Results of hepatic resection and postoperative arterial chemotherapy for hepatocellular carcinoma*

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Summary. To improve the outcome of patients who had undergone hepatic resection for hepatocellular carcinoma (HCC), we employed postoperative adjuvant hepatic arterial infusion chemotherapy (AHAI) in 23 patients. Patients showing various risk factors for the recurrence of HCC were given one shot of doxorubicin and mitomycin C suspended in an oily medium (lipiodol) and an infusion of 5-fluorouracil. The 3-year survival value calculated for patients who were treated with AHAI was 75%, which was significantly higher than that found for patients who did not receive AHAI ($n = 156$; $P < 0.05$). In addition, among the patients who underwent hepatic lobectomy, the survival of those who received AHAI was also significantly greater than that of those who did not ($n = 46$; $P < 0.01$). AHAI did not cause any severe complications. These results indicate that AHAI may be an effective therapy for patients with HCC.

Introduction

In Japan, hepatic resection has been performed in many patients with hepatocellular carcinoma (HCC) in the presence or absence of underlying liver cirrhosis, thanks to recent advances in diagnostic procedures and in intra- and postoperative management of patients undergoing liver surgery [4, 10]. The long-term outcome, however, has not been satisfactory due to the high rate of complication of liver cirrhosis and/or the high incidence of recurrence in the remnant liver during the early postoperative period [5]. To improve the patients' outcome following hepatic resection for HCC, we adopted postoperative adjuvant hepatic arterial infusion chemotherapy (AHAI) for the last 3 years to prevent the intrahepatic recurrence of HCC. The present paper evaluates the effects of AHAI in relation to the method of hepatic resection and the stage of HCC.

Patients and methods

A total of 240 patients with HCC underwent partial hepatic resection at the Department of Surgery II of Nagoya University Hospital between January 1980 and September 1990. Overall, 187 cases (78%) were associated with liver cirrhosis.

In all, 69 patients underwent lobectomy; 50, segmentectomy; 43, subsegmentectomy; and 78, limited partial resection. Of the cases requiring lobectomy, 57% were associated with liver cirrhosis (Table 1). According to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan [3], the radicality of resection was divided into four grades: absolute curative, relative curative, relative non-curative, and absolute non-curative. Following the exclusion of 20 cases of hospital death and 15 patients who underwent absolute non-curative resection, 205 patients were evaluated for postoperative long-term outcome.

AHAI was performed in 23 patients. All of these subjects displayed at least one of the following high-risk factors for recurrence after hepatic resection: a surgical margin of less than 10 mm, a lack of capsule formation, the presence of intrahepatic metastasis, and the presence of a tumor embolus in the second or more proximal branches of the portal vein as operative findings [7]. A heparin-coated catheter (PU catheter; Toray Industries, Japan) was inserted into the common hepatic artery through either the right gastroepiploic artery or the deep femoral artery; it was connected to a reservoir (Catheter Access; Nipro Co., Japan).

AHAI was started within 6 weeks after surgery. For drug administration, a daily dose of 250 mg 5-fluorouracil (5-FU) was infused over a period of 3 h for 14 days from the reservoir, and 0.4 mg/kg doxorubicin (Adriamycin) and 0.12 mg/kg mitomycin C suspended in an oily medium

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Table 1. Types of hepatic resection performed for HCC in 240 patients

Operation	Number	Liver cirrhosis
Partial resection	78	69 (88%)
Subsegmentectomy	43	40 (93%)
Segmentectomy	50	39 (78%)
Lobectomy	69	39 (57%)
Totals	240	187 (78%)

Table 2. Cause of death in 106 patients after hepatic resection for HCC

| Operation	HCC	Liver failure	GI bleeding	Hospital death	Other
Subsegmentectomy or partial resection	26	8	6	8	4
Segmentectomy or lobectomy	25	12	1	12	4
Totals	51 (48%)	20 (19%)	7 (7%)	20 (18%)	8 (8%)
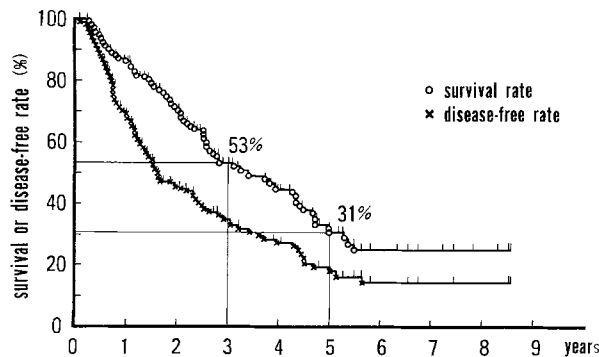
Fig. 1. Postoperative survival and disease-free rates found for 205 patients who underwent hepatic resection for HCC
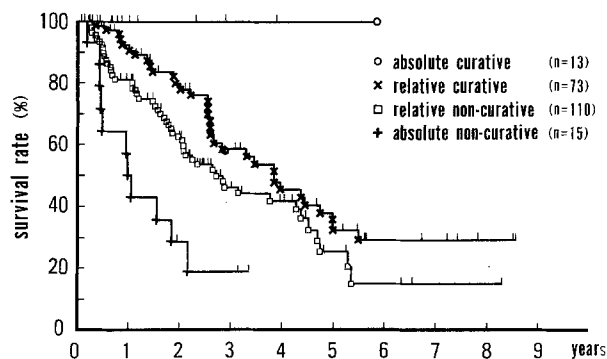
Fig. 2. Comparison of the postoperative survival of 211 patients with HCC as a function of the radicality of hepatic resection

(lipiodol) were injected twice as a bolus dose on the 1st and 8th days. The above was defined as one course of AHAI, and it was repeated every 3 months. 5-FU was given orally between courses. The resected liver specimens of all patients were histopathologically investigated. The cumulative percentage of survival and the disease-free survival were estimated by the product-limited (Kaplan-Meier) method.

Results

The main cause of death in 106 patients for whom the cause could be confirmed was recurrent disease (48%), but liver failure due to deteriorated remnant-liver function was also an important cause (19%; Table 2).

The 3- and 5-year survival values found for the 205 evaluable patients who underwent hepatic resection for
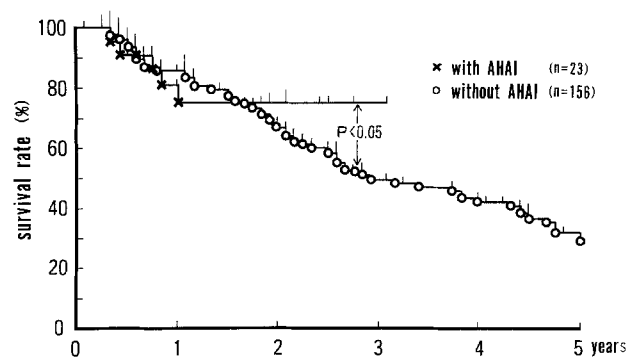
Fig. 3. Survival of patients after hepatic resection for HCC as determined in the presence or absence of AHAI, excluding patients who had tumors measuring less than 2 cm in maximal diameter and showed no vascular invasion
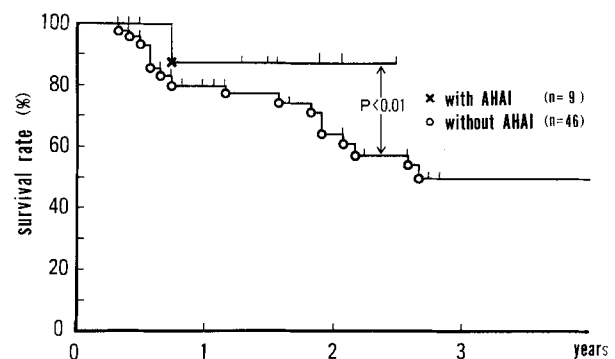
Fig. 4. Survival of patients as determined in the presence or absence of AHAI following either relative curative or relative non-curative hepatic lobectomy for HCC

HCC were 53% and 31%, respectively. The 3- and 5-year disease-free survival values were 36% and 20%, respectively (Fig. 1). With regard to the aspect of the radicality of the surgery, the 5-year survival value for patients who underwent absolute curative resection was 100%. No significant difference was found between the patients who underwent relative curative resection and those who underwent relative non-curative resection (Fig. 2). The 3-year survival of the 23 patients who were treated with AHAI was 75%. Of the 205 patients, 26 had stage I tumors (lesions measuring less than 2 cm in maximal diameter that had not invaded vessels), 23 were treated with AHAI, and 156 did not undergo AHAI. A comparison of the 3-year survival values found for the group that was treated with AHAI and those calculated for the group that did not undergo AHAI revealed that the survival of the former significantly greater than that of the latter (P <0.05; Fig. 3). In addition, in patients undergoing either relative curative or relative non-curative lobectomy, the 3-year survival of the patients who underwent AHAI was also significantly greater than that of patients who did not (P <0.01; Fig. 4). During the course of AHAI, some patients complained of epigastric discomfort. In these cases, gastric erosion and/or mucosal redness were observed endoscopically. A transient fever also developed occasionally. However, no serious complication was encountered.

Discussion

The number of patients undergoing hepatic resection for HCC has increased over the last 10 years. Their long-term prognosis after hepatic resection has been reported by many surgical institutions, but it does not seem to be satisfactory [2]. In our experience, the 5-year survival value was 31%, although we performed extended resection even in cirrhotic patients whenever possible. The main cause of death in these patients was tumor recurrence, mostly in the remnant liver (48%), and the 3-year disease-free survival was only 20%. Therefore, for improvement of the prognosis after hepatic resection, effective countermeasures to prevent intrahepatic tumor recurrence are needed.

There have been many reports on the use of chemotherapy for the treatment of unresectable HCC by either the systemic or the transarterial route [8, 9]. Konno et al. [1] reported that ethiodized oil (lipiodol) was retained only by the tumor tissue in the liver and that it was useful as a carrier of anticancer drugs. We also reported that hepatic arterial chemotherapy employing Adriamycin and mitomycin C suspended in lipiodol with 5-FU was effective against unresectable HCC [6]. On the basis of these experiences, we have used AHAI after hepatic resection. As shown in Fig. 2, the outcome of patients who underwent absolute curative resection was extremely good. Therefore, AHAI was carried out in patients who displayed various risk factors for recurrence as described earlier. As a result, the 3-year survival of the patients treated with AHAI was significantly greater than that of the patients who did not undergo AHAI, although no intergroup difference was found in the 2-year survival. The efficacy of AHAI was also demonstrated in patients who underwent hepatic lobectomy. More courses of AHAI could be given to these patients because their hepatic function was relatively good. Therefore, the efficacy of AHAI was more evident in the lobectomy group than in the other hepatic resection groups.

No severe postoperative complications developed in the patients evaluated in this study. When patients complained of epigastric discomfort due to gastritis and/or a fever, the infusion was immediately discontinued; it was resumed after the subjects had recovered sufficiently. Furthermore, since most patients with HCC also show chronic hepatic damage, the AHAI therapy was started after sufficient postoperative recovery of both the liver and the general condition of the subjects.

In conclusion, AHAI after hepatic resection may be effective in improving the prognosis of patients with HCC. For the establishment of its significance, further studies using a longer follow-up period and improved methods are needed.

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