

Outcome of Oligonodular Hepatocellular Carcinoma after Hepatectomy

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DOI: <https://doi.org/10.3329/jafmc.v15i1.48643>

Abstract

Introduction: Hepatocellular carcinoma (HCC) is a common cancer and is the third most common cause of cancer-related death worldwide. Frequent recurrence of HCC after resection is a major surgical limitation. Early recurrence is the most disappointing outcome after surgery for multinodular HCC. Several studies found good results after hepatectomy for oligonodular (2 or 3 nodules) HCC.

Objectives: To observe the recurrence rate three months after hepatectomy for oligonodular HCC and study the possible risk factors.

Materials and Methods: The study population consisted of 102 patients with oligonodular HCC and received hepatectomy in Combined Military Hospital (CMH) between July 2011 and July 2017 according to the following criteria: (1) numbers of tumour nodules determined by preoperative imaging (computed tomography or magnetic resonance imaging) and intraoperative exploration; (2) diagnosis of HCC confirmed by postoperative histopathology; (3) incision margins negative; (4) complete clinicopathologic data; (5) adjuvant chemotherapy advised one month after operation. Multicentric occurrence (MO) and intrahepatic metastasis (IM) were determined in each patient according to the histopathologic examination.

Results: Among 102 patients, 43(42.2%) had small tumor stain three months after surgery, 22(21.6%) and 21(20.6%) were defined as single and multiple recurrence respectively. The recurrence rate of patients with microvascular involvement was higher (64.3%) than those without (33.8%), ($p < 0.05$). IM or MO, complete tumor capsule or not, number of tumors (2 versus 3), liver condition (cirrhosis versus chronic hepatitis) showed no significant difference.

Conclusion: There was a high rate of very early recurrence for patients with oligonodular HCC three months after hepatectomy, and the hepatic resection seems no-account for these patients regardless of very early recurrence or not a curative resection. Microvascular involvement was a risk factor while IM or MO is not.

Key-words: Hepatocellular carcinoma, Oligonodular, Intrahepatic metastasis and Recurrence.

Introduction

Hepatocellular carcinoma (HCC) is a common cancer and is the third most common cause of cancer-related death worldwide and is particularly prevalent in China^{1,2}. With advances in surgical

techniques and perioperative care, hepatic resection for HCC can be performed with a low hospital mortality rate, even in patients with chronic liver disease^{3,4}. The results of hepatic resection⁵⁻⁷ for early-stage HCC were favorable with 5-year survival rates ranging from 40% to 70%. However, the frequent recurrence of HCC after resection is a major surgical limitation. Recurrence rates range from 78% to 96% and may be the result of intrahepatic metastases (IM) or multicentric occurrence (MO)⁸. The time interval from resection of HCC to recurrence has been reported to be an independent prognostic factor of survival after recurrence⁹.

The role of resective surgery in patients with multinodular HCC is still under debate, although several studies have declared good results of hepatic resection for patients with two or three nodules^{10,11}. Early recurrence is the most disappointing reason, and if patient presents recurrence one month after hepatectomy, the hepatic resection seems no-account. Therefore, in this study, we made an observation of recurrence one month after hepatectomy for oligonodular (2 or 3 nodules) HCC.

Materials and Methods

This interventional study was conducted from July 2011 to July 2017, there were 102 patients with two or three HCC nodules received hepatectomy in our hospital. All the patients had good liver function (Child-Pugh's class A) and were offered hepatic resection. These 102 patients were enrolled in this study according to the following criteria: (1) number of tumor nodules determined by preoperative imageology (computed tomography or magnetic resonance imaging) and intraoperative exploration; (2) diagnosis of HCC confirmed by postoperative histopathology; (3) incision margins negative; (4) complete clinicopathologic data; Clinicopathologic data from 102 patients were collected. 31 patients were excluded for the following reasons: one patient died after surgery during the first hospital admission for liver resection; and 30 patients did not report for chemotherapy one month after operation.

The number of tumors were calculated by either main tumor and satellite nodules or separated nodules. When comparing the two or three nodules in each patient, MO and IM were determined in accordance with conventional histological criteria¹². Briefly, MO have the following features: (1) each nodule should be separately registered as a principal tumor; (2) separated nodules that consist of early HCC of well differentiated type or that imply tumors of moderately or poorly differentiated HCC that have a margin of

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well differentiated HCC; (3) different subtype of HCC is diagnosed in each nodule. The other tumors not meeting the MO criteria were defined as IM, which mainly have such features: (1) tumors clearly growing from portal vein thrombi; (2) tumors surrounding a large main tumor with multiple satellite nodules; (3) a small solitary tumor near the main tumor that is histologically similar or less differentiated than the main tumor. Data were collected and analyzed with SPSS 13.0. The differences between categorical variables were analyzed with a chi-square test and p values <0.05 were considered statistically significant.

Results

There were 96 males and 6 females, for a male-to-female ratio of 16:1. The median patients' age was 50 years (range 29-75 years). All the patients had viral hepatitis, of which 98 patients had hepatitis B virus (HBV). There were 2 HCC nodules in 84(82.4%) patients and 3 in 18(17.6) patients. According to the histologic findings, liver cirrhosis was appeared in 69(67.6%) patients, median tumor size was 4.0 cm (rang 0.5-21 cm), 28(27.5%) patients manifested microvascular involvement, 57(55.9%) and 45(44.1%) patients were considered to be IM and MO respectively (Table-I). A total 43(42.2%) patients had small tumor stain one month after surgery. 21.6%(22/102) and 20.6%(21/102) were defined as single and multiple recurrence respectively. The recurrence rate of patients with microvascular involvement was significantly higher than those without microvascular involvement (64.3% versus 33.8%), (p<0.05), while other variables showed no significant difference (Table-II).

Table-I: Clinicopathological features of patients (n=102)

Variables		Frequency	Percentage
Age	<40 years	16	15.7
	≥40 years	86	84.3
Gender	Male	96	94.1
	Female	6	5.9
Hepatitis etiology	HBV	98	96.0
	HCV	2	2.0
	HBV&HCV	2	2.0
Number of tumors	2 HCC	84	82.4
	3 HCC	18	17.6
Serum AFP level	≤100 ng/ml	40	39.2
	>100 ng/ml	62	60.8
Liver condition	Cirrhosis	69	67.6
	Chronic hepatitis	33	32.4
Complete tumor capsule	Present	55	53.9
	Absent	47	46.1
HCC grade	I	1	1.0
	II	17	16.6
	III	83	81.4
	IV	1	1.0
Microvascular involvement	Yes	28	27.5
	No	74	72.5
IM or MO group	IM	57	55.9
	MO	45	44.1
Recurrence one month after surgery	Single	22	21.6
	Multiple	21	20.6
	None	59	57.8

Note: HBV: hepatitis B virus; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; AFP: alph-fetoprotein; IM: intrahepatic

metastasis; MO: multicentric occurrence; &: Edmondson-Steiner grading.

Table-II: The comparison of clinicopathological features among single, multiple and none recurrence

Variables		Recurrence			p Value
		Single N (%)	Multiple N (%)	None N (%)	
IM or MO group	IM	12 (21.1)	13 (22.8)	32 (56.1)	> 0.05
	MO	10 (22.2)	8 (17.8)	27 (60.0)	
Microvascular involvement	Yes	6 (21.4)	12 (42.9)	10 (35.7)	< 0.05
	No	16 (21.6)	9 (12.2)	49 (66.2)	
Complete tumor capsule	Present	15 (27.3)	10 (18.2)	30 (54.5)	> 0.05
	Absent	7 (14.9)	11 (23.4)	29 (61.7)	
Number of tumors	2 HCC	18 (21.2)	18 (21.2)	49 (57.6)	> 0.05
	3 HCC	4 (23.5)	3 (17.6)	10 (58.8)	
Liver condition	Cirrhosis	14 (20.3)	15 (21.7)	40 (58.0)	> 0.05
	Chronic hepatitis	8 (24.2)	6 (18.2)	19 (57.6)	

Note: IM: intrahepatic metastasis; MO: multicentric occurrence.

Discussion

Recent advances in liver resection techniques and perioperative management have enable the aggressive surgical intervention for patients with advanced liver cancer such as multinodular HCC. Several authors have proposed hepatic resection in selected groups of patients for multiple HCC demonstrating encouraging results¹³. However, whether hepatic resection is always appropriate for patients who have oligonodular HCCs is not clear, as the lesions may contain IM that lessen the therapeutic efficacy. A more recent study reported by Ruzzenente et al¹¹ making an observation of 464 patient with advanced HCC. They applied a routine intraoperative ultrasonography to evaluated the presence of additional tumors and concluded that patients with oligonodular HCC could benefit from liver resection where survival is longer than after local ablative therapies (LAT) or supportive therapy (ST), but in patients with more than three HCCs, liver resection have similar results of LAT. Thus, how to identify the actual number of tumors before surgery become the key point for patients with oligonodular HCCs. As we know, HCC is diagnosed mainly by imaging techniques such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). Although advances in imaging techniques have enable the detection of small HCC¹⁴⁻¹⁶, some small HCC nodules still can not be detected¹⁷. Moreover, HCCs often MO and are frequently accompanied by IM^{12,18,19}. Therefore, hepatic surgeons will face a puzzle to make a decision of surgery or LAT for patients with two or three tumor nodules.

The present study observed that 42.2% patients had tumour one month after surgery where 21.6% and 20.6% were defined as single and multiple recurrence respectively. Early recurrence is defined as intrahepatic, regional or systemic recurrence within 1 year. For these patients had recurrence within 1 month, we would like to name it very early recurrence or consider the prior surgery not a curative resection. The disappointing thing of this study is that there is no data of long-term survival at the present time, so we can not concluded that these patients could not benefit from hepatectomy arbitrarily. However, it has been reported that early recurrence after curative resection, is one of the most important

factors impacting the prognosis and outcome of the disease. Recurrent disease has been found to be the leading cause of death during the first year²⁰. Thus, we proposed that these patients would have a poor prognosis, regardless of very early recurrence or not a curative resection and the long-term survival will be reported in the further studies when we finish the follow-up.

There were 27.5% patients manifested as microvascular involvement while other 72.5% patients were not. Further analysis demonstrated that microvascular involvement or not was significantly different among the three groups of recurrence, while there was no significant difference between IM and MO. Some groups have reported the incidence of MO in patients with HCC related to HCV reaches approximately 50%, and HCC with IM recurs earlier and has a poorer prognosis than its MO counterpart^{21,22}. Nevertheless, the discrimination of IM and MO in the above studies depended on the histopathologic examination. In fact, by clonal analysis using Southern blot hybridization, Hsu et al, found unicentric origin IM in 93.8% patients with multiple HCCs that were histologically regarded as multicentric in origin²³. This mean that most of the patients with multiple HCCs may be regarded as having IM, and multicentric HCCs with synchronous occurrence are thought to be clinically less important than those with metachronous occurrence¹². Without survival analysis, we could not estimate the differences of long-term prognosis between IM and MO, further study will be carried out to disclose the doubt.

Conclusion

The present study observed a high rate of very early recurrence for patients with oligonodular HCC just three months after hepatectomy. However, the hepatic resection seems no-account for these patients regardless which is true. Furthermore, the recurrence rate of patients with microvascular involvement was significantly higher than those without microvascular involvement, and there was no significant difference of recurrence between IM and MO.

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