

## Experience with Indonesian patients who had hepatocellular carcinoma

\*Masayuki Yamamoto, \*\*Yoshihiro Akahane, \*\*Takao Ainota,  
\*Jun Itakura, \*Kaoru Nagahori, \*Hideki Fujii,  
\*\*Masayuki Fujino, \*Yoshiro Matsumoto, \*\*\*Hiroshi Suzuki

To go abroad to receive medical treatment in a foreign country with a different culture and different language can be stressful. Our hospital has received 19 Indonesian patients since 1985.

It is a great honour that these patients from overseas rely on us, but the lack of experience with foreign patients and the inability to communicate have caused several problems. In the present report, we describe our experience with Indonesian patients with hepatocellular carcinoma (HCC), in particular, those who underwent liver resection. We hope this report will help Indonesian HCC patients receive comfortable treatments in Yamanashi and also help our Japanese staff understand patients from other cultures.

**Key words:** Indonesian, hepatocellular carcinoma, liver resection

### Details of patients

In 1985, we received our first 4 patients from Indonesia. One 46-year-old female patient with irritable colon came to the First Department of Medicine of our University hospital for an examination. Her husband was a researcher in the same department at that time. The other 3 patients came to get medical treatments for their liver diseases; 2 had liver cirrhosis and one had a highly advanced metastatic liver tumor from pancreatic cancer. The latter stayed only for 10 days in our hospital.

Thus, our actual experience with Indonesian patients undergoing liver resection began in 1988, after our Yamanashi delegation lead by Professor

Suzuki, the former director of the First Department of Medicine and the present President of our University, visited the University of Indonesia in Jakarta [1] and Airlangga University in Surabaya [2] for a joint symposium on HCC. On that occasion, we demonstrated our techniques in ultrasonography (US), selective angiography of the liver (SAG) as well as liver resection. Since then, 15 patients have come here to receive treatment for their liver tumors diagnosed as advanced HCC; 1 in 1988, 1+(1) in 1989, 5+(2) in 1990, 3+(5) in 1991, 4+(1) in 1992, and 1+(2) in 1993. The number in parentheses indicates patients being re-admitted; 2 times for 3 patients, 3 times for 1 and 4 times for 2. Three returned for second surgery for recurrence and one for an incisional hernia. Age distribution ranged from 33 years to 68 years old; mean age  $\pm$ SD was  $54 \pm 9$  years old. There was one female and 14 males. All patients could speak English, although it was not their native language. Some could not speak it fluently, although it was adequate for communication. Accompanying these patients were family or accompanying doctors who could speak English

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\*The First Department of Surgery, Yamanashi Medical University

\*\*The First Department of Medicine, Yamanashi Medical University

\*\*\*President of Yamanashi Medical University

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well. Twelve patients were Islamic ; 2 Christian and one Buddhist of Chinese origin. Except for a 68-year-old male who had a 4 cm tumor in the S8 region, all had been informed about their disease and status. Islamic patients did not eat pork or raw foods. None of the patients had a habit of drinking alcohol. Their occupations varied but all were well established, either as a politician, governmental officer, bank employee, medical doctor, business man or famous football player.

*Clinical history before admission to our hospital :*

All patients were introduced to Professor Suzuki by professors in Jakarta or Surabaya who specialize in the liver. Before their departure for Japan, the patients already had a substantial history of treatment. They were first referred to the professors in Jakarta or Surabaya from other Indonesian cities and received several examinations including US, SAG, and computed tomography (CT) to determine their operability in Indonesian hospitals. Those patients who were judged as inoperable in Indonesia, but who maintained relatively good liver functions despite large tumors were advised to go to Professor Suzuki in Yamanashi to be evaluated for liver resection.

For example, in August 1988, our Yamanashi delegation diagnosed the first patient with a 6-cm tumor by US examination in Jakarta and advised him to come to Yamanashi for removal of the solitary tumor. On October 24, he was admitted to the Department of Medicine here and underwent surgery on November 22. As a surgical finding, however, this patient had a main tumor, 7 cm in diameter, located at the border between the right and left lobes with multiple small metastatic nodules in the lateral segment (Fig. 1). It is quite possible that the tumor became enlarged and the metastatic lesions developed during the waiting period.

Another example is a young Chinese Indonesian, a 33-year-old male whose father was a successful businessman and he had education in USA. The patient was a carrier of hepatitis B virus

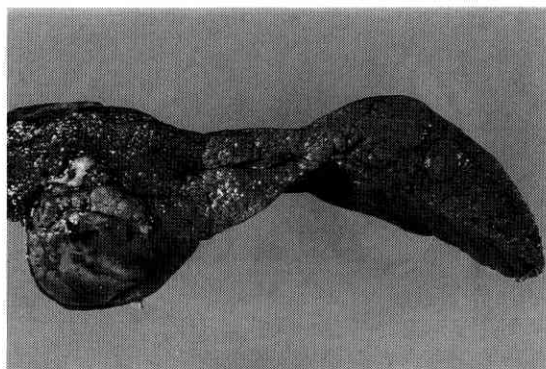


Fig. 1

Surgical specimen of the first HCC patient. Small satellite nodules around the main tumor, about 7 cm in diameter, in the medial segment close to the Cantlie line, the border line between the right and left lobes, and another tumor-nodule in the lateral segment far from the main tumor are shown.

(HBV) and had chronic hepatitis. In January 1990, he had a sudden pain in the abdomen and was diagnosed with rupture of HCC. He underwent lateral segmentectomy in Shanghai, but during surgery another large tumor located in the right lobe was noted. His family sought suitable treatment for the remnant liver tumor in Indonesia, China and USA, but additional liver resection was not recommended. In May, a subcutaneous tumor appeared at the lower presternal region and the family decided to come to us in August. Surgery was performed to remove the rapidly growing skin metastasis, 7 cm in diameter, and 7 intraperitoneal tumors, about 2 to 6 cm in diameter, but liver resection was not performed because of high advanced status (Fig. 2).

All patients had similar situations, waiting more than 2 months for surgery after they were diagnosed inoperable or advised to go to Japan. Prior to arrival at our surgical department, all patients received transcatheter arterial embolization (TAE) or infusion of anticancer drugs (TAI); even for one female patient who proved to have hemangioma, no malignant disease.

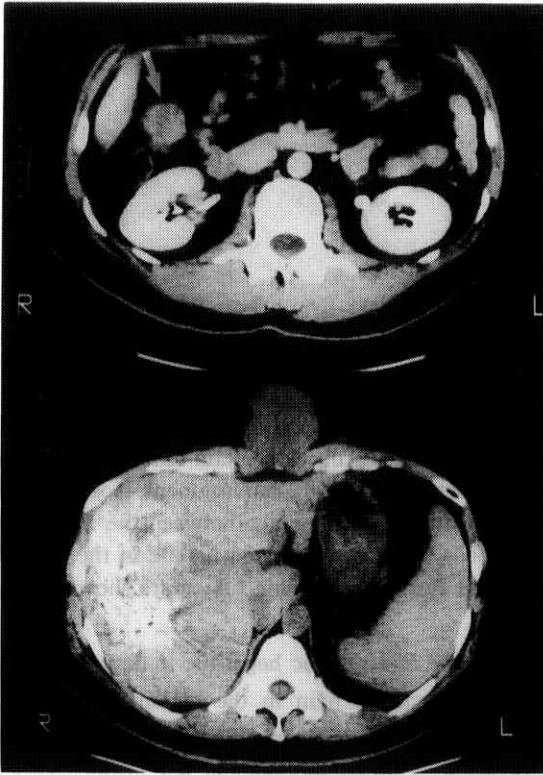


Fig. 2  
CT images of one intraperitoneal metastatic tumor, as indicated by arrow (above) and the skin metastasis and liver tumor (below) in Case 7.

#### Examinations after admission and preoperative diagnosis:

US, SAG, CT, and gastrointestinal examination including endoscopy were performed in all 15 patients, although these had been done previously in Indonesia. Magnetic resonance imaging (MRI) was also done to differentiate HCC from other benign tumors in some patients. By these examinations, 1 patient was diagnosed with cavernous hemangioma, a benign liver tumor, and 2 patients proved to have metastatic liver cancer, one colon cancer and the other lung cancer, although they had received diagnoses of primary liver cancer in Indonesia. The latter case was histologically small cell carcinoma and the patient also had rectal cancer in a polyp as a form of carcinoma in adenoma. The macroscopic

Table 1. Clinical Stage

Findings	Stage		
	I	II	III
Ascites	None	Treatment effective	Treatment ineffective
Serum bilirubin (mg/dl)	below 2.0	2.0–3.0	over 3.0
Serum albumin (g/dl)	over 3.5	3.0–3.5	below 3.0
ICG R <sub>15</sub> (%)	below 15	15–40	over 40
Prothrombin activity value (%)	over 80	50–80	below 50

There are three Clinical Stages of hepatocellular carcinoma classified by clinical and laboratory findings. The degree of progress is obtained by evaluating the patient's condition for each item, and when at least two items within any given stage are found to apply, that stage is then assigned [3]. In our experience patients of Clinical Stage I are tolerable to massive liver resection more than lobectomy, while patients of Stage III are very difficult to undergo even minor liver resection.

In each item, Mean±SD of the 12 HCC patients were as follows: Alb, 3.7±0.5 g/dl; T. Bil, 1.1±0.4 mg/dl; ICG R<sub>15</sub>, 19±13%; PT%, 97±23%; there was no ascites in any patient. Mean±SD of 6 HCC patients who underwent liver resection were: Alb, 4.0±0.3 g/dl; T. Bil, 0.9±0.4 mg/dl; ICG R<sub>15</sub>, 14±6%; PT%, 109±23% in the same order, while that of 6 HCC patients who were inoperable were: Alb, 3.4±0.5 g/dl; T. Bil, 1.3±0.3 mg/dl; ICG R<sub>15</sub>, 24±16%; PT%, 84±17%. Between the two groups, only serum albumin levels were higher in the surgically treated group (P<0.05), while the remaining items were within similar ranges.

stage (UICC) of 12 hepatocellular carcinoma patients were estimated by imaging techniques as Stage II in 2, Stage III in 3, Stage IV-A in 6, and Stage IV-B in 1.

Accompanying liver diseases included HBsAg positive in 3, HBeAg positive in 0, anti-HCV positive in 7. Nine patients were diagnosed with liver cirrhosis and 2 with chronic hepatitis. Resectability with respect to liver function was estimated by Clinical Stage (Table 1) [3], that is the degree of liver dysfunction categorized by serum albumin, serum total bilirubin, prothrombin activity (%), ICG 15 minute-retention rate (ICG R<sub>15</sub>), and ascites. Fourteen patients were in Clinical Stage I and 1 in

Table 2. Details of 7 patients who underwent liver resection; 6 with hepatocellular carcinoma and one with liver metastasis from colon cancer

No	Sex	Age	Preoperative			Operative			Tumor		Hospital (Surgical Dept.) Stay (days)		
			Diagnosis	HBsAg anti-HCV HBsAg	AFP (ng/ml)	Procedure	Blood loss Bloodtransfusion (ml)	Duration	Longest diameter (cm)	Differentiation (Edmondson)		Macroscopic Stage (TNM)	
1.	M	56	HCC, EV, LC(HCV), GBstone	- -	+	90.2	Left lobectomy	1651 1000	5'27'	7.0	II	III (T3N0M0)	66(34)
2.	M	54	Colon Ca., Liver meta., Asthma bronch., GBstone	- -	-	<10 (CEA 38)	Lateral segmentectomy, Partial liver resection(S8), Left hemi- colectomy, Setting of subcutane- ous port, (Tracheotomy)	372 0	6'45'	4.5(Colon) 6.0(Liver)	(Mod. diff. adenoca.)	(Colon Ca.: Stage V)	54(41)
3.	M	49	HCC, LC(HCV)	- -	+	67	Medial & anterior segmentectomy	1170 800	7'15'	4.5	necrotic	III (T3N0M0)	63(45)
4.	M	68	HCC, LC, (post-rupture state)	- -	-	1318	Partial resection(S8)	357 320	4'15'	4.5	II-III	IV-B (T2N0M1)	61(40)
5.	M	55	HCC, CH(HBV), Asthma bronch., Bleeding duodenal ulcer, GBstone	+ -	-	15	Left lobectomy, Subtotal gas- trectomy	858 400	9'05'	6.5	III-IV	II (T2N0M0)	54(32)
6.	M	50	HCC, (post-rupture state), CH(HBV)	- -	- (HBeAb+)	106	Right lobectomy	1518 600	6'05'	10.5	II	II(or IV-A) (T2N0M0) (or T4N0M0)	67(48)
7.	M	33	HCC, EV, LC(HBV, HCV), Skin metas- tasis	+ -	+	103	Wedge liver resection, Extirpation of metasta- tic skin tumor & 7 intra-perito- neal tumors, Setting of subcutaneou- s port	370 400	5'43'	7(skin) 6(intra-peri- toneum)	III	IV-B (T4N0M1)	54(33)

All patients received preoperative TAE. Cholecystectomy was performed in all patients.

Abbreviations are: HCC, hepatocellular carcinoma; EV, esophageal varices; LC, liver cirrhosis; HCV, hepatitis C virus; GBstone, cholecystolithiasis; HBV, hepatitis B virus; Mod. diff. adenoca., moderately differentiated adenocarcinoma.

In Case 3, the resected tumor was necrotic, probably due to preoperative TAE. But within one year possible minute tumor nodules appeared in the posterior segment. Although these possible HCC disappeared by TAE, in the fourth year one metastatic lesion on the rib appeared.

In Case 6, pre- and postoperative lipiodol CT indicated minute lipiodol depositions in the left lobe, but they were not identified as HCC by other diagnostic imaging procedures.

In Cases 4 and 6 a solitary nodular metastatic tumor, 10 cm and 12 cm in the longest diameter, respectively, in the abdomen, free from other organs, appeared in the next year and they were removed by the second operation.

Stage II, but none were in Stage III. Thus, liver dysfunction did not contraindicate liver resection in any case. On the other hand, in the present cases, 2 patients had severe bronchial asthma (Cases 2 and 4 in Table 2).

*Determination of operability :*

Liver tumors in 8 of 12 HCC patients were diagnosed as resectable and 5 of them underwent complete removal of liver tumors (Table 2). In the 33-year-old Chinese Indonesian only wedge resection including an intrahepatic metastatic nodule was performed to biopsy the tumor tissue because multiple intraperitoneal metastatic tumors were found during laparotomy (Case 7). Two politicians did not have laparotomy ; one because of his political schedule and the other because of no allowance of operation from his family. Therefore, in these 3 cases the cannulation to the hepatic artery and connection of the cannula to a subcutaneous port or pump was performed for TAI in Indonesia.

In addition, in one colon cancer patient one large metastatic tumor in the lateral segment and a small one in the anterior segment of the liver were diagnosed as resectable and they were removed together with descending colon cancer, and then similarly a subcutaneous port was set for possible occult remnant metastatic lesions.

One patient with metastatic tumors of pancreas cancer and 4 with HCC were diagnosed as inoperable because of multiple liver tumors and portal invasion. The subcutaneous port for 2 HCC patients and the infusion pump for another HCC patient were set after the hepatic arterial cannulation. The remaining cases received TAE alone. The hemangioma patient returned to Indonesia with no treatment after diagnosis of hemangioma.

*Liver resection :*

Thus, liver resection was performed in 7 patients ; two segmentectomy in 4, lateral segmentectomy together with partial resection of the anterior segment in 1, partial resection in 1 and wedge resection in 1 (Table 2). All patients under-

went cholecystectomy for prevention of cholecystitis induced by subsequent TAE or TAI. In addition, hemigastrectomy for accompanying bleeding duodenal ulcer in one HCC patient was performed, since he fell into hypovolemic shock due to bleeding two days before surgery. The colon cancer patient had poor pulmonary function (%VC 50%, FEV1% 52.8%) due to asthma and on the 4th postoperative day needed a tracheotomy. In two patients (Cases 4 and 6) surgical findings strongly suggested prior tumor rupture by the strong adhesion of protruding tumors to the surrounding tissues. In both cases, recurrence appeared within one year as a form of intraperitoneal tumor, possibly disseminated by rupture, and slowly developed within one year. The details of operations performed as well as tumors removed were indicated in Table 2. In all patients blood loss during surgery was not more than our previous preparation, but hospital stay seems to be longer than that of Japanese patients. It can be shortened by an arrangement of preoperative waiting periods.

*Postoperative course :*

Postoperative courses were uneventful except for Case 2. In this case, tracheotomy was performed for his poor pulmonary function.

Since, even in the 5 HCC patients with complete removal of tumors and normalization of AFP and/or PIVKA-II, large tumors were located close to the main vasculature or had shown signs of post-tumor-rupture, we recommended to the Indonesian doctors that a postoperative follow-up program to find recurrent tumors in an early stage include US every month, CT every 6 months and SAG once a year. In the 2 post-tumor-rupture cases, recurrent tumors were removed by subsequent surgery at our hospital. Two cases (Cases 1 and 3) had received TAE for a possible small intrahepatic metastatic lesions during SAG once a year after discharge but in the 4th year distant organ metastasis, both adrenal glands in Case 1 and the rib in Case 3, appeared. Unfortunately, these metastases were not detected

in Indonesia and had been treated as recurrence-free. Two cases (Cases 2 and 7) who received palliative treatments died within one year after discharge in Indonesia.

*Expenses for hospital stay in Japan :*

The cost of liver resection was about ¥2,000,000 that is ¥500,000 for preoperative examinations including TAE or TAI in the First Department of Medicine and ¥1,500,000 for surgery and postoperative care. The cost for patients who did not receive liver resection was ¥800,000 to ¥1,000,000. For some patients, this amount was not compensated by government or employer and they had to cover it by themselves. As we report here, most patients must continue to receive treatment and they visit us again. The total amount for frequent treatments costs a lot by Indonesian standards.

## Discussion

In the isolated Kofu basin, surrounded by mountains over 2000 m, about 120 km west of Tokyo, Yamanashi Medical University Hospital was founded 10 years ago. The area belongs to Yamanashi prefecture and has 800,000 inhabitants. The municipal office is in Kofu city of 200,000 inhabitants. The hospital is located not in Kofu, but in a newly developing area in the midst of rice fields, Tamaho Town which has about 8,600 inhabitants, about 10 km south of the center of Kofu. Indonesia, as everybody knows, is a tropical country, composed of many islands in South Asia. Most of 160,000,000 inhabitants are Islamic.

The small town of Tamaho, unfamiliar even to most Japanese, was first connected to Indonesia by Dr. Hiroshi Suzuki, Professor of the First Department of Medicine, the current president of our medical college. He has devoted himself to making friends with South Asian countries, in the field of medicine, in particular hepatology, for more than 15 years. In Indonesia, one of his most enthusiastic friendships has developed.

Our experience with Indonesian HCC patients has just started. To improve the outcome after surgical treatment, it is evident that patients should be treated earlier. The eight- to ten-hour flight from Jakarta is not long. It is necessary to have a good communication between medical doctors on both sides, so that patients do not waste time in Indonesia after diagnosis or in Japan before admission to the hospital. Patients come here with family members and during their hospital stay, their family must stay in a hotel in Kofu. There is not a good transportation system between Kofu and the hospital. Taxi is the only choice. This is complicated and expensive, as we can imagine. All prices in Japan are tremendously expensive, compared with those in Indonesia.

In some patients medical expenses were not covered by their government or company. They had to pay the costs themselves. In only one patient, not all of the expenses were paid to hospital, partly due to a misunderstanding during the days he was in critical situation. This kind of misunderstanding occurs because fluency in English is limited, since English is not the mother tongue on either side. It is necessary for us to prepare an information booklet for patients, which explains the approximate period of hospital stay, type of examination after admission and before surgery, the approximate cost of medical treatments, etc.

Of course, we need to make a guideline for Indonesian physicians with respect to resectability of advanced HCC patients from Indonesia. Recently, HCC treatments have varied in Japan. Surgical removal of the tumor is not the absolute choice in some advanced cases, and a multidisciplinary treatment, sometimes including mass-reduction surgery, is regarded best for advanced HCC cases according to tumor characteristics. For Stage IV-A HCC patients, intrahepatic multiple tumors without distant organ metastasis, we have advocated tumor-mass reduction surgery [4] and subsequent immunochemotherapy for remnant tumors [5], since

these tumors may be a conglomerate of well-differentiated HCC which developed multicentrically. However, in our previous experience, it seems difficult to maintain such postoperative treatments using the subcutaneous pump or port in Indonesia, because of lack of experience and difficulty in obtaining the apparatus and drugs for the treatment. Some patients had to bring back some of them to Indonesia.

Moreover, according to our slight experience with Indonesian patients with advanced HCC, the progression pattern of Indonesian HCC seems to be different in some cases from that of Japanese HCC; tumors seemed to rupture easily and more frequent intraperitoneal dissemination occurred thereafter. Liver dysfunction caused by accompanying liver diseases was not so severe as to abandon liver surgery. Thus, we Japanese staff should have greater opportunities to discuss with Indonesian doctors with respect to proper treatment for Indonesian HCC patients, and find a better treatment through mutual understanding.

As reported, all our patients were well-established Indonesians. However, we can not forget many other Indonesian HCC patients need treatment, but can not come here. Of course, most of them don't understand English. We must solve many

obstacles to help many other ill patients.

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