carcinoma with difficulty in preoperative diagnosis. J Gastroenterol Hepatol 2003;18:345–9.
16. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 1999;29:62–7.
17. Okusaka T, Okada S, Ishii H, Nose H, Nagahama H, Nakasuka H, et al. Prognosis of hepatocellular carcinoma patients with extrahepatic metastases. Hepatogastrocnterology 1997;44:251–7.
18. Obi S, Yoshida H, Toune R, Unuma T, Kanda M, Sato S, et al. Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. Cancer 2006;106:1990–7.
19. Nagano H, Sakon M, Eguchi H, Kondo M, Yamamoto T, Ota H, et al. Hepatic resection followed by IFN-alpha and 5-FU for advanced hepatocellular carcinoma with tumor thrombus in the major portal branch. Hepatogastroenterology (in press).
20. Yatsuhashi H, Fujino T, Matsumoto T, Inoue O, Koga M, Yano M. Immunohistochemical analysis of hepatic interferon alpha-beta receptor level: relationship between receptor expression and response to interferon therapy in patients with chronic hepatitis C. J Hepatol 1999;30:995–1003.
21. Wagner TC, Velichko S, Chesney SK, Biroc S, Harde D, Vogel D, et al. Interferon receptor expression regulates the antiproliferative effects of interferons on cancer cells and solid tumors. Int J Cancer 2004;111:32–42.
22. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.

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Original Article

New chemotherapy for patients with advanced hepatocellular carcinoma: Pilot study of β-interferon and doxorubicin one-shot intra-arterial chemotherapy

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Background: Patients with advanced hepatocellular carcinoma (HCC) need an effective treatment modality because of the poor prognosis of the disease. From an *in vitro* study, β-interferon (IFN-β) has been reported to enhance the antiproliferative effects of doxorubicin on HCC cell lines. In the present study, we investigated the therapeutic effects of combined IFN-β and doxorubicin intra-arterial injection therapy on patients with advanced HCC.

Methods: IFN-β (3 MIU) and doxorubicin (10 mg/bodyweight) were given by one-shot intra-arterial injection through an arterial port to patients with advanced HCC. One treatment course consisted of three intra-arterial injections per week for 4 weeks. Three courses were conducted and evaluation was done monthly.

Results: Eleven patients with advanced HCC were treated with combined IFN-β and doxorubicin. One patient entered complete remission (CR), seven patients were evaluated as having stable disease (SD) and three as having progressive disease (PD). The mean overall survival was 10 months. The mean survival for CR and SD patients was 15 months, and that for PD patients was 6 months ($P = 0.0464$, log–rank test). Decrease of serum total bilirubin was observed for all patients.

Conclusion: Combined IFN-β and doxorubicin intra-arterial therapy offers an effective chemotherapy option for patients with advanced HCC by improving liver function and having tolerable side-effects.

Key words: advanced hepatocellular carcinoma, β-interferon, doxorubicin, intra-arterial injection

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is principally associated with hepatitis B virus (HBV) or hepatitis C virus (HCV), and its incidence is especially high in Asia and Africa.[1] Recently, its incidence has been increasing in Europe and America.[2,3] There are various options for treatment of HCC, including radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transcatheter arterial embolization (TAE) using interventional radiology (IVR), surgical resection, and liver transplantation.[4] However, the prognosis is poor for patients with advanced hepatic carcinomas, which develop in multiple segments in the liver and/or are accompanied by portal vein tumor thrombus, because no efficacious treatment modality has yet been developed.[5] Recently, for patients with advanced HCC without metastatic foci whose performance status (PS) is good, approximately 50% effectiveness has been reported for combined α-interferon (IFN-α) and 5-fluoruracil (5-FU) arterial injection therapy.[6,7] For patients with poor liver function who cannot accept IFN-α and 5-FU combination therapy, a new chemotherapy regimen is needed. Thus, we designed a protocol that minimizes hepatic toxicity and also enables one-shot arterial injection for patients with advanced HCC, who are not candidates for operation, liver

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transplantation, or local treatment such as IVR, PEIT or RFA due to the number of tumors, portal vein thrombosis, or liver dysfunction (BCLC staging system B or C).[8]

β-interferon (IFN-β) is usually given by injection into the bloodstream and has fewer side-effects than IFN-α.[9] Recently, an *in vitro* study has shown that IFN-β could suppress the proliferation of HCC more strongly than IFN-α both alone and in combination with anticancer agents.[10] In particular, the antitumor agent doxorubicin showed synergism with IFN-β in the antiproliferation effect against HCC using HCC cell lines.[11] As myocardial damage and hepatic toxicity are the main side-effects of doxorubicin,[12,13] a small-volume one-shot arterial injection was selected for giving IFN-β. This led us to design a new chemotherapy regimen of combined IFN-β and doxorubicin intra-arterial injection therapy. The present study was conducted to determine whether this combined chemotherapy could be used for outpatient treatment after a short hospital stay in order to maintain the patient's quality of life (QOL) with fewer side-effects.

METHODS

Patient enrollment

PATIENTS WITH CIRRHOSIS and advanced HCC who were enrolled in this study were not eligible for surgical resection, liver transplantation or local treatment such as IVR, PEI or RFA because of diffuse or multiple tumors in both lobes with or without portal vein tumor thrombus and/or impaired liver function due to cirrhosis. To realize chemotherapy on an outpatient basis, patients with PS 0 or 1 were selected. Informed consent was obtained after explaining the purpose of the study and possible side-effects. Clinical tumor stages of patients with HCC were evaluated by abdominal contrast enhanced computed tomographic (CT) scans, magnetic resonance images (MRI) or angiography. Other criteria were a neutrophil count ≥1000/mm³, platelet count ≥40 000/mm³, serum level of creatinine ≤1.4 mg/dL, total bilirubin of ≤3.5 mg/dL, and no abnormalities of cardiac function by ultrasound and electrocardiography. The exclusion criteria included intractable pleural effusion or ascites, severe infectious disease, severe myocardial damage, severe impairment of intelligence, encephalosis, metastasis to the central nervous system, hemorrhage from varicose veins within 1 month prior to enrollment, and pregnancy.

Therapeutic design

All of the enrolled patients had a catheter placed by gastroduodenal artery (GDA) coil or other method and a port implanted subcutaneously. One course of chemotherapy consisted of one-shot intra-arterial injection of IFN-β (3 MIU) and doxorubicin (10 mg/bodyweight) through the port, three times per week for 4 weeks. Three courses were conducted, when possible, and monthly evaluation of chemotherapy effects on HCC was based on serum tumor markers and CT scans.

Evaluation of therapeutic effects

The antitumor effect was evaluated by tumor volumes using contrast enhanced CT scans every 4 weeks from the start of combined IFN-β and doxorubicin intra-arterial injection therapy. The antitumor effect and toxicity were evaluated according to National Cancer Institute Common Toxicity Criteria (NCI-CTC)[14] and Response Evaluation Criteria in Solid Tumors (RECIST)[15] guidelines. Peripheral blood cells, biochemical tests, serum levels of α-fetoprotein (AFP) and/or PIVKA-II were examined every 4 weeks. The overall survival was calculated from the first treatment until death or the final day of follow up. The primary end-point of the current study was the development of toxicity and overall survival.

The criteria of complete response (CR), stable disease (SD) and progressive disease (PD) were as follows: CR, complete disappearance of tumors and no evidence of new lesions; SD, < 50% reduction or < 25% increase of tumor volume and no evidence of new lesions; PD, ≥25% increase of tumor volume, evidence of new lesions, or rise in tumor markers.

Statistics

The overall survival time from the start of the chemotherapy was analyzed by the Kaplan–Meier method and differences in survival were evaluated by log-rank tests.

RESULTS

Patient characteristics

ELEVEN PATIENTS WERE enrolled at Osaka University Hospital between November 2003 and August 2005. HCC was diagnosed by contrast-enhanced CT scan or MRI. Angiography and pathological diagnosis were not done. The serum levels of AFP and PIVKA-II were elevated. The pretreatment characteristics of enrolled patients are shown in Table 1.

Table 1 Pretreatment characteristics of patients with advanced hepatocellular carcinoma

No.	Age (years)	Sex	Etiology	Child–Pugh grade	Portal venous thrombosis (Vp)	Previous treatment
1	56	M	HBV/HCV	B	+	TAE
2	78	M	HCV	A	+	TAE, RFA
3	73	M	HBV	A	–	Operation, TAE
4	58	M	HCV	B	–	TAE
5	71	M	HCV	B	–	TAE
6	49	M	HCV	C	+	TAE, RFA
7	69	M	Non B/non C	B	+	None
8	63	M	HBV	A	+	TAE, RFA
9	62	F	HCV	B	–	TAE
10	61	M	HCV	A	+	TAE, RFA
11	56	M	HCV	A	–	None

HBV, hepatitis B virus; HCV, hepatitis C virus; RFA, radiofrequency ablation; TAE, transcatheter arterial embolization.

All patients were enrolled after being diagnosed as having liver cirrhosis by biochemical tests and/or radiological findings. Histological confirmation of liver cirrhosis was not done. The liver function of patients with cirrhosis was classified according to Child–Pugh grading criteria. Pretreatment tumor stages of patients with advanced HCC were classified according to the American Joint Committee on Cancer (AJCC) Tumor-Lymph Node Metastasis (TNM) classification system,[16] and according to the Cancer of the Liver Italian Program (CLIP) score[17] (Table 2). Seven patients had HCV infection, two had HBV, one had both HBV and HCV. One patient suffered from cirrhosis with neither HBV nor HCV infection.

Tolerability and side-effects

Eleven patients were started with intra-arterial administration of 3 MIU IFN-β and 10 mg doxorubicin. The median period of combined chemotherapy was 11 weeks (range 8–12 weeks). The dose of doxorubicin was reduced from 10 mg/bodyweight to 5 mg/bodyweight for two patients (nos. 2 and 6) because of grade 3 and 4 neutropenia. A 78-year-old man (no. 2) developed grade 4 neutropenia after the first course, and doxorubicin was reduced to 5 mg/bodyweight and granulocyte-colony stimulating factor (G-CSF) was given, and then grade 4 stomatitis appeared after two courses leading to discontinuation of the chemo-

Table 2 Therapeutic effect according to RECIST on patients and tumor stages of HCC patients according to the CLIP score and TNM classification system

No.	T-Bil (mg/mL)	AFP (ng/mL)	PIVKA II (mAU/mL)	CLIP score	TNM	Duration of therapy	Therapeutic effect	Prognosis
1	1.9	<5.3	<40	4	III	3 cycles	SD	15 M Dead
2	1.7	2 145	<40	4	IVA	2 cycles	PD	6 M Dead
3	0.6	24	148	1	III	3 cycles	SD	8 M Dead
4	3.3	24	140	2	III	3 cycles	SD	35 M Alive
5	1.6	25	462	3	III	2 cycles	SD	6 M Dead
6	2.1	10 400	32 852	6	IVB	3 cycles	SD	6 M Dead
7	1.3	226 820	12 317	5	IVA	3 cycles	PD	5 M Dead
8	2.4	582	63	3	IVA	3 cycles	CR	20 M Alive
9	2.9	41	1 397	2	IVA	2 cycles	SD	12 M Dead
10	0.7	255	1 341	3	III	3 cycles	PD	10 M Dead
11	2.4	309	13 900	1	III	3 cycles	SD	25 M Alive

AFP, α-fetoprotein; CLIP score, Cancer of the Liver Italian Program score; CR, complete remission; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; T-Bil, total bilirubin; TNM, Tumor-lymph Node Metastasis classification system.

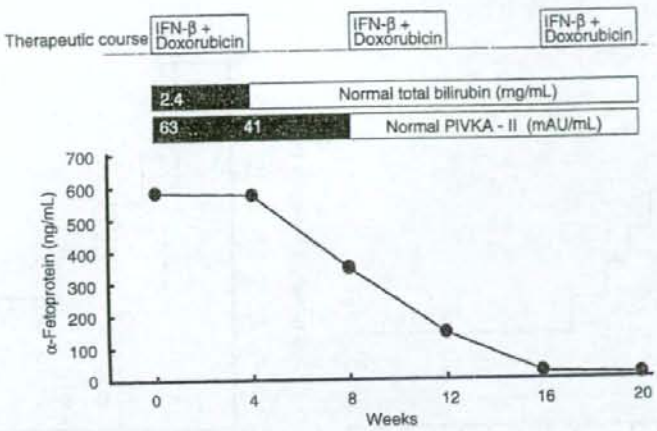

Figure 1 Time course of tumor markers in a complete remission case. A 63-year-old man with diffused type advanced hepatocellular carcinoma (HCC) (no. 8) was treated with three courses of combined β-interferon (IFN-β) and doxorubicin intra-arterial injection therapy without severe side-effects. Serum levels of PIVKA-II decreased after the first course of combined chemotherapy, entered the normal range during the second course and remained in the normal range after three courses. The serum level of α-fetoprotein decreased after the second course and entered the normal range 1 month after three courses of combined therapy. No HCC lesions were detected in the patient's liver by contrast enhanced CT scans and MRI after three courses of combined chemotherapy and 6 months later.

therapy. A 71-year-old man (no. 5) and a 62-year-old woman (no. 9) with Child–Pugh grade B complained of severe fatigue after two courses, and the chemotherapy was stopped. They had been treated by TAE for the tumors more than five times previously. Previous treatments, especially transarterial chemoembolization (TACE) may have affected the severity of the toxicity of the present combined chemotherapy regimen, although other factors such as age and Child–Pugh grade can be considered as having affected the development of intolerable side-effects. Discontinuation of drug therapy led to quick recovery from the adverse reactions. Of the eight remaining patients, three dropped out of the study and five completed three courses of treatment.

Therapeutic effects of combined intra-arterial IFN-β and doxorubicin injection therapy

All patients had advanced HCC, seven with and four without portal thrombus. All HCC were evaluated for volume changes by contrast-enhanced CT scans after 8 or 12 weeks. A 63-year-old man (no. 8) with HBV infection showed significant reduction of AFP and PIVKA-II into the normal range. Diffuse HCC disappeared after three courses of combined IFN-β and doxorubicin intra-arterial injection therapy, being confirmed by contrast-enhanced CT scan and MRI. Thus, we concluded that patient no. 8 had attained CR (Fig. 1).

All patients showed a high serum level of AFP and/or PIVKA-II before treatment (Table 2). The serum levels of AFP and/or PIVKA-II decreased after one course of combined chemotherapy in all patients. However, the CT scans demonstrated no significant volume reduction of HCC in seven patients, and tumor enlargement in three. Seven patients were classified as SD and three as PD from contrast-enhanced CT scans (Table 1).

Overall survival

All of the patients were observed from November 2003 to October 2006. The estimated duration of overall median survival was 10 months (Fig. 2a). The mean survival time was 15 months for CR and SD patients, which is significantly longer than 6 months for PD patients ($P = 0.0464$, log-rank test) (Fig. 2b). The mean survival time of only SD patients (12 months) was not significantly longer than that for PD patients ($P = 0.0786$, log-rank test). The one-year survival rate for CR and SD patients was 62.5% (5/8) and that for PD was 0% (0/3). The progression-free survival time for CR or SD was longer than that for PD ($P = 0.0004$, log-rank test)

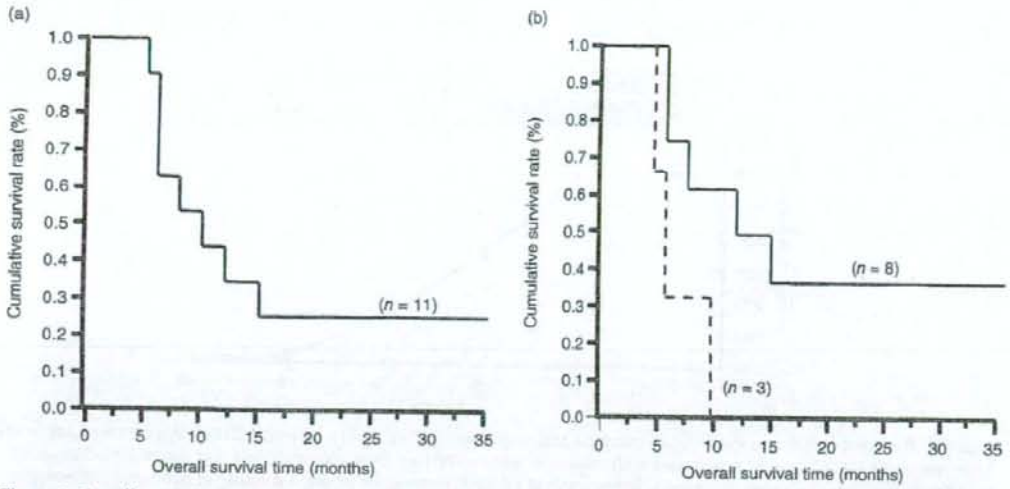

Figure 2 Overall survival periods of patients with advanced hepatocellular carcinoma who received combined β-interferon (IFN-β) and doxorubicin intra-arterial injection therapy. (a) Overall survival periods of 11 patients who received combined IFN-β and doxorubicin intra-arterial injection therapy. The mean survival period was 10 months. (b) Overall survival periods of seven patients with stable disease (SD) and three with progressive disease (PD) after combined IFN-β and doxorubicin intra-arterial injection therapy. The mean survival period was 15 months for SD patients and 6 months for PD patients. (——), CR-SD; (- - -), PD. CR, complete response. ($P = 0.0464$, log-rank test).

(Fig. 3). Eight patients died of liver failure, including five SD and three PD patients. A 73-year-old man (no. 3) died of sepsis that developed from catheter problems, after completion of three cycles of treatment. Three patients are alive, including one CR patient (25 months) and two SD patients (35 and 20 months). The QOL of PD patients was maintained until the end of the treatment. The Eastern Cooperative Oncology Group (ECOG) performance status at the end of the treatment had not deteriorated.

Total bilirubin of the HCC patients who had received IFN-β and doxorubicin intra-arterial combination therapy decreased significantly after one cycle ($P = 0.0344$) and two cycles ($P = 0.0051$) of treatment (Fig. 4). In all patients, anorexia and lassitude were alleviated, offering remarkable benefits for advanced HCC patients.

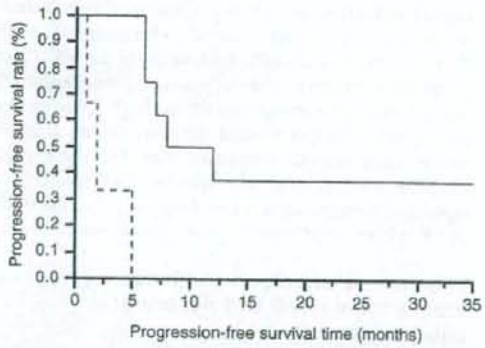

Figure 3 Progression-free survival times of patients with advanced hepatocellular carcinoma according to responses to β-interferon and doxorubicin combination therapy. One-year survival rate for CR or SD patients was 62.5% (5/8) and that for PD was 0% (0/3). The progression-free survival time for CR or SD was longer than that for PD. (——), CR-SD; (- - -), PD. CR, complete response. ($P = 0.0004$, log-rank test).

DISCUSSION

HEPATOCELLULAR CARCINOMAS RECEIVE nourishment from the hepatic artery, not the portal

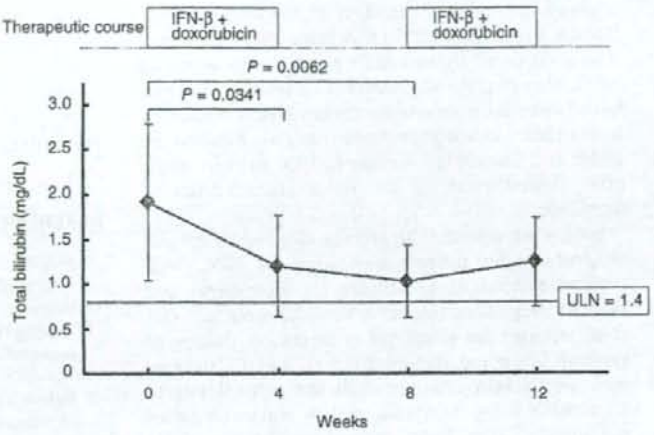

Figure 4 Serum bilirubin ameliorated during combined β-interferon (IFN-β) and doxorubicin intra-arterial injection therapy. Serum levels of total bilirubin decreased significantly and entered the normal range after the first course of combined chemotherapy, and remained in the normal range during the further courses. Values are averages ± SD. Upper limit of normal (ULN) serum values of total bilirubin, 1.4 mg/dL.

flow. Thus, a therapeutic effect should be attainable by giving antitumor agents via the hepatic artery. By direct delivery into the hepatic artery, the concentrations of anticancer agents in the liver increase to 10-fold or more than those by administration via the peripheral veins.[18] By direct injection of anticancer drugs into blood vessels draining to local areas, higher therapeutic effects can be expected when higher ratios of drug concentration appear in the internal organs on their first pass (first-pass effect).[19] When doxorubicin is infused from the hepatic artery, the first-pass effect in the liver is considered to be approximately 60% in rabbits. As the antitumor effects are dose dependent, anthracyclines, including doxorubicin, should be suitable for intra-arterial chemotherapy by single bolus injection.[20] Doxorubicin is metabolized in the liver by hepatic cytochrome P450 and is excreted in bile and urine.[21] On being metabolized by the typical P450 CYP3A4, 40% or more of doxorubicin is ultimately excreted via the bile. Its metabolism and excretion are delayed in patients with hepatic dysfunction such as cirrhosis or with obstructive jaundice, in whom the side-effects of anthracyclines tend to develop easily. In the present study, myelosuppression was observed in two patients (nos. 2 and 6), and in one case G-CSF had to be used. We have examined the concentration of doxorubicin of 10 patients including these patients. The blood concentration of doxorubicin was measured by high-performance liquid chromatography using patients' serum. In two patients with myelosuppression, the blood concentrations of doxorubicin exceeded 10 ng/mL at 60 min after the start of administration. In these patients, no significant hepatic damages were observed. Another eight patients without significant myelosuppression, whose blood concentration of doxorubicin could be measured, showed lower blood concentration than 10 ng/mL. These findings suggested that patients, in whom the blood doxorubicin concentration is 10 ng/mL or more at 60 min after the start of administration, seem to be susceptible to the side-effects, especially hematological toxicity. In general, the serum concentration of doxorubicin at 60 min after its administration is less than 10 ng/mL in normal subjects. But it could be well considered that the serum concentration of doxorubicin at 60 min after its administration to the patients with liver dysfuction is more than 10 ng/mL due to the delayed metabolism and excretion of doxorubicin. The monitoring of serum concentration of doxorubicin seems to be important in patients with liver cirrhosis.

IFN-β and doxorubicin intra-arterial combination therapy significantly reduced total bilirubin, but did not improve other liver function tests such as prothrombin time and albumin, This seems to be the most distinct hallmark of this therapy. In the present study, no patients had tumor thrombus in the bile duct, However, in the cases of advanced HCC, tumors may compress the small bile duct. After the treatment of combination therapy, compression of the small bile duct by tumors may be relieved because of the reduction of tumor size. However, giving IFN to bile duct-ligated rats has been reported to result in significant preservation of histology, inhibition of collagen accumulation and partial

improvement of serum markers of cholestasis.[21] Thus, IFN used with doxorubicin may bring about the partial improvement of cholestasis in patients with advanced HCC. However, the mechanism of reduction of serum bilirubin by this combination chemotherapy remains to be clarified. Marked improvement of total bilirubin by IFN-β and doxorubicin therapy in HCC patients might offer clinical proof of the novel characteristics of interferon.

Yang *et al.* reported the efficacy of gemcitabine and doxorubicin for patients with advanced HCC, with median survival of 4.6 months for all patients and median progression-free survival of 2.5 months.[22] Obi *et al.* reported the efficacy of combination therapy of systemic IFN-α and intra-arterial 5-FU for HCC patients with portal vein invasion, with the survival rate at 12 months being 34% and median survival time of 6.9 months.[23] The 1-year survival rate for CR or SD patients was 62.5% and that for all patients, including PD patients, was 45%, and the mean survival time for all patients was 10 months in the present study, although the number of the patients was small. The present findings suggested that IFN-β is more effective than gemcitabine or IFN-α for advanced HCC. This might explain the effectiveness of IFN-β injected into the tumor site in the liver directly through the catheter. To confirm the superior effects of intra-arterial IFN-β administration, further studies with more patients and longer treatment periods should be done.

All patients enrolled in the present study had extensively advanced HCC, with five cases including portal tumor thrombus Vp3. Patients with Child–Pugh grades A and B are also eligible for this combined chemotherapy regimen, but the dose and the interval of administration should be considered for patients with ascites or a serum level of total bilirubin at 3.0 mg/dL or more, such as Child–Pugh grade C.

Small amounts of IFN-β and doxorubicin do not tend to cause severe side-effects. Under the new enrollment criteria, HCC patients need only 2 or 3 days of hospital stay for port implantation, and outpatient therapy can be started immediately. Moreover, this one-shot intra-arterial injection therapy can be conducted within a short time to minimize restriction of the patient. Based on these findings, one-shot intra-arterial combination chemotherapy of IFN-β and doxorubin could be recommended for outpatient therapy of patients with advanced HCC.

In conclusion, for patients with progressive hepatocellular carcinoma, this preliminary study shows that combined IFN-β and doxorubicin intra-arterial chemotherapy has the potential of prolonging survival time while maintaining QOL in an outpatient clinic. This combination chemotherapy, with tolerable side-effects, has the potential of serving as an optimal treatment option for advanced HCC, by improving liver function and maintaining the QOL for outpatients.

REFERENCES

1 McGlynn KA, London WT. Epidemiology and natural history of hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol* 2005; 19: 3–23.
2 El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999; 340: 745–50.
3 Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; 127: S35–50.
4 Tateishi R, Shiina S, Teratani T *et al.* Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. *Cancer* 2005; 103: 1201–9.
5 Fujii T, Takayasu K, Muramatsu Y *et al.* Hepatocellular carcinoma with portal tumor thrombus: analysis of factors determining prognosis. *Jpn J Clin Oncol* 1993; 23: 105–9.
6 Sakon M, Nagano H, Dono K *et al.* Combined intraarterial 5-fluorouracil and subcutaneous interferon-α therapy for advanced hepatocellular carcinoma with tumor thrombi in the major portal branches. *Cancer* 2002; 94: 435–42.
7 Ota H, Nagano H, Sakon M *et al.* Treatment of hepatocellular carcinoma with major portal vein thrombosis by combined therapy with subcutaneous interferon-alpha and intra-arterial 5-fluorouracil; role of type 1 interferon receptor expression. *Br J Cancer* 2005; 93: 557.
8 Llovet JM, Brù C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC-staging classification. *Semin Liver Dis* 1999; 19: 329–38.
9 Perez R, Pravia R, Artimez ML *et al.* Clinical efficacy of intramuscular human interferon-beta vs interferon-alpha 2b for the treatment of chronic hepatitis C. *J Viral Hepat* 1995; 2: 103–6.
10 Obora A, Shiratori Y, Okuno M *et al.* Synergistic induction of apoptosis by acyclic retinoid and interferon-beta in human hepatocellular carcinoma cells. *Hepatology* 2002; 36: 1115–24.
11 Damdinsuren B, Nagano H, Sakon M *et al.* Interferon-beta is more potent than interferon-alpha in inhibition of human hepatocellular carcinoma cell growth when used alone and in combination with anticancer drugs. *Ann Surg Oncol* 2003; 10: 1184–90.
12 Von Hoff DD, Layard MW, Basa P *et al.* Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979; 91: 710–17.
13 Benjamin RS, Riggs CE Jr, Bachur NR. Plasma pharmacokinetics of adriamycin and its metabolites in humans with

normal hepatic and renal function. *Cancer Res* 1977; 37: 1416–20.
14 Trotti A, Colevas AD, Setser A *et al.* CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003; 13: 176–81.
15 Therasse P, Arbuck SG, Eisenhauer EA *et al.* New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; 92: 205–16.
16 Varotti G, Ramacciato G, Ercolani G *et al.* Comparison between the fifth and sixth editions of the AJCC/UICC TNM staging systems for hepatocellular carcinoma: multicentric study on 393 cirrhotic resected patients. *Eur J Surg Oncol* 2005; 31: 760–7.
17 A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology* 1998; 28: 751–5.
18 Eksborg S, Cedermark BJ, Strandler HS. Intrahepatic and intravenous administration of adriamycin – a comparative pharmacokinetic study in patients with malignant liver tumours. *Med Oncol Tumor Pharmacother* 1985; 2: 47–54.
19 Doherty MM, Pang KS. First-pass effect: significance of the intestine for absorption and metabolism. *Drug Chem Toxicol* 1997; 20: 329–44.
20 Di Marco A, Gaetani M, Scarpinato B. Adriamycin (NSC-123,127): a new antibiotic with antitumor activity. *Cancer Chemother Rep* 1969; 53: 33–7.
21 Muriel P. Alpha-interferon prevents liver collagen deposition and damage induced by prolonged bile duct obstruction in the rat. *J Hepatol* 1996; 24: 614–21.
22 Yang TS, Wang CH, Hsieh RK, Chen JS, Fung MC. Gemcitabine and doxorubicin for the treatment of patients with advanced hepatocellular carcinoma: a phase I–II trial. *Ann Oncol* 2002; 13: 1771–8.
23 Obi S, Yoshida H, Toune R *et al.* Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. *Cancer* 2006; 106: 1990–7.

Doxorubicin/IFN-β併用化学療法と肝切除術により長期生存し得た右心房内腫瘍栓を伴う進行肝細胞癌の1例

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丸橋 繁*1 宮本 敦史*1 武田 裕*1 堂野 恵三*1 梅下 浩司*2
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A Case of Hepatocellular Carcinoma with Right Atrium Tumor Thrombus Treated with Combined Doxorubicin and Interferon-β/Intra-Arterial Injection Chemotherapy and Hepatectomy: Masahiro Murakami*1, Hiroaki Nagano*1, Takehiro Noda*1, Hiroshi Wada*1, Shogo Kobayashi*1, Shigeru Marubashi*1, Atsushi Miyamoto*1, Yutaka Takeda*1, Keizo Dono*1, Koji Umeshita*2 and Morito Monden*1 (*1*Dept. of Surgery and* *2*Dept. of Health Science, Graduate School of Medicine, Osaka University*)

Summary

A-58-year-old male was admitted to Osaka University Hospital for advanced hepatocellular carcinoma in July 2005. The main tumor was located in the posterior segment and hepatic vein tumor thrombus extended to the right cardiac atrium. He felt of pressure in his chest and a serum total bilirubin level was beyond normal range because of the tumor progress. We started a doxorubicin and interferon-β combined chemotherapy. Although anti-tumor effect was NC, his symptom rather improved and a serum total bilirubin level went into the normal range. Consequently, we performed an extended posterior segmentectomy and tumor thrombectomy of IVC and right cardiac atrium. The patient survived for 13 months after the initial treatment, but he died of distant metastasis. It was suggested that the doxorubicin and interferon-β combined chemotherapy might be the promising modality for advanced hepatocellular carcinoma as one of the multimodel treatment. Key words: Hepatocellular carcinoma, Interferon-β, Doxorubicin

要旨 症例は58歳，男性。B型肝炎，多量飲酒歴あり。2005年4月疲労感などを主訴に近医を受診し，精査にて進行肝細胞癌と診断され当院へ紹介。7月精査加療目的で入院した。画像上，肝後区域の主腫瘍と肝部下大静脈から右心房内に至る腫瘍栓を認めた。入院時より胸部圧迫感や下腿浮腫などが出現，血清総ビリルビン値（T-Bil）は2.2 mg/dLと上昇し，腫瘍進展による肝不全徴候を認めた。doxorubicin/IFN-β併用化学療法の施行により，画像上の抗腫瘍効果はNCであったものの，症状の改善とT-Bilの正常化を認めたことより，10月肝拡大後区域切除，右心房内・下大静脈内腫瘍栓摘出術を施行した。術後経過は特に問題なく退院し，最終的に遠隔転移により癌死したが，初回治療より13か月の長期生存を得た。以上よりdoxorubicin/IFN-β併用化学療法は，進行肝細胞癌に対して集学的治療の有用な選択肢の一つとなり得ると思われた。

緒　言

今回われわれは肝部下大静脈をほぼ充満し，右心房内に至る広範な腫瘍栓を伴う進行肝細胞癌で腫瘍進展に伴う肝不全徴候の出現した症例に対して，doxorubicin/IFN-β併用化学療法を施行後に根治肝切除術を施行し，長期生存を得た症例を経験したので報告する。

I. 症　例

患者: 58歳，男性。HBs抗原陽性。

既往歴: 20年前より高血圧で内服中。

飲酒歴: 日本酒3合/日×38年と多量飲酒。

現病歴: 2005年4月疲労感および咳嗽を主訴に近医を受診し，心房細動を指摘。その時の腹部CT検査で進行肝細胞癌と診断され，7月精査加療目的にて入院した。入院時，胸部圧迫感や下腿浮腫などの右心房内腫瘍栓によると思われる症状が出現していた。

入院時血液検査: PT値76%と軽度低下，T-Bil 2.2 mg/dLと上昇し，腫瘍進展による肝不全徴候を認めた。腫瘍マーカーはAFP 4,014 ng/mLとPIVKA-II 56

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表 1 入院時血液検査所見

WBC	5,100/μL	APTT	30 sec
RBC	418×10⁴/μL	PT	76%
Hb	13.8 g/dL	HPT	76%
Hct	40.6%	ICG R_{15}	20%
Plt	14.6×10⁴/μL	HBs-Ag	(+)
TP	7.5 g/dL	HBs-Ab	(−)
Alb	3.8 g/dL	HBe-Ag	(−)
T-Bil	2.2 mg/dL	HBe-Ab	(+)
D-Bil	1.0 mg/dL	HBc-Ab	(+)
AST	37 IU/L	HCV-Ab	(−)
ALT	29 IU/L	AFP	4,014 ng/mL
γ-GTP	391 IU/L	L_3 分画	35.8%
ALP	366 IU/L	PIVKA-II	56 mAU/mL

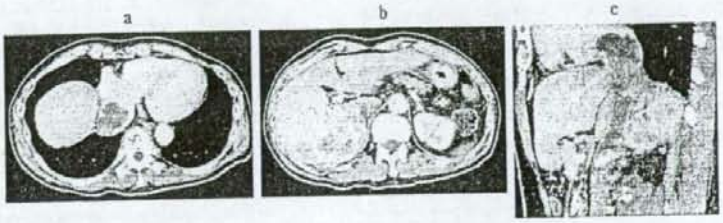

図 1 腹部 CT 検査 (a, b, c)
肝後区域の主腫瘍と肝部下大静脈から右心房内へ進展する腫瘍栓を認める。

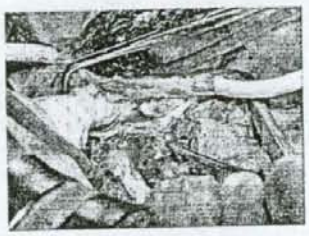

図 2 術中所見
肝切除施行後，肝部下大静脈を切開し，右心房内・下大静脈内腫瘍栓を摘出した。

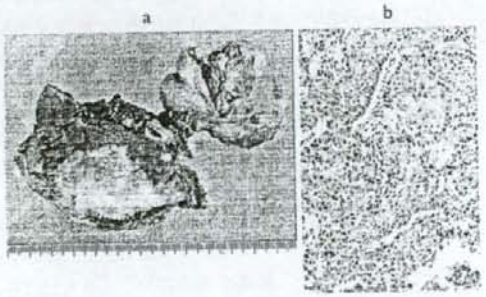

図 3
a: 摘出標本
最大腫瘍径 8 cm，白色の充実性腫瘍で下大静脈内に腫瘍進展を認めた。
b: 病理組織学的所見
HE 染色。低分化型，Edmondson III 型の肝細胞癌の所見であった。

mAU/mL の上昇を認めた（表 1）。

腹部 CT 検査: 肝後区域中心に径 7 cm の主腫瘍と肝部下大静脈をほぼ充満し，さらには右心房内へ進展する腫瘍栓を認めた（図 1）。また右副腎腫大も認め，転移が疑われた。

以上より右心房内腫瘍栓を伴う進行肝細胞癌と診断。2005 年 7 月肝動脈リザーバー留置術の後，doxorubicin/IFN-β 併用化学療法（プロトコールは doxorubicin 10 mg/body + IFN-β 300 万単位/回の肝動脈内注入を週 3 回，計 4 週間[1]）を 1 クール施行した。抗腫瘍効果は NC であったが，胸部圧迫感などの症状は改善し T-Bil が正常範囲内に復したことより，10 月 17 日に肝拡大後区域切除，右心房内・下大静脈内腫瘍栓摘出，右副腎・横隔膜合併切除，胆嚢摘出術を施行した（図 2）。

摘出標本: 切除肝重量は 442.2 g。原発巣の割面は白色の充実性腫瘍で，最大腫瘍径は 8 cm。原発性肝癌取扱い規約[2]に基づく術後診断は，Ig，Fc（−），Sf（+），massive，S2，N0，Vp2，Vv3，Va0，B0，IM0，P1，SM（−），CH で T3N0M0，Stage III であった（図 3a）。

病理組織学的所見：術後の病理学的検索では低分化型，Edmondson Ⅲ型の肝細胞癌で，vp2，vv3，va0，s2，b1，p1，sm(−)(図3b)。背景肝に硬変像はなく，HAI scoreはGrade 1，Stage 3であった。

術後経過は特に問題なく退院し，社会復帰した。外来通院中の2006年1月より肺や骨，リンパ節への遠隔転移を来したため，S-1/IFN-α療法[3,4]を施行したが，治療効果を認めず，初回治療から13か月後に癌死した。

Ⅱ. 考　察

脈管侵襲を伴う肝細胞癌は極めて予後不良である。教室ではこのような進行肝細胞癌に対して，5-FUの肝動注にIFN-αの皮下投与を併用した化学療法(FU arterial infusion and IFN therapy; FAIT)を機軸とした集学的治療を行い，その良好な成績について報告してきた[5-8]。しかしながら，過度の腫瘍進展により黄疸や腹水などの肝不全徴候を来したため，治療適応外となり，残念ながら緩和医療へと移行せざるを得ない症例も少なからず存在する。このような症例に対しても治療を断念することなく，予後の改善を図るためには肝不全徴候下にあっても施行し得る何らかの抗腫瘍治療が必要である。

教室では，これまでに*in vitro*でIFN-βと各種抗癌剤の併用による抗腫瘍効果の有用性を報告し[9,10]，さらにはパイロットスタディとして，doxorubicin/IFN-β併用化学療法をT-Bilが上昇しているような進行肝細胞癌を対象としてこれまで11例に施行した[1]。本療法においては既報のごとく，たとえT-Bilの上昇があっても肝不全徴候を増強することなく治療の完遂が可能であり，さらにほとんどの症例においてT-Bilの低下など肝機能の改善が得られ，中間生存期間が12か月と予後の向上を認めた。そこで本症例においてもまず，doxorubicin/IFN-β併用化学療法を施行，腫瘍進展を抑制し，さらには肝不全徴候の改善後に根治切除を施行することで長期生存を得た。

以上，既報のパイロットスタディと本症例での経験より，doxorubicin/IFN-β併用化学療法は進行肝細胞癌に対するneoadjuvantとしての可能性を含めた，集学的治療の有用な選択肢の一つとなり得ると考える。

本論文の要旨は第29回日本癌局所療法研究会において発表した。

文　献

1) Uyama H, Nagano H, Nakamura H, *et al*: New chemotherapy for patients with advanced hepatocellular carcinoma: Pilot study of beta-interferon and doxorubicin one-shot intra-arterial chemotherapy. *Hepatol Res* 23: 2007. (in press)
2) 日本肝癌研究会/編：原発性肝癌取扱い規約，第4版，金原出版，東京，2001.
3) Nakamura M, Nagano H, Wada H, *et al*: A case of hepatocellular carcinoma with multiple lung, spleen, and remnant liver metastasis successfully treated by combination chemotherapy with the novel oral DPD-inhibiting chemotherapeutic drug S-1 and interferon-alpha. *J Gastroenterol* 41(11): 1120-1125, 2006.
4) 中村将人，永野浩昭，丸橋　繁・他：肝細胞癌に対するS-1．癌と化学療法 33(*Suppl* I): 230-235, 2006.
5) Sakon M, Nagano H, Dono K, *et al*: Combined intraarterial 5-fluorouracil and subcutaneous interferon-alpha therapy for advanced hepatocellular carcinoma with tumor thrombi in the major portal branches. *Cancer* 94: 435-442, 2002.
6) Ota H, Nagano H, Sakon M, *et al*: Treatment of hepatocellular carcinoma with major portal vein thrombosis by combined therapy with subcutaneous interferon-alpha and intra-arterial 5-fluorouracil; role of type 1 interferon receptor expression. *Br J Cancer* 93: 557-564, 2005.
7) Nagano H, Sakon M, Eguchi H, *et al*: Hepatic resection followed by IFN-alpha and 5-FU for advanced hepatocellular carcinoma with tumor thrombus in the major portal branch. *Hepatogastroenterology* 54: 172-179, 2007.
8) Nagano H, Miyamoto A, Wada H, *et al*: Interferon-α and 5-fluorouracil combination therapy following palliative hepatic resection in patients with advanced hepatocellular carcinoma, portal venous tumor thrombus in the major trunk and multiple nodules. *Cancer*: 2007. (in press)
9) Damdinsuren B, Nagano H, Sakon M, *et al*: Interferon-beta is more potent than interferon-alpha in inhibition of human hepatocellular carcinoma cell growth when used alone and in combination with anticancer drugs. *Ann Surg Oncol* 10: 1184-1190, 2003.
10) Damdinsuren B, Nagano H, Wada H, *et al*: Stronger growth-inhibitory effect of interferon (IFN)-beta compared to IFN-alpha is mediated by IFN signaling pathway in hepatocellular carcinoma cells. *Int J Oncol* 30: 201-208, 2007.

下大静脈内に連続する腫瘍栓を伴う肝細胞癌に対する肝右葉切除術

Hepatic right lobectomy for hepatocellular carcinoma with tumor thrombus in the inferior vena cava.

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●要旨● 「下大静脈内に腫瘍栓を伴う肝細胞癌に対する肝右葉切除術」についてその一般的手技と応用などについて概説する。このような症例においては，術前・術中の画像診断による腫瘍進展度診断とともに，十分な血管処理を施行するにたりる視野の展開と血管の剝離が重要である。また，下大静脈切除における体外循環については，肝上部下大静脈を十分に剝離した後，腹腔内より心嚢を切開しその進展度について確認後，鉗子による右心房から胸腔内下大静脈の遮断が可能か否かによって判断する。

● key words：肝右葉切除術，肝細胞癌，腫瘍栓，下大静脈

はじめに

肝臓は周辺に門脈，下大静脈などの大血管が存在し，腫瘍の部位と大きさなど，その進展形式によってはこれら大血管合併切除術が必要になる。その手技については，原発巣の性状，進展度によって方法や対策が異なる。そのなかで腫瘍栓が肝静脈から下大静脈，さらには右心房内までに及ぶような肝細胞癌は，肺塞栓や心不全などの致死的な合併症を引き起こす可能性が高い。このような症例に対する効果的な治療法の一つに外科手術があるが，必ずしも安全に施行できるとは言い難い。本稿においては，「下大静脈内に腫瘍栓を伴う肝細胞癌に対する肝右葉切除術」についてその一般的手技と応用などについて概説する。

基本となる重要な手順

下大静脈内に腫瘍栓を伴う肝細胞癌に対する肝右葉切除術の手術術式の概要について述べる。ただし，下大静脈内腫瘍栓を伴う肝細胞癌症例の肝切除術に際しては，下大静脈内腫瘍栓の先端部位（頭側・尾側）と腫瘍栓を形成する静脈の種類によって異なる。この基本術式については，症例数としてもっとも多いと考えられる，肝右葉の肝細胞癌が右肝静脈より下大静脈内に腫瘍栓を形成し，その先端は肝上部下大静脈内にとどまる症例について述べることにする。

(1) 術前の画像診断により腫瘍栓の先端部位についての十分な診断を施行する。手術創については，基本的に術後の回復を考慮し手術侵襲をできるだけ少なくするためには，最初から開胸はせずに開腹手術のみで下大静脈内腫瘍栓の摘出を試みる。まず，上腹部正中切開に高位横切開（逆T字切開）を加えて開腹する。

しかしながら，後述するように腫瘍栓の進展度によっては，開胸，胸骨縦切開を必要とする症例もある（図1）。

(2) 開腹後，術中エコー[1]を施行する。肝内の腫瘍の位置，下大静脈内腫瘍栓の位置について確認する（図2）。

(3) ついで，胆嚢摘出術を施行する。

(4) 肝門部処理については，門脈内腫瘍栓を伴わない症例では，グリソン鞘一括処理[2]を用いる。肝右葉切除術を施行するにあたり，肝門部処理により肝十二指腸間膜（全肝）および右葉にテーピング後は，肝切

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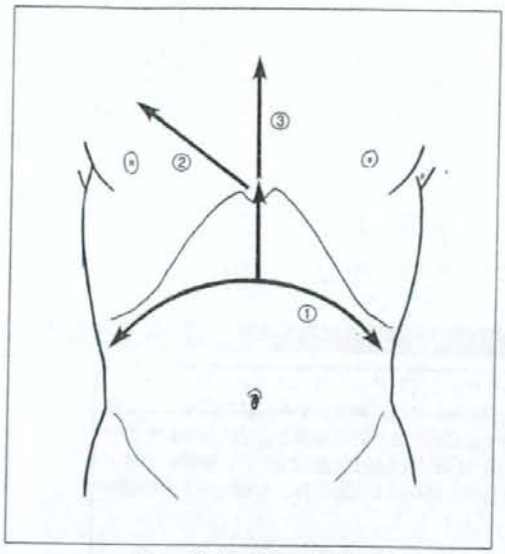

図1 開創に関する模式図
①高位横切開＋上腹部正中切開，②開胸，③胸骨縦切開。基本的には，①の開腹創で手術に臨むが，症例によっては，②：開胸，③：胸骨縦切開を要する症例もある

離終了まで肝右葉の血流は遮断しつづけたままで，以下の処理を施行する（図3）。

(5) 全例においてKocherの授動術を施行し，下大静脈前面を露出し腫瘍栓尾側末端部位の確認を行い，下大静脈の血流遮断を施行するにあたり，視野と遮断部位が不十分でないようにする（図4）。

(6) 肝右葉を脱転する。この際に，肝右葉側を十分に下大静脈より剝離しその前面を露出することが重要である。したがって，短肝静脈については，下大静脈前面にあるものは可能な限り結紮切離する。

(7) 肝右葉脱転後，右肝静脈，左・中間静脈共通幹を同定し十分に剝離した後，それぞれをテーピングする（図5）。

(8) Belghitiのhanging manuever[9]を応用し，下大静脈前面にペンローズドレーンを挿入し，肝切離のメルクマールとする（図6）。

(9) CUSA，モノポーラ型電気メスを用いて中肝静脈の右側で肝切離[10]を施行する。

(10) 肝右葉のグリソン鞘を一括に，結紮切離する。

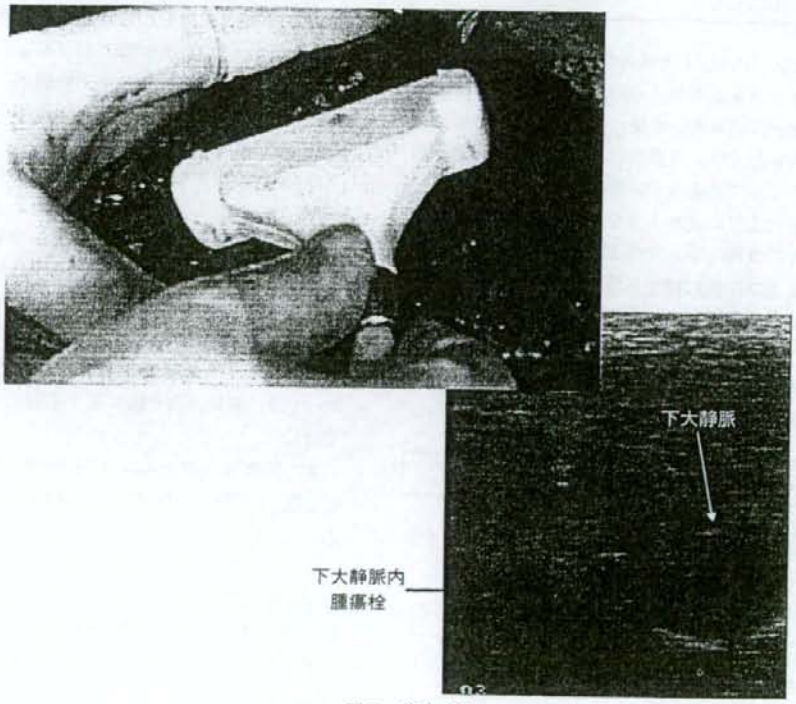

図2 術中US
下大静脈内に充満する腫瘍栓が示されている

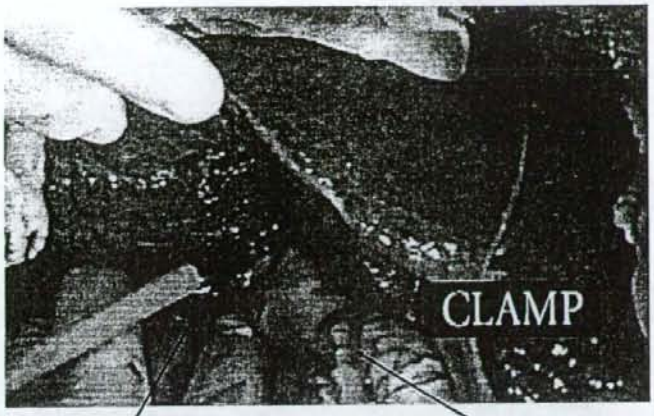

図3　グリソン鞘一括処理による肝門部血流遮断
肝右葉側は，肝切離終了まで遮断する

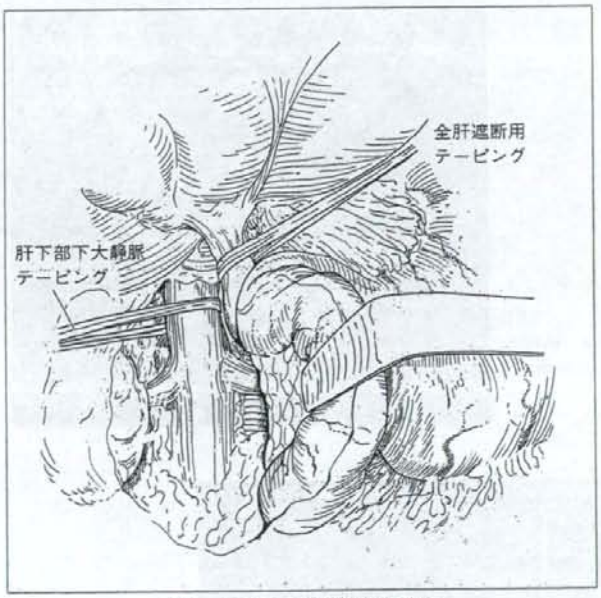

図4　Kocher の授動術の模式図
肝下部下大静脈を十分に露出し，腫瘍栓の尾側先端部位を
確認後テーピングを施行する

右グリソン鞘の切離断端は結紮縫合閉鎖する。

(11)　この時点で肝右葉は右肝静脈のみで連続していることになる。したがって，右肝静脈を切離して腫瘍栓を摘出することで肝切除術は終了する。まず，肝上部下大静脈にテーピングする。ついで，肝下部下大静脈に腎静脈の頭側でテーピングする。さらに右肝静脈と左・中肝静脈共通幹のテーピングについて確認する。

(12)　肝上部下大静脈，肝下部下大静脈，左・中肝静脈共通幹の血流遮断を施行しうる血管鉗子（図7）をそれぞれに準備する。

(13)　一般的に腫瘍栓は下大静脈内では周辺の血管壁

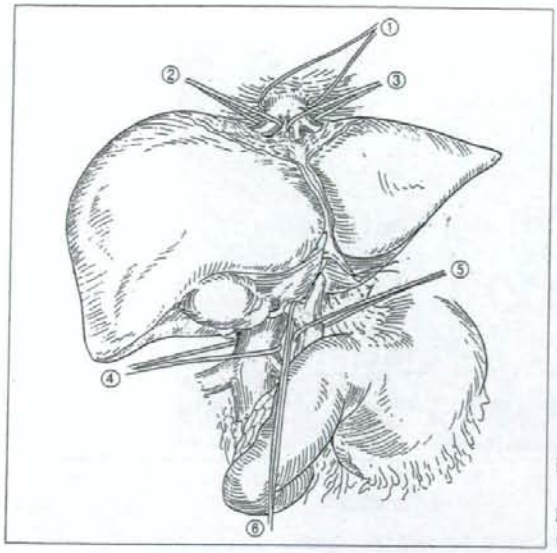

図5　肝切離前の肝外での各血管のテーピングの模式図
①肝上部下大静脈，②右肝静脈，③左・中肝静脈，④肝下部下大静脈，⑤肝門部（全肝遮断），⑥右肝門部，にそれぞれ肝外でテーピングする

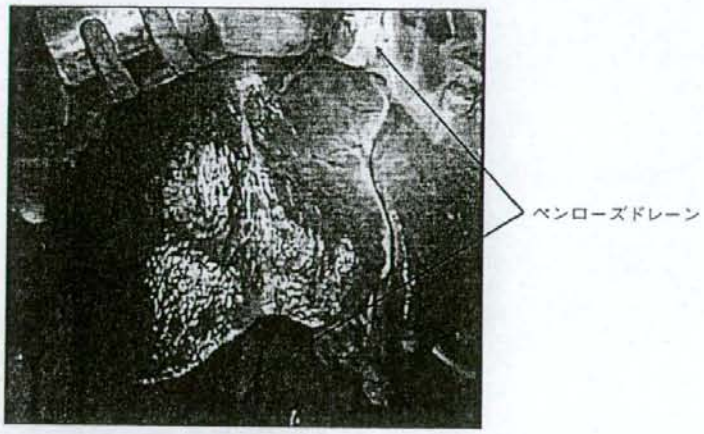

図6
Dr. Belghiti の liver hanging maneuver を modify し，肝部下大静脈前面にペンローズドレーンを挿入している

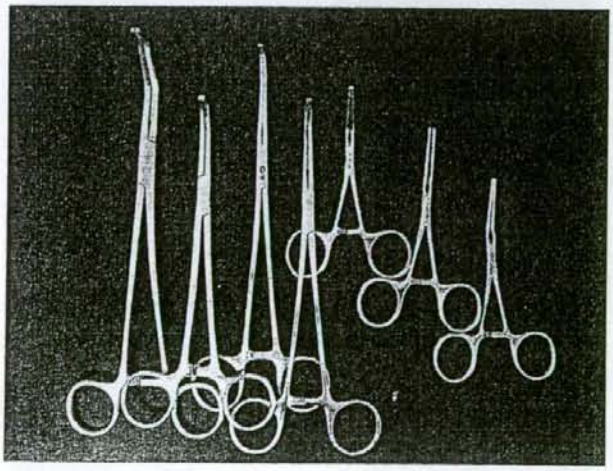

図7　血管鉗子

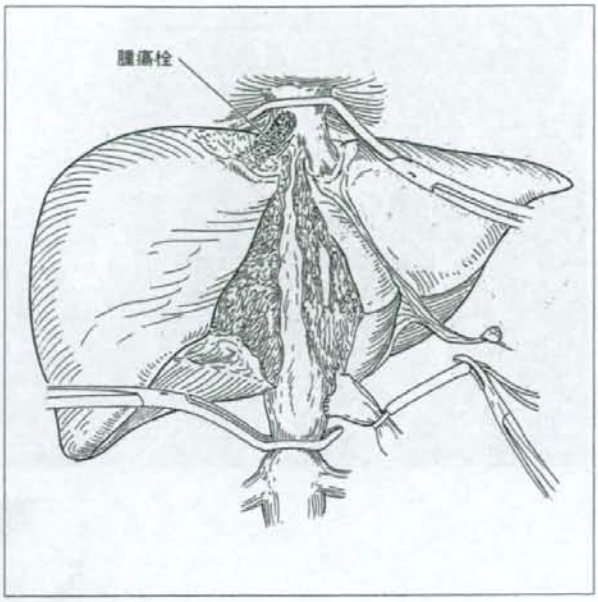

図8　肝切離が終了し下大静脈内腫瘍栓摘出直前の模式図
肝門部血流遮断と肝上部・肝下部下大静脈の血流が完全に遮断されている（THVE）

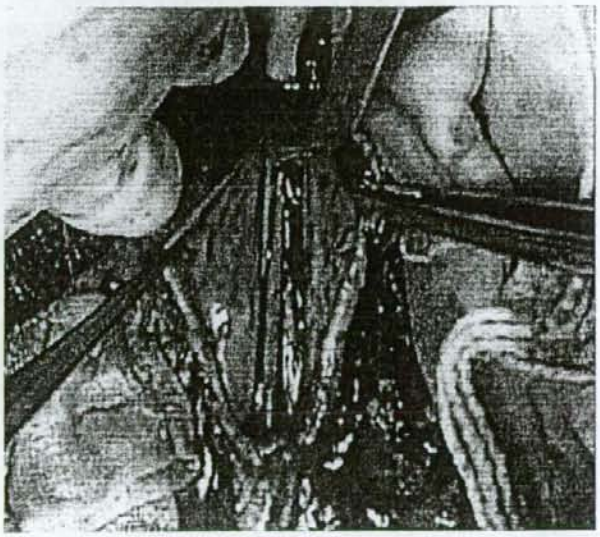

図9　下大静脈内腫瘍栓摘出直後の肝部下大静脈
下大静脈の欠損部位が大きくなければこのまま一次縫合閉鎖を施行する

に浸潤しておらず，ほとんどの症例では血管内を浮遊している状態である。したがって，右肝静脈のみで肝右葉が下大静脈と連続している状況であれば，肝右葉を足側に牽引することにより，腫瘍栓は横隔膜より腹腔内に存在する状況となる。

(14)　この時点で，肝門部の全肝血流遮断をした後に，肝上部下大静脈，肝下部下大静脈をそれぞれ血管鉗子を用いて血流遮断を施行（図8）し，右肝静脈を切開し肝右葉とともに下大静脈内腫瘍栓を摘出する（図9）。

(15)　下大静脈内をヘパリン加生理食塩水を用いて十分に洗浄した後，5-0の非吸収性モノフィラメント糸を用いて連続縫合により一次縫合閉鎖を行い，腫瘍栓を伴う肝細胞癌の肝右葉切除術を終了する（図10）。

図10　下大静脈内腫瘍栓摘出を伴う肝右葉切除術の終了時写真

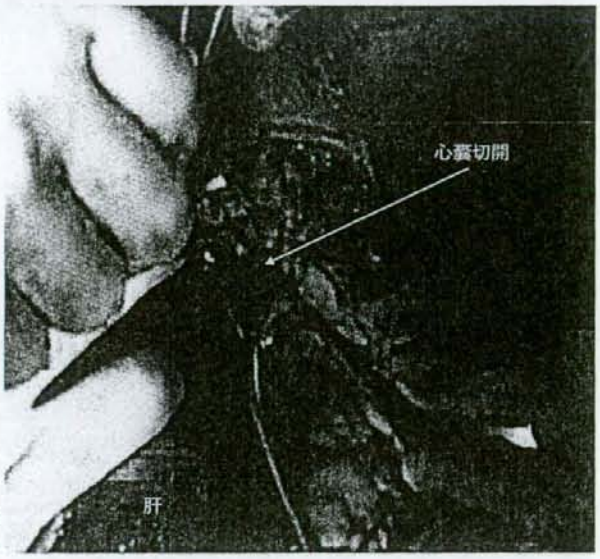

図11　開腹創からの心嚢切開による胸腔内下大静脈から右心房にいたる腫瘍栓先端部位の確認

操作が困難な際の応用的手法

1．腹腔内心嚢切開による腫瘍栓の存在部位の確認（図11）

術前の画像診断により，下大静脈内腫瘍栓の頭側・尾側の先端部位の詳細については十分に確認し開腹手術に臨むが，最終的には術中エコーにて確認する。腫瘍栓が胸腔内に及び右心房にまで到達している可能性がある症例については，開腹後に腹腔内より心嚢を切開し直視下に腫瘍栓の先端部位を確認する。また，経食道エコーによる心房内腫瘍栓の先端部位の確認が有用なこともある。

2．腫瘍栓の存在部位による開創法

上記の方法により腫瘍栓先端部位を確認し，右心房内にまで腫瘍栓が到達していた場合には，開創法を変更することがある。腫瘍栓が右心房の近くまで進展しており下大静脈を胸腔内で血流遮断する必要がある症例では開胸を，腫瘍栓摘出のために体外循環を必要とする症例では胸骨縦切開が必要になる。

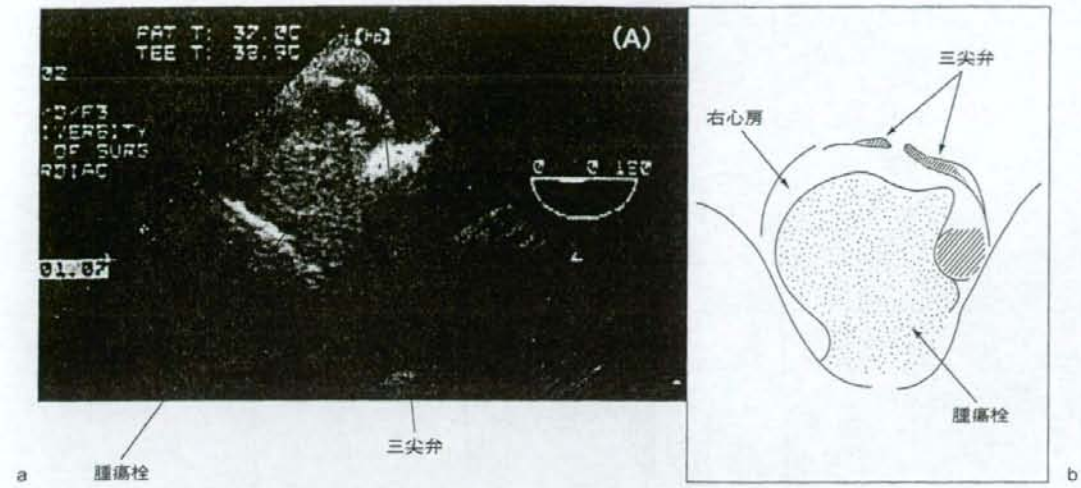

図12　右心房内腫瘍栓のエコー像（a）と模式図（b）
腫瘍栓と三尖弁輪との関係が描出されている。この三尖弁輪を損傷することなく血管鉗子をかけることができれば，体外循環は必要としない

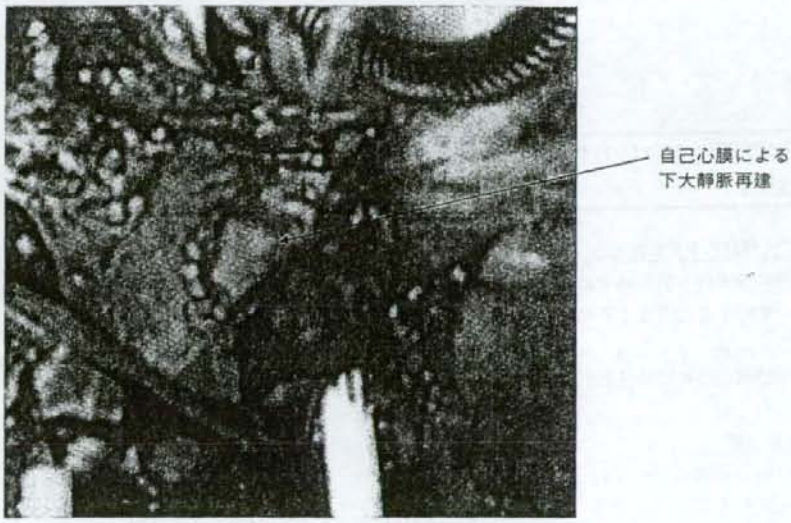

図13　自己心膜を用いた下大静脈再建

3.　腫瘍栓の存在部位による体外循環使用の有無

下大静脈切除における体外循環は，肝上部下大静脈を十分に剝離した後，腹腔内より心嚢を切開し術中エコーを用いてその進展度について確認した後，鉗子による右心房から胸腔内下大静脈の遮断が可能か否かによって判断する。教室では，腫瘍栓が三尖弁輪の手前で血管鉗子を右心房にかけることが可能であれば，人工心肺による体外循環は必要ないと考えている（図12）。また，下大静脈内腫瘍栓の摘出に際して，肝門部，肝上部下大静脈，肝下部下大静脈をそれぞれ血管鉗子を用いて血流遮断を施行した際（THVE）に，全身の循環動態の変動がなければ，V-V bypass なども必要ないと考えている。

現在までに，人工心肺を必要とした症例が1例あったが，V-V bypass を単独で必要とした症例はなかった。

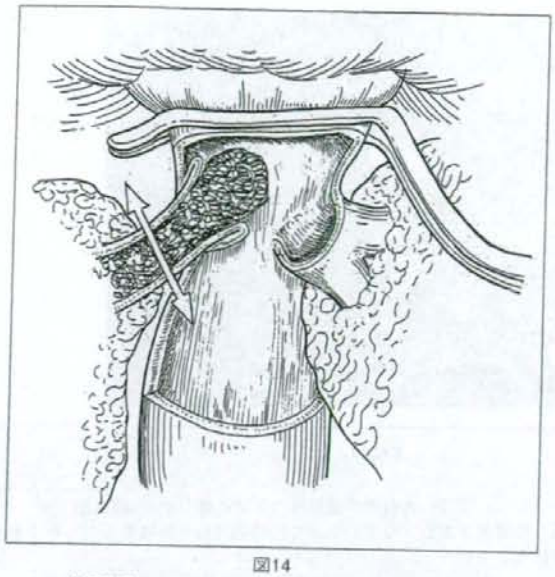

図14
右肝静脈より下大静脈内に進展する腫瘍栓摘出の際の右肝静脈切開部位。できるだけ，肝側で切開することが重要。腫瘍栓は浸潤傾向がないため摘出については問題ない

合併症発生を少しでも回避するための注意点

1. 下大静脈の十分な露出

大血管切除を伴う肝切除では，十分な血管露出を心がける。切除する血管を十分に剝離し，種々の血管鉗子を利用し血管のみを処理することが何よりも出血と合併症の軽減のためには肝要である。

2. 再建血管

下大静脈の再建については，ゴアテックス® シート，リング付きゴアテックス®，牛心膜などを用いるが，いずれも異物であり，症例によっては，自己心膜（図13）も有用である。

より安全な操作のコツ

1. 肝静脈切離線

血管グラフトを使用しないためには，腫瘍栓の存在する血管のできるだけ末梢側で切離することにより，下大静脈の再建が一次縫合閉鎖で終了する（図14）。

2. 肝血流遮断

下大静脈内腫瘍栓摘出については，先述したようにTHVEが必要になるが，肝血流遮断については術後の肝虚血再灌流障害予防のためには短時間のほうが望ましい[5)6)]。したがって，そのためには右肝静脈周囲の下大静脈が十分に剝離可能であれば，THVE下に腫瘍栓を摘出した後に，肝静脈頭側の肝上部下大静脈で血流遮断している血管鉗子を，肝静脈流入部足側へかけ直せば，全肝の血流遮断を解除することが可能になり肝血流遮断時間を短縮することが可能である。

途中で切除をあきらめるポイント

一般的に肝細胞癌で下大静脈内腫瘍栓を伴う手術において，切除を断念する症例としては，心房内腫瘍栓に伴う肝うっ血出現のために肝切除術を断念せざるをえなかった症例がある。症例を提示する。

<症　例>

58歳，男性。後区域の肝細胞癌で，右肝静脈より下大静脈を経て右心房内に腫瘍栓を形成していた（図15）。肝動注化学療法施行後，開腹手術を施行した。術中，肝障害度を確認するうえで，肝線維化，炎症度