process in three patients, in the paracaval portion and caudate process in five patients, and in the Spiegel and paracaval portion in 7 patients. The comparative data are shown in Table 1.

### Surgical procedures

The operative procedures are listed in Table 2. Sixteen patients (44.4%) received an isolated complete or partial caudate lobectomy, whereas 20 (55.6%) underwent a

Table 2 Operative procedures

Operations	<i>n</i> (%)
Isolated caudate lobectomy	16 (44.4)
Complete caudate lobectomy	8
Partial caudate lobectomy	8
Concomitant procedures	
Partial IVC resection + repair	2
Approaches	
Left-side	2
Right-side	2
Bilateral	12
Combined caudate lobectomy	20 (55.6)
Complete caudate lobectomy + left hepatectomy	2
Complete caudate lobectomy + left lateral sectionectomy	2
Complete caudate lobectomy + right hepatectomy	1
Complete caudate lobectomy + right posterior hepatectomy	1
Partial caudate lobectomy + left hepatectomy	7
Partial caudate lobectomy + left lateral sectionectomy	3
Partial caudate lobectomy + right hepatectomy	2
Partial caudate lobectomy + right posterior hepatectomy	2
Concomitant procedures	
Partial IVC resection + repair	4
Approaches	
Left-side	4
Right-side	2
Bilateral	14

IVC: Inferior vena cava.

complete or partial caudate lobectomy combined with an additional partial hepatectomy. Five patients required a partial resection and repair of the IVC because of tumor invasion into the anterior wall of the IVC. The left-sided, right-sided and bilateral approaches were used in 6, 4 and 26 patients, respectively.

### Surgical outcomes

The surgical outcomes were compared between isolated caudate lobectomy and caudate lobectomy combined with an additional partial hepatectomy. The median operating time was 198 min (range 150-310 min) and the median blood loss was 620 mL (range 150-1470 mL). Patients that underwent an isolated caudate lobectomy had significantly longer operative time, length of hospital stay and blood loss than patients who underwent caudate lobectomy combined with an additional partial hepatectomy ( $P < 0.05$ ). There were no perioperative deaths in both groups of patients. Patients that underwent an isolated caudate lobectomy had a higher complication rate than those who underwent caudate lobectomy combined with an additional partial hepatectomy (31.3% *vs* 10.1%,  $P < 0.05$ , Table 3).

The 1-, 3- and 5-year disease-free survival rates for the isolated caudate lobectomy and the combined caudate lobectomy groups were 54.5%, 6.5% and 0% and 85.8%, 37.6% and 0%, respectively ( $P < 0.05$ , Figure 1A). The corresponding overall survival rates were 73.8%, 18.5% and 0% and 93.1%, 43.6% and 6.7% ( $P < 0.05$ , Figure 1B). Multivariate analysis identified combined resection as significantly influencing the overall survival rate and the disease-free survival rate (Table 4).

Table 3 Surgical outcomes

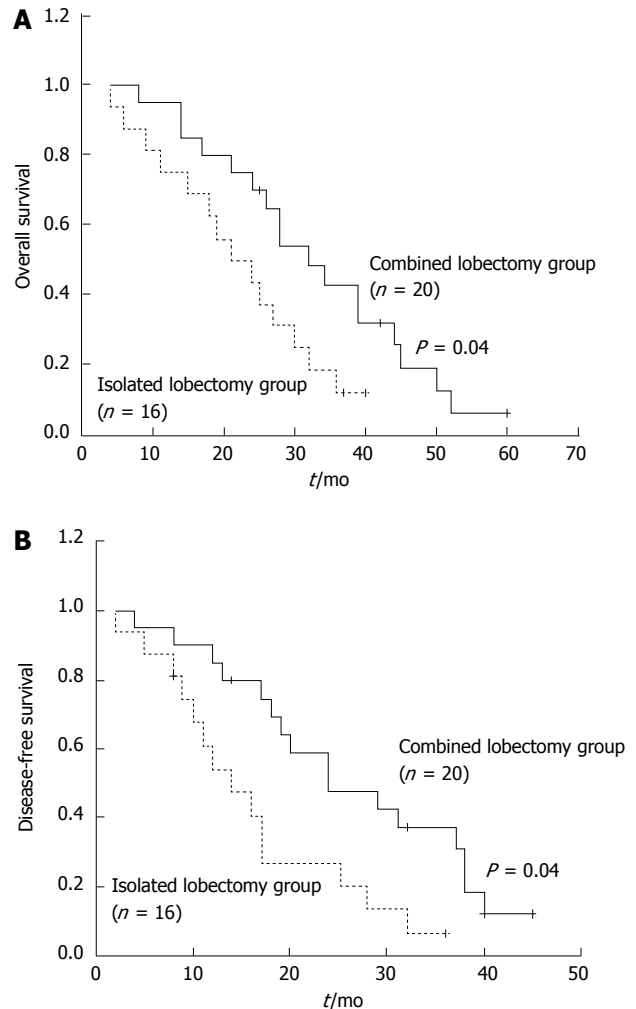
	Isolated caudate lobectomy group ( <i>n</i> = 16)	Combined caudate lobectomy group ( <i>n</i> = 20)	<i>P</i> value
Time of vascular control, median (range), min	52 (32-68)	33 (25-39)	0.04
Blood loss, median (range), mL	780 (250-1470)	460 (150-980)	0.03
No. of patients with blood transfusion	14	11	0.02
Operative time, median (range), min	240 (170-310)	170 (150-225)	0.04
Hospital stay, median (range), d	18 (11-22)	13 (9-17)	0.04
Mortality	0	0	-
Complications			0.03
Liver failure	0	0	
Post-operative hemorrhage	2	0	
Bile leak	2	0	
Intra-abdominal collection	2	1	
Pleural effusion	1	1	

## DISCUSSION

Although studies on caudate lobectomies have been increasingly reported, most of them were single case reports or small series reports<sup>[13-15]</sup>. Some series contained cases of caudate lobectomy carried out for microscopic involvement of hilar cholangiocarcinoma<sup>[16]</sup>. Comparative studies are very rare.

Caudate lobectomy is classified as a total or partial resection, and is also classified as an isolated or combined resection<sup>[17]</sup>. Several approaches have been described for caudate lobectomy, including the left-sided approach, right-sided approach, combined left- and right-sided approach and the anterior transhepatic approach. Peng *et al.*<sup>[18]</sup> also described the retrograde approach for resecting tumors in the caudate lobe that had invaded the IVC. The selection of an appropriate surgical approach is essential for a safe caudate lobectomy. When the tumor is large or the IVC and/or major hepatic vein is compressed by the tumor, caudate lobectomy is technically very difficult and the resection has to be carried out using a combination of different approaches<sup>[19]</sup>.

In an isolated caudate lobectomy, especially for a bulky tumor, it is important to recognize the danger of tearing the middle hepatic vein posteriorly when the caudate lobe is dissected away from this vein. To prevent major hemorrhage from a torn middle hepatic vein, the common trunk of the middle and left hepatic veins should be isolated and slung with a vascular loop before any attempt is made to dissect the caudate lobe within the tunnel formed by the IVC and the hepatic veins<sup>[20]</sup>. In a caudate lobectomy that is combined with either a right or left hepatectomy, a caudate lobectomy can be performed with little danger of bleeding from the middle hepatic vein since this vessel is usually controlled extrahepatically, or it can be sacrificed and resected together with the



**Figure 1** Overall survival rate curves and disease-free survival rate curves after isolated and combined resections for hepatocellular carcinoma originating from caudate lobe. A: Overall survival rate curves after isolated and combined resections for hepatocellular carcinoma originating from caudate lobe; B: Disease-free survival rate curves after isolated and combined resections for hepatocellular carcinoma originating from the caudate lobe.

specimen. Thus, an isolated caudate lobectomy is technically more difficult than a caudate lobectomy combined with either a right or a left hepatectomy.

The choice of isolated or combined resection is based primarily on the extent of HCC invasion and liver function reserve. The group that had an isolated resection of the tumor was characterized by well-differentiated, capsule intact, and poor liver function reserve, which could be easily removed. On the contrary, the group that had a combined resection of the tumor was characterized by poorly-differentiated, capsule incomplete, and better liver function reserve, which could be ablated with an extended resection to achieve the purpose of a complete resection.

We found that the isolated resection group had a worse long-term prognosis than the combined resection group. The main reasons were related to the following factors. First, the caudate lobe HCC was very close to the other lobe with limited growth space. Especially when the tumor was located in the paracaval part, it often infil-



Table 4 Multivariate analysis

Variables	Hazard ratio	95% CI	P value
Overall survival			
Absence of cancer spread <sup>1</sup>	0.44	0.24-0.69	0.007
Child-Pugh class A	0.86	0.66-1.33	0.17
Combined resection	0.57	0.32-0.92	0.04
Tumor size < 30 mm	0.61	0.32-1.05	0.08
Total bilirubin < 1 mg/dL	0.52	0.28-1.06	0.07
$\alpha$ -Fetoprotein < 100 ng/mL	0.61	0.33-1.19	0.07
Disease-free survival			
Absence of cancer spread <sup>1</sup>	0.61	0.37-0.82	0.001
Combined resection	0.66	0.42-0.94	0.03
Negative tumor exposure	0.39	0.20-0.77	0.04
Total bilirubin < 1 mg/dL	0.56	0.37-0.89	0.02

<sup>1</sup>Cancer spread was defined by presence of microscopic vascular invasion and/or intrahepatic metastasis.

trated the other lobe, such as segment IV, V, VI, VII or VIII. Due to the unclear boundary, an isolated resection of the tumor could not achieve a complete resection. Second, the caudate HCC was often close to the main branch of the main portal and hepatic veins, which increased the likelihood of vascular invasion leading to an inadequate surgical margin. A caudate lobe resection combined with the other lobe could obtain a clear exposure and acquire a more adequate surgical margin. Third, from the no-touch point of view, repeated over-turning and pulling on the caudate lobe can cause HCC cells to transfer to other locations along the portal vein and hepatic vein, increasing the possibility of metastasis in the isolated resection. Although the anterior approach can avoid this problem, its application is limited by varying degrees of liver cirrhosis. The anterior approach required segment IV resection, which prolonged the operation time and increased the amount of bleeding<sup>[21]</sup>. Obtaining a negative margin may not be easy particularly in large and very large HCC, especially for those located in the caudate lobe<sup>[22-24]</sup>. Therefore, the style of the combined resection can solve the above problem, which is an optimal method. We advocate that the caudate lobe should be ablated from the combined adjacent lobe to get an adequate margin and reduce the stretching and compression of the tumor, thereby achieving a good long-term prognosis.

If confounders in a multivariate analysis are limited only to the significant factors in a univariate analysis, some factors, which are not significant despite their potential importance, may be excluded. Therefore, according to Tralh o *et al.*<sup>[25]</sup>, we chose 12 factors as confounders, after weighing their clinical importance, whether or not they were significant in the univariate analysis. Indeed, this method was also adopted in a previous study<sup>[26,27]</sup>. The present study indicated that anatomic resection would be a suitable option of choice for HCC. Our multivariate analysis showed that liver function was an important prognostic factor for the overall survival, though the Child-Pugh class between the two groups showed no difference. In the other study, we found that segmentectomy or lobectomy might be recommended as an initial treatment for patients with good hepatic func-

tion and a solitary hepatic nodule because such patients have a chance of achieving long-term survival and wider surgical resections could minimize the chance of microscopic residual tumors or occult metastases<sup>[28-32]</sup>.

Approaches to a caudate lobectomy thus depend largely on the size and location of the lesion and liver functional reserve. For patients with sufficient liver functional reserve, partial or complete caudate lobectomy combined with other partial hepatic resections is preferred because such an operation is technically less demanding. For patients with a poor liver function, we are left with no choice but to carry out an isolated caudate lobectomy. HCC originating from the caudate lobe is relatively rare. As the study sample is small, a more accurate conclusion requires a multi-center randomized controlled study to confirm our results.

## COMMENTS

### Background

The caudate lobe is a segment of the liver that is surgically difficult to approach because of its location deep in the hepatic parenchyma, which is surrounded by branches of the porta hepatis, the hepatic veins and the inferior vena cava (IVC). Caudate lobectomy is commonly indicated for hepatocellular carcinoma (HCC). Currently, caudate lobectomy remains a technical challenge, even for experienced hepatic surgeons. This study gives some instructions for hepatectomy for HCC located in the caudate lobe, with the choice of isolated or combined lobectomy.

### Research frontiers

Caudate lobectomy is classified as total or partial lobectomy; it is also classified as isolated caudate lobectomy or caudate lobectomy combined with an additional partial hepatectomy. The selection of an appropriate surgical approach is essential for a safe caudate lobectomy.

### Innovations and breakthroughs

Although increasing numbers of studies on caudate lobectomy have been reported in the medical literature, most are single case reports or small series studies. Some series contained cases of caudate lobectomy carried out for microscopic involvement of hilar cholangiocarcinoma. Comparative studies are very rare. In this paper, 36 patients with HCC underwent caudate lobectomy at a single tertiary referral center between January 1995 and June 2010. The surgical outcomes of patients who underwent isolated caudate lobectomy or caudate lobectomy combined with an additional partial hepatectomy were compared. For patients with sufficient liver functional reserve, caudate lobectomy combined with an additional partial hepatectomy is preferred because such an approach is technically less demanding and offers an adequate surgical margin. For patients with a marginal liver functional reserve, the viable surgical option is an isolated caudate lobectomy.

### Applications

This study showed that, in patients with sufficient liver functional reserve, a caudate lobectomy combined with an additional partial hepatectomy is preferred because such an approach is technically less demanding and achieves adequate surgical margin. However, for patients with marginal liver functional reserve, the viable surgical option is an isolated caudate lobectomy.

### Terminology

Caudate lobectomy is classified as total or partial resection, and is also classified as an isolated or combined resection. Several approaches have been described for caudate lobectomy, such as the left-sided approach, right-sided approach, combined left- and right-sided approach and the anterior transhepatic approach. Recently, a retrograde approach for resecting tumors in the caudate lobe that have invaded the IVC has also been described.

### Peer review

This manuscript emphasizes the optimal surgical approach for HCC in the caudate lobe. The manuscript sections are very clearly described and the conclusion is an opened door for further investigation. They observed that the 16 patients who underwent isolated lobectomy had longer operative times, greater blood loss, a higher complication rate, longer hospital stays and higher mortality. They concluded that, in patients with adequate functional reserve, combined hepatectomy is the preferred choice.

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