ANTICANCER RESEARCH *24*: 1929-1934 (2004)

Preoperative Chemolipiodolization of the Whole Liver for Hepatocellular Carcinoma

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Abstract. *Background: Preoperative transarterial chemoembolization is not routinely recommended before hepatectomy for resectable hepatocellular carcinoma. This study evaluated the effect of preoperative whole-liver chemolipiodolization. Patients and Methods: A retrospective comparison of background characteristics, operative results and long-term outcome was performed between 36 patients with chemolipiodolization confined to the tumor (selective group) and 23 patients with chemolipiodolization also involving the noncancerous liver (whole-liver group). Results: There were no serious side-effects in either group and the operative outcome did not differ between the two groups. Tumor diameter was significantly greater in the selective group, but other pathological characteristics were comparable. The 5-year disease-free and overall survival rates for the selective and whole-liver groups were 11.9% and 33.0% (p=0.0191) and 44.9% and 73.2% (p=0.0121), respectively. Conclusion: These results indicate that preoperative whole-liver chemolipiodolization reduces postoperative recurrence and prolongs survival in patients undergoing resection of hepatocellular carcinoma.*

Advances in surgical techniques and perioperative management have transformed the resection of hepatocellular carcinoma (HCC) into a relatively safe operation with a low mortality rate (1). However, long-term survival is still unsatisfactory because of the high recurrence rate after curative resection (2). Macroscopic or microscopic portal vein involvement and intrahepatic metastasis are the factors that are most consistently reported to indicate a poor prognosis after surgery (3, 4). Development of new tumors in the remnant liver, *i.e.*, *de novo* primary HCC, is also thought to occur (5). In order to achieve a better prognosis, it is most important to prevent recurrence after the initial resection of HCC, but there is currently no standard therapy for intrahepatic metastasis.

Transarterial chemoembolization (TAE) has been used since the early 1980s as neoadjuvant therapy for HCC, in an attempt to reduce postoperative recurrence and improve long-term survival (6, 7). Based on the currently available evidence, preoperative TAE is not recommended as a routine procedure before hepatectomy for resectable HCC. Furthermore, TAE may be contraindicated in patients with cirrhosis, because it leads to progressive deterioration of liver function (8).

The present study evaluated the effects of preoperative whole-liver chemolipiodolization, involving both the tumor and the noncancerous liver.

Patients and Methods

Patients. Between June 1992 and December 1999, 166 patients with HCC underwent curative hepatic resection at our institution. A curative operation was defined as one in which all detectable tumors were macroscopically resected. Among these 166 patients, TAE was performed preoperatively in 59. These 59 patients were randomized to have either chemolipiodolization with gelatin sponge for the existing HCC (selective group, n=36), or chemolipiodolization with gelatin sponge for the tumor plus chemolipiodolization without gelatin sponge for the noncancerous liver (whole-liver group, n=23). All patients gave informed consent to their treatment.

Chemolipiodolization. A catheter was selectively inserted into the right or left hepatic artery, a segmental artery, or a subsegmental artery by the Seldinger method. In the selective group, TAE was performed *via* the right hepatic artery in 18 patients, the left hepatic artery in 6 patients, a segmental artery in 5 patients and a subsegmental artery in 7 patients from the selective group. In the whole-liver group, TAE was performed *via* the right or left hepatic artery to target the HCC and chemolipiodolization alone was carried out on the noncancerous side (the left hepatic artery in 11 patients and right hepatic artery in 6 patients). TAE was performed *via* the right or left subsegmental artery to target the HCC and chemolipiodolization was performed *via* the right or left hepatic

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Key Words: Hepatocellular carcinoma, chemo-lipiodolization, hepatectomy.

Table I. *Method of selective TAE and whole-liver chemolipiodolization.*

	Selective Group	Whole-liver Group	
	Tumor	Tumor	Noncancerous liver
Material			
Farmorbicin (mg)	47.2±16.5	27.6±6.0	19.1±5.5
Lipiodol (ml)	3.2±2.3	2.4±1.0	1.6±0.5
Gelatin sponge	+	+	-
Artery			
RHA	18	RHA, LHA	11
LHA	6	LHA, RHA	6
Segmental	5	(R) Subsegmental, RHA, LHA	3
Subsegmental	7	(L) Subsegmental, LHA, RHA	3

Data represent the means±standard deviation or the number of patients. RHA, right hepatic artery; LHA, left hepatic artery; R, right; L, left.

artery in 6 patients. As the catheter was withdrawn, chemolipiodolization of the noncancerous liver was performed *via* the left or right hepatic artery in these patients. The embolic materials used were gelatin sponge and iodized oil (Lipiodol). Epirubicin (Farmorbicin) (mean±SD: 47.2±16.5 mg), lipiodol (3.2±2.3 ml) and gelatin sponge were infused in the selective group. In the whole-liver group, epirubicin (27.6±6.0 mg), lipiodol (2.4±1.0 ml) and gelatin sponge were used to target the HCC, while only epirubicin (19.1±5.5 mg) and lipiodol (1.6±0.5 ml) were infused into the noncancerous liver (Table I).

Clinicopathological variables and operative procedures. Prior to undergoing surgery after selective TAE or whole-liver chemolipiodolization, each patient underwent indocyanine green clearance, technetium-99m-diethylenetriamine pentaacetic acid-galactosyl human serum albumin liver scintigraphy and conventional liver function tests. In addition, hepatitis screening was done by measurement of the hepatitis B surface antigen and hepatitis C antibody, while α-fetoprotein and protein-induced vitamin K antagonist-2 were measured in all patients. The operative procedure has been reported previously (9). Major resection was defined as a bisegmentectomy, a segmentectomy (resection of more than one segment but less than a hemihepatic lobe), or a subsegmentectomy (anatomic resection of hepatic portions smaller than a segment). All other nonanatomic resections were defined as minor resection. A single senior pathologist reviewed each specimen for histologic confirmation. Tumor size was recorded as the maximum diameter and the distance from the tumor edge to the resection margin was measured and called the margin width. The TNM method was used for tumor staging (10). Postoperative and perioperative complications or deaths were defined as occurring within one month of surgery or during hospitalization, respectively.

Follow-up after hepatic resection. All patients were followed at outpatient clinics after discharge. Routine imaging, such as ultrasonography, computed tomography, or magnetic resonance imaging, was performed every 2-3 months in addition to the assessment of serum α-fetoprotein and protein-induced vitamin K antagonist-2 levels. Tumor recurrence that was limited to the remnant liver was treated by either TAE or repeat resection.

Statistical analysis. Continuous variables are presented as the mean±standard deviation (SD). The significance of differences between the two groups was assessed by the Chi-squared test or the unpaired Student's *t*-test as appropriate. The Kaplan-Meier life-table method was used to calculate disease-free and overall survival rates as of June 2002 and differences were estimated using the generalized log-rank test. A probability value <0.05 was considered statistically significant.

Results

There were no serious side-effects either during or after selective TAE or whole-liver chemolipiodolization. The interval between selective TAE and hepatic resection was 24.5 (±11.2) days, while it was 22.7 (±15.0) days after whole-liver chemolipiodolization. Table II shows the preoperative characteristics of patients in the selective and whole-liver groups. There were no significant differences between the groups with respect to gender, age, etiology of hepatitis or cirrhosis, alcohol abuse, preoperative liver function, or serum α-fetoprotein level. The operative results and pathological characteristics of each group are listed in Table III. The surgical procedures, operating time, amount of blood loss and blood transfusion requirement did not differ between the two groups. Postoperative complications such as major bile leakage, intractable ascites and pleural effusion attributable to surgery occurred in 7 (19.4%) patients from the selective group and 2 (8.7%) patients from the whole-liver group. No patient from either group died within one month of the operation. Although the tumor diameter was significantly greater in the selective group than in the whole-liver group, the other pathological characteristics were comparable.

In the selective group, 19 patients died of recurrent cancer, 2 died of causes unrelated to cancer, 9 are still alive with recurrent HCC and 6 are disease-free. In the whole-liver group, 7 patients died of recurrent cancer, 1 died of an unrelated cause, 7 are still alive with recurrent HCC and 8 are disease-free. The disease-free survival rates of the selective and whole-liver groups were respectively 50.0% and 82.4% at 1 year, 25.0% and 59.5% at 3 years and 11.9% and 33.0% at 5 years (Figure 1). The disease-free survival rate was significantly better in the whole-liver group ($p=0.0191$). Among the living or deceased patients without tumor recurrence, the overall survival rates in the selective and whole-liver groups were 88.9% and 91.3% at 1 year, 68.8% and 77.8% at 3 years and 44.9% and 73.2% at 5 years, respectively (Figure 2). The overall survival rate was significantly better in the whole-liver group than in the selective group ($p=0.0121$).

Table II. *Preoperative characteristics of the patients.*

	Selective Group (n=36)	Whole-liver Group (n=23)	*P* value
Gender (male/female)	28/8	21/2	0.1768
Age (yr)	61.4±7.8	62.1±6.6	0.7121
Etiology (HBV/HCV/other)	3/30/3	3/16/4	0.4453
Alcohol abuse (+/–)	15/21	13/10	0.2651
Platelet count (10^4/μl)	15.8±8.2	13.0±8.6	0.2145
Total bilirubin (mg/dl)	0.84±0.27	0.93±0.38	0.3262
Albumin (g/dl)	3.80±0.47	3.73±0.37	0.5098
ALT (IU/l)	47±27	55±30	0.2397
Prothrombin time (%)	89±10	86±12	0.4490
Hepaplastin test (%)	87±13	83±22	0.4319
ICG R15 (%)	16.8±6.3	18.2±8.6	0.5137
K-ICG (min^{-1})	0.129±0.040	0.117±0.032	0.2797
GSA Rmax (mg/min)	0.444±0.176	0.379±0.167	0.2086
AFP (ng/ml)	67±147	83±157	0.6952

The data represent the mean±standard deviation or the number of patients.
HBV, hepatitis B virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; ICG R15, indocyanine green retention rate at 15 min; K-ICG, ICG disappearance rate; GSA Rmax, maximal removal rate of technetium-99m-diethylenetriamine pentaacetic acid-galactosyl human serum albumin; AFP, α-fetoprotein.

Table III. *Operative results and pathological classification of resected specimens.*

	Selective Group (n=36)	Whole-liver Group (n=23)	*p* value
Operative procedure (major/minor)	17/19	11/12	0.9639
Operating time (min)	287±110	288±126	0.9799
Operative blood loss (ml)	1695±2362	1686±1861	0.9871
Blood transfusion (+/–)	17/19	13/10	0.4859
Complications (+/–)	7/29	2/21	0.2627
Tumor size (cm)	4.36±3.13	2.95±1.52	0.0484
No. of tumors (solitary/multiple)	27/9	19/4	0.4916
Histology (Well/Moderately/Poorly)	4/31/1	5/17/1	0.4971
fc (+/–)	35/1	21/2	0.3129
TW (+/–)	12/24	4/19	0.1792
vp and/or vv (+/–)	23/13	9/14	0.0626
im (+/–)	7/29	3/20	0.5227
Associated liver disease (normal/fibrosis or hepatitis/cirrhosis)	4/18/14	1/11/11	0.5959
Tumor stage (I/II/III/IV A)	7/13/10/6	4/12/5/2	0.6269

Data represent the mean±standard deviation or the number of patients. fc, microscopic capsular formation; TW, surgical margin <5 mm; vp, microscopic invasion of the portal vein; vv, microscopic invasion of the hepatic vein; im, microscopic intrahepatic metastases.

Discussion

TAE is recognized as a treatment for HCC, either as an adjuvant to resection or as a definitive procedure in patients with tumors that are considered unresectable (11, 12). Uchida *et al.* (8) reported a decreased survival rate in cirrhosis patients undergoing TAE prior to resection of HCC compared with patients who did not have TAE. They therefore recommended against the preoperative use of TAE because the procedure itself may accelerate deterioration of the compromised hepatic parenchyma, particularly in the setting of cirrhosis. Lu *et al.* (13) performed a retrospective analysis of 120 HCC patients and concluded that preoperative TAE might benefit patients with tumors >8 cm, but not those with tumors measuring 2-8 cm. In contrast, it was reported that downstaging or total necrosis of the tumor induced by preoperative TAE occurred in 62% of 103 HCC patients with cirrhosis, being associated with improved disease-free survival after both liver resection and transplantation (14). Therefore, preoperative performance of TAE is controversial.

To our knowledge, there has been no previous report about the effect of preoperative whole-liver chemolipiodolization on the long-term outcome after resection of HCC. In the present study, we showed that preoperative chemolipiodolization of the whole liver resulted in significant prolongation of disease-free survival and overall survival. The precise mechanism remains unclear, but some possible explanations for this finding are: 1) subclinical micrometastases due to portal vein dissemination or multicentric primary tumors may be eliminated by whole-liver therapy, and 2) a reduction of the tumor burden before surgery may lessen the development of resistance to chemotherapy.

The selective group had significantly larger tumors than the whole-liver group. It has been reported that a larger tumor size, especially >5 cm, leads to a significantly higher risk of HCC recurrence (15-18). This has been attributed to the increased invasiveness of larger tumors, as demonstrated by a higher incidence of intrahepatic metastasis and portal vein invasion (19, 20). In patients with larger HCC lesions, survival depended on progression of the tumor itself, including the size and/or number of lesions irrespective of preoperative whole-liver chemolipiodolization. The difference of tumor size between the two groups in our study may not have contributed to the long-term outcome after curative resection in patients with a small HCC lesion.

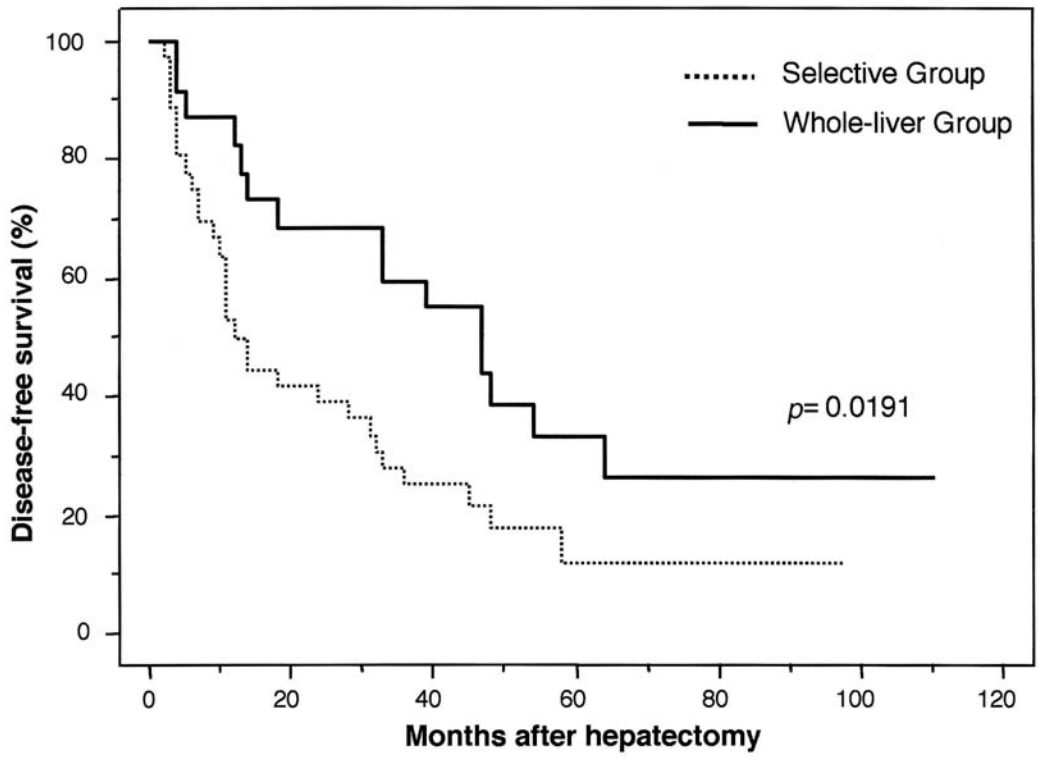

Figure 1. *Comparison of disease-free survival after resection of HCC between patients receiving selective TAE (Selective Group, n=36) or whole-liver chemolipiodolization (Whole-liver Group, n=23) preoperatively. The disease-free survival rate of the latter group was significantly better (p=0.0191).*

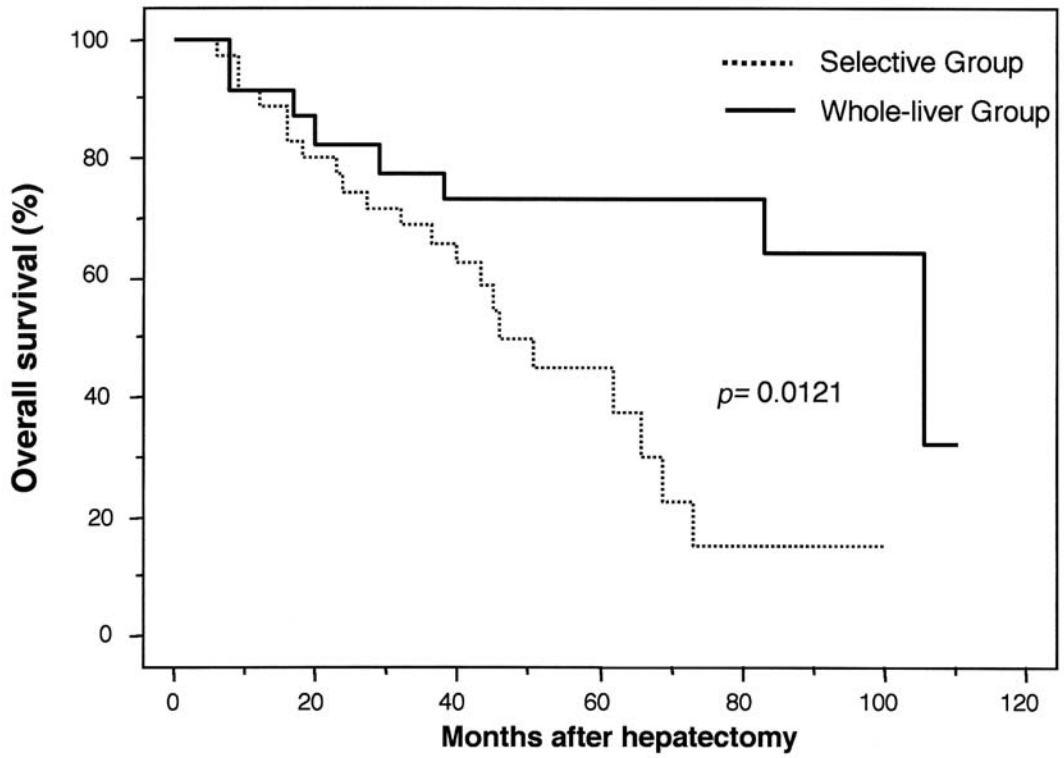

Figure 2. *Comparison of overall survival after resection of HCC between patients receiving selective TAE (Selective Group, n=36) or whole-liver chemolipiodolization (Whole-liver Group, n=23) preoperatively. The overall survival rate of the latter group was significantly better (p=0.0121).*

In conclusion, preoperative chemolipiodolization of the whole liver is effective for reducing the incidence of postoperative recurrence and prolonging survival in patients with resectable HCC. Further studies (preferably a prospective, randomized trial) are needed to confirm the value of whole-liver preoperative chemolipiodolization before hepatectomy for HCC.

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Received January 2, 2004
Accepted March 5, 2004