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BRIEF ARTICLE

Prognostic factors in the surgical treatment of caudate lobe hepatocellular carcinoma

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Abstract

AIM: To evaluate the short- and long-term outcomes of liver resection for caudate lobe hepatocellular carcinoma (HCC).

METHODS: We retrospectively analyzed 114 consecutive patients with HCC, originating from the caudate lobe, who underwent resection between January 2001 and January 2007. Univariate and multivariate analyses were performed on several clinicopathologic variables to determine the factors affecting long-term outcome and intrahepatic recurrence.

RESULTS: Overall mortality and morbidity were 0% and 18%, respectively. After a median follow-up of 31 mo (interquartile range, 11-66 mo), tumor recurrence had occurred in 76 patients (66.7%). The 1-, 3-, and 5-year disease-free survival rates were 65.7%, 38.1%, and 18.4%, respectively. The 1-, 3-, and 5-year overall survival rates were 76.1%, 54.7%, and 31.8%, respectively. Univariate analysis showed that subsegmental location of the tumor (45.7% *vs* 16.2%, $P = 0.01$), liver cirrhosis (12.3% *vs* 47.9%, $P = 0.03$), surgical margin (18.5% *vs* 54.6%, $P = 0.04$), vascular invasion (37.9% *vs* 23.2%, $P = 0.04$) and extended caudate resection (42.1% *vs* 15.4%, $P = 0.04$) were related to poorer long-term survival. Multivariate analysis showed that only subsegmental location of the tumor, liver cirrhosis and surgical margin were significant independent prognostic factors.

CONCLUSION: Hepatectomy was an effective treatment for HCC in the caudate lobe. The subsegmental location of the tumor, liver cirrhosis and surgical margin affected long-term survival.

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Key words: Hepatectomy; Hepatocellular carcinoma; Caudate lobe; Prognostic factors

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INTRODUCTION

Refined surgical and anesthetic techniques, a better understanding of liver anatomy[1,2], and improvements in postoperative management have increased the indications for hepatectomy in patients with hepatocellular carcinoma (HCC) in the caudate lobe. Hepatic resections can now

be performed in high-volume centers with an acceptable morbidity of 50%-60% and no mortality[3,4]. Caudate HCC has a poorer prognosis than HCC originating from other lobes due to its proximity to the portal trunk and inferior vena cava, which facilitates intrahepatic and systemic spread early in the disease[5,6]. Although some surgeons have reported successful surgical treatment of caudate HCC with transarterial chemoembolization (TACE)[7,8] or local ablation[9-11], hepatic resection has been considered to be the treatment of first choice[12-14]. The most important factor currently limiting the disease-free interval is the high rate of tumor recurrence, which ranges from 50%-60% at 3 years[15,16]. In order to improve surgical outcome, it is necessary to evaluate the potential risk factors for long-term survival and to establish guidelines for the appropriate use of hepatectomy for caudate lobectomy. We therefore retrospectively evaluated 114 consecutive patients who underwent hepatic resection for HCC originating in the caudate lobe, in order to assess the influence of common clinicopathologic variables on recurrence and long-term survival.

MATERIALS AND METHODS

Between January 2001 and January 2007, 114 consecutive patients with HCC in the caudate lobe underwent hepatic resection at the Eastern Hepatobiliary Surgery Hospital, Second Military Medical University. Computed tomography (spiral-CT), detection of serum α-fetoprotein level (AFP), and hepatic ultrasound-guided fine-needle biopsy were used for preoperative diagnosis of HCC. Needle biopsy was not performed in patients with an elevated serum level of AFP and typical imaging of HCC, to avoid needle tract seeding of tumor cells. Clinicopathologic and follow-up data for each patient were recorded in a computerized database, regularly updated for tumor recurrence and survival status. Resection was considered "extended" if the caudate lobe as well as other lobes or segments were removed, according to Couinaud's classification. Intraoperative ultrasound was routinely performed in all patients, in order to detect tumor invasion into the major branches of the portal vein and hepatic veins, or the presence of lesions in the contralateral lobe. Tumor clearance at the resection margins of at least 5 mm was considered adequate to define the surgical procedures as curative (R0)[17]. Hospital mortality was defined as death within 30 d after operation, including operative deaths. Tumor recurrence was considered as evidence of hepatic tumoral lesions after a curative resection. All patients discharged were followed-up at our department every 3 mo in the first year, every 6 mo in the second year, and every 6 mo thereafter. The follow-up consisted of physical examination, blood tests, serologic liver function test, detection of serum AFP level and liver ultrasound or CT scan.

Liver resection was carried out using a clamp-crushing technique in all patients. Intraoperative ultrasonography was routinely used to locate the carcinoma, exclude daughter nodules, and identify the relationship of the tumor with the major vessels, so minimizing blood loss and avoiding injury to the main trunk vessels. We used multiple occlusion techniques, including continuous or intermittent Pringle maneuver, hemihepatic vascular clamping, or total hepatic vascular exclusion, determined on a case-by-case basis.

Statistical analysis

Continuous data were expressed as medians and interquartile ranges. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. For comparison of survival, continuous variables were dichotomized using the respective medians as the cut-off values. Only the variables that were significant in univariate analysis were entered into a Cox regression model to identify the clinicopathologic factors with independent prognostic significance. Patients with hospital mortality (within 30 d) were excluded from the evaluation of these factors with regard to long-term and disease-free survival. Statistical analysis was carried out using SPSS computer software (SPSS Inc., Chicago, IL, USA). Differences were considered significant if the P value was < 0.05.

RESULTS

The clinicopathologic characteristics of the 114 resected patients are shown in Table 1. There were 87 males (76%) and 27 females (24%). The median age was 49 years. The Child-Pugh grading system for the prognosis of liver cirrhosis was applied in all patients. All patients were classified as Child-Pugh grade A. Data regarding serum AFP levels were available for all patients, and 90 patients (79%) were AFP-positive. The median preoperative AFP level was 195 ng/mL. Seventy-eight (68.4%) patients had undergone isolated caudate lobectomy and 36 (31.6%) had undergone extended caudate lobectomy (Table 2).

A curative resection (surgical margin > 5 mm) was achieved in 59% of cases (67 patients). Histopathologic examination showed that 84% of patients had a differentiated tumor (74% trabecular type, 1% fibrolamellar type, and 9% mixed type), while 16% had undifferentiated tumors. Vascular invasion was found in 38% of patients. There was no postoperative mortality. The hospital morbidity rate was 18% (21 patients). The most frequent complications were infections (abdominal abscess, pleural effusion and bronchopneumonia), liver failure, hemorrhage, ascites and mild lower limb edema.

The median follow-up period was 31 mo (interquartile range, 11-66 mo). A total of 65 patients (57.0%) died during the follow-up period. Eight patients (7.0%) were lost to follow-up at 4, 7, 9, 18, 30, 42, 50 and 54 mo. Up to the last follow-up date (January 2007), 41 patients (36.0%) were alive, of whom, 21 were disease-free (18.4%). Tumor recurrence occurred in 49 patients (75.4%), and disease progression was the leading cause of death in 65 patients (57.0%). The 1-, 3-, and 5-year disease-free survival rates were 65.7%, 38.7%, and 18.8%, respectively. The 1-, 3-, and 5-year overall survival rates were 76.1%, 54.7%, and 31.8%, respectively (Figure 1).

Statistical analysis

The prognostic influences of the clinicopathologic char-

Table 1 Clinical and pathologic characteristics of 114 HCC patients

Characteristics	*n* (%)
Age (yr)	
≤ 65	89 (77)
> 65	25 (23)
Gender	
Male	87 (76)
Female	27 (24)
Cirrhotic liver	
No	36 (32)
Yes	78 (68)
Tumor size (cm)	
≤ 5	50 (44)
> 5	64 (56)
Serum AFP (ng/mL)	
≤ 200	69 (61)
> 200	45 (39)
Subsegmental location	
Spiegel lobe	39 (34)
Paracaval portion	54 (47)
Caudate process	21 (19)
Tumor number	
Solitary	91 (80)
Multiple	23 (20)
Pringle maneuver	
No	34 (30)
Yes	80 (70)
Surgical treatment	
Isolated caudate lobectomy	78 (68)
Extended hepatectomy	36 (32)
Surgical margin (mm)	
≤ 5	47 (41)
> 5	67 (59)
Histologic grading	
Differentiated	96 (84)
Undifferentiated	18 (16)
Capsule	
No	95 (93)
Yes	19 (17)
Vascular invasion	
No	71 (81)
Yes	43 (38)
Daughter nodules	
No	83 (73)
Yes	31 (27)

HCC: Hepatocellular carcinoma; AFP: α-fetoprotein.

Table 2 Hepatectomy for caudate lobe hepatocellular carcinoma

Operations	*n* (%)
Isolated caudate lobectomy	78 (68.4)
Spiegel lobe	27
Paracaval portion and caudate process	31
Spiegel and paracaval portion	2
Paracaval portion	7
Caudate process	4
Complete caudate lobectomy	7
Extended hepatectomy	36 (31.6)
Spiegel and left hemihepatectomy	5
Spiegel and segment Ⅳ	2
Spiegel and Ⅱ, Ⅲ	3
Spiegel and Ⅵ, Ⅶ	1
Spiegel and Ⅶ	1
Paracaval portion and caudate process and right hemihepatectomy	4
Paracaval portion and caudate process and segment Ⅳ	2
Paracaval portion and caudate process and Ⅶ	1
Paracaval portion and caudate process and segment Ⅱ, Ⅲ	3
Paracaval portion and caudate process and Ⅴ, Ⅵ	2
Paracaval portion and segment Ⅱ, Ⅲ	3
Paracaval portion and segment Ⅵ, Ⅶ	1
Complete caudate lobe and right hemihepatectomy	1
Complete caudate lobe and segment Ⅳ	1
Complete caudate lobe and left hemihepatectomy	4
Complete caudate lobe and segment Ⅱ, Ⅲ	1
Complete caudate lobe and segment Ⅵ	1

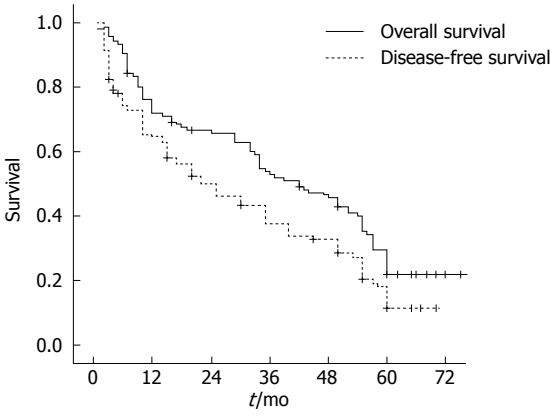

Figure 1 Disease-free and overall survival curves.

acteristics are shown in Table 3. There were no associations between age or sex and survival rate. No significant differences in survival rate were noted between patients with AFP levels > or ≤ 200 ng/dL, with tumor sizes ≤ or > 5 cm, with or without capsulated tumors, or among patients with well-differentiated or poorly-differentiated HCC. The extent of the hepatic resection (isolated *vs* extended) did not influence the long-term survival. The effect of tumor subsegmental location was also investigated and it was shown that there was a significant survival difference between patients with tumors in the Spiegel lobe compared to the paracaval portion and caudate process ($P < 0.01$). There was no significant difference in 3-year survival between solitary and multiple tumors, but a significant difference in overall survival was observed between patients with or without liver cirrhosis. The 5-year survival rate of patients without cirrhosis was significantly higher than in patients with viral cirrhosis (47.9% *vs* 12.3%, $P = 0.03$). The presence or absence of vascular invasion was also a significant prognostic factor for survival; patients without vascular invasion had significantly higher 5-year survival rates than those with vascular invasion (37.9% *vs* 23.2%, $P = 0.05$).

In multivariate analysis, only subsegmental location, liver cirrhosis and surgical margin were confirmed as independent prognostic factors for overall survival (Table 4). None of the clinicopathologic factors analyzed were significantly correlated with disease-free survival (Table 5).

DISCUSSION

Although HCC arising from the caudate lobe has been reported to be relatively rare, its surgical treatment

Table 3 Overall survival: univariate analysis of prognostic clinicopathologic factors

	3-yr survival (%)	5-yr survival (%)	*P*-value
Age (yr)			
≤ 65	52.8	34.2	0.24
> 65	63.1	52.0	
Gender			
Male	56.1	38.4	0.41
Female	60.6	50.0	
Cirrhosis			
Yes	35.0	12.3	0.03
No	60.6	47.9	
Serum AFP (ng/mL)			
≤ 200	55.9	34.6	0.57
> 200	55.4	45.5	
Tumor location			
Spiegel lobe	63.1	45.7	0.01
Paracaval portion	22.9	16.2	
Caudate process	25.2	14.9	
Tumor size (cm)			
≤ 5	58.4	43.3	0.48
> 5	57.0	39.4	
Pringle maneuver			
No	67.7	42.1	0.73
Yes	62.5	37.9	
Surgical margin (mm)			
≤ 5	20.4	18.5	0.02
> 5	60.7	54.6	
Surgical treatment			
Isolated caudate lobectomy	52.1	42.1	0.04
Extended hepatectomy	27.9	15.4	
Histologic grading			
Differentiated	57.7	33.6	0.79
Undifferentiated	52.2	29.4	
Capsule			
No	65.3	41.5	0.70
Yes	56.1	35.9	
Vascular invasion			
No	52.4	37.9	0.05
Yes	29.2	23.2	
Daughter nodules			
No	56.1	36.8	0.38
Yes	45.3	25.0	

Table 4 Overall survival: multivariate analysis of prognostic clinicopathologic factors

	Hazard ratio	95% CI	*P*-value
Location of tumor	0.176	0.046-0.701	0.02
Liver cirrhosis	4.874	1.107-19.339	0.04
Surgical margin	1.36	0.210-2.375	0.04

Table 5 Disease-free survival: univariate analysis of prognostic clinicopathologic factors

	3-yr survival (%)	5-yr survival (%)	*P*-value
Age (yr)			
≤ 62	46.7	21.7	0.76
> 62	38.2	31.4	
Gender			
Male	49.4	26.4	0.43
Female	25.1	20.7	
Cirrhosis			
Yes	42.6	37.2	0.19
No	51.9	29.3	
Serum AFP (ng/mL)			
≤ 200	36.5	20.1	0.66
> 200	32.4	29.7	
Tumor location			
Spiegel lobe	50.5	34.4	0.07
Paracaval portion	36.9	20.6	
Caudate process	41.0	26.2	
Tumor size (cm)			
≤ 5	40.6	23.0	0.69
> 5	44.0	26.4	
Pringle maneuver			
No	40.4	22.6	0.66
Yes	36.1	19.8	
Surgical margin			
Positive	42.6	22.8	0.08
Negative	55.2	30.7	
Surgical treatment			
Isolated caudate lobectomy	43.4	24.0	0.35
Extended hepatectomy	41.7	35.8	
Histologic grading			
Differentiated	42.1	24.2	0.42
Undifferentiated	33.9	28.7	
Capsule			
No	36.3	19.0	0.65
Yes	43.8	26.3	
Vascular invasion			
No	45.0	29.7	0.25
Yes	34.0	21.3	
Daughter nodules			
No	56.1	36.8	0.09
Yes	45.3	25.0	

presents a challenge and is associated with high risks for the surgeon, due to its unique anatomic location and its complicated relationship with the major vasculature. To the best of our knowledge, the tumor with the largest reported volume was a HCC in the caudate lobe. Local ablation of HCC in the caudate lobe has been reported and evaluated[12-14], but hepatic resection remains the mainstay for the treatment of HCCs, and is the only approach that provides consistent, long-term survival[18-21].

Due to the lack of large series of patients with HCC in the caudate lobe, studies have produced conflicting reports on the effect of this surgery and prognosis following liver resection. During the late 1980s to early 1990s, several groups[5,12,17] reported that HCCs originating in the caudate lobe easily produced intrahepatic metastases because of the corresponding short portal veins, giving these patients a poor prognosis. Others during the late 1990s[6,16,22], however, reported comparable survival rates for patients with HCCs in the caudate lobe and those with HCCs in other parts of the liver. Our results were in accord with the former findings. In this study, we performed multivariate analysis and calculated survival rates for patients with caudate HCC after resection, in relation to clinicopathologic factors. Our data showed that long-term survival of patients with HCC after hepatectomy depended on the background of cirrhosis, subsegmental location of HCC, surgical resection margin, and extended caudate resection. The overall survival rates in our group after resection of HCC of the caudate lobe were 76.1% at 1 year, 54.7% at 3 years and 31.8% at 5 years. The disease-free survival rates were

65.7% at 1 year, 36.1% at 3 years and 18.8% at 5 years. The results showed poorer overall survival at 5 years than that reported by Ikegami *et al*[16] (66.7%). However, the diameter of the tumors in most of the patients in this earlier study was < 5 cm, which was the reason for the limited hepatic resection performed. In contrast, the median tumor diameter in our series was 5.7 cm, which could account for the poorer prognosis. Overall survival rates of 85.3% at 1 year, 67.0% at 3 years and 50.5% at 5 years were reported in a series of 12 118 patients after resection of HCC by Ikai *et al*[23]. From this point of view, the overall survival of patients with HCC of the caudate lobe after resection was poorer than that of patients with HCCs of other lobes. This survival difference may be related to the anatomy and characteristics of the caudate lobe.

Univariate and multivariate analyses showed significant differences in overall survival depending on subsegmental location of HCC. The results of the current study showed that patients with tumors located in the Spiegel lobe had a better prognosis than those whose tumors were located in the paracaval portion. HCC located in the paracaval portion is contiguous with the major vessels and adequate surgical tumor margins cannot be obtained, especially in the case of liver cirrhosis, making expanded hepatic resection impossible. Asahara *et al*[24] suggested that caudate lobectomy should extend past the right border of the inferior vena cava for adequate resection of the paracaval portion. Counterstaining can be used to identify the border between the paracaval portion and the posterior segments, but although this can demonstrate the border at the liver surface, it is still difficult to accurately identify the border deep within the liver parenchyma. Exposure of the paracaval portion is also difficult due to its deep location, and the greater manipulation required increases the risk of intrahepatic metastasis through the portal vein to the remnant liver.

The importance of chronic liver disease in the prognosis of patients undergoing resection for HCC is well known[23,25-27], and patients with hepatitis C- or hepatitis B-related cirrhosis have poorer prognoses than those with cirrhosis due to other causes[28]. In our study, the cumulative survival rates at 3 and 5 years were 60.6% and 47.9% in non-cirrhotic patients, and 35.0% and 12.3% in cirrhotic patients, respectively. After liver resection for HCC, some reports found that chronic active hepatitis and cirrhosis were the most significant risk factors for intrahepatic recurrence through multicentric carcinogenesis, so-called "multicentric occurrence". This can be explained by the fact that repeated inflammation and cellular necrosis in patients with chronic hepatitis or cirrhosis enhance proliferation and accelerate the development of new foci of HCC, associated with an increased rate of random mutations and promotion due to gene instability[23,26].

A surgical margin of < 5 mm was also identified as an independent risk factor for poor survival following resection of caudate HCC. Although the importance of the size of the surgical margin is controversial, particularly in large tumors, and although satellite nodules have been found at some distance from the tumor, it is usually believed that the risk of recurrence is lower when the surgical margin is large[29-32]. However, obtaining a negative margin may be difficult, particularly in large HCCs, and especially in those located in the caudate lobe. Although we aimed to preserve a wide margin where possible in the current series, it measured < 5 mm in 44% of patients. After analysis of 209 consecutive liver resections in patients with HCC, Tralhão *et al*[33] failed to identify any factors significantly predictive of a thin surgical margin, but thin margins were more common in patients with large tumors, and particularly in those with centrally located tumors. Even in patients with small but centrally located tumors, surgical margins of > 10 mm were infrequent. In our study, 64% of tumors were > 5 cm and related to the paracaval portion, which may be the main reason for the lower incidence of negative margins. Although extensive hepatectomy can obtain a high negative margin rate, only 32% of patients in this study underwent extended caudate lobectomy due to the presence of liver cirrhosis and underlying hepatitis. These results support the prognostic significance of surgical margin and extended resection for overall survival, and suggest that efforts should be made to increase the tumor-free margin. Extended caudate lobectomy is recommended, so long as acceptable liver function is maintained. It has been suggested that adjuvant intraarterial chemotherapy and/or preoperative TACE may reduce the risk of tumor recurrence and improve long-term survival following liver resection for caudate HCC[7]. However, this was not confirmed in our study. Prospective, randomized clinical trials are needed to investigate the role of perioperative TACE for caudate HCC.

In conclusion, hepatectomy was an effective treatment for HCC in the caudate lobe. The subsegmental location of the tumor, presence of liver cirrhosis and the surgical margin affected long-term survival.

COMMENTS

Background

Hepatic resection is considered, in principle, to be the first choice for treatment of hepatocellular carcinoma (HCC) in the caudate lobe. However, the surgical treatment for HCC in the caudate lobe presents a major challenge and is associated with high risks for the surgeon, due to its unique anatomic location and complicated relationship with the major vasculature. Until now, the prognosis for patients following resection of caudate lobe HCC has not been fully determined.

Research frontiers

Caudate HCC has a poorer prognosis than HCC originating from other lobes, due to its proximity to the portal trunk and inferior vena cava, which facilitate its intrahepatic and systemic spread early in the disease. A large number of studies have confirmed that liver disease, tumor grade, tumor size, tumor margin, blood loss and other factors influence the incidence of tumor recurrence and long-term survival after resection of HCC.

Innovations and breakthroughs

Hepatectomy was an effective treatment for HCC in the caudate lobe. The subsegmental location of the tumor, presence of liver cirrhosis and surgical margin affected long-term survival.

Applications

The results of this research suggest that surgeons should make every effort to increase the tumor-free margin. Extended caudate lobectomy is recommended, so long as liver function can be maintained.

Terminology

The caudate lobe is generally divided into three regions: the left Spiegel, the

process portion, and the paracaval portion. Isolated caudate lobectomy involves the removal of all or part of the caudate lobe, and extended hepatectomy involves resection of all or part of the caudate lobe, in conjunction with other lobes of the liver.

Peer review

The authors report a series of 114 liver resections in patients with HCC in the caudate lobe. The perioperative data, complications and outcome were analyzed. This study addressed an important and interesting issue.

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