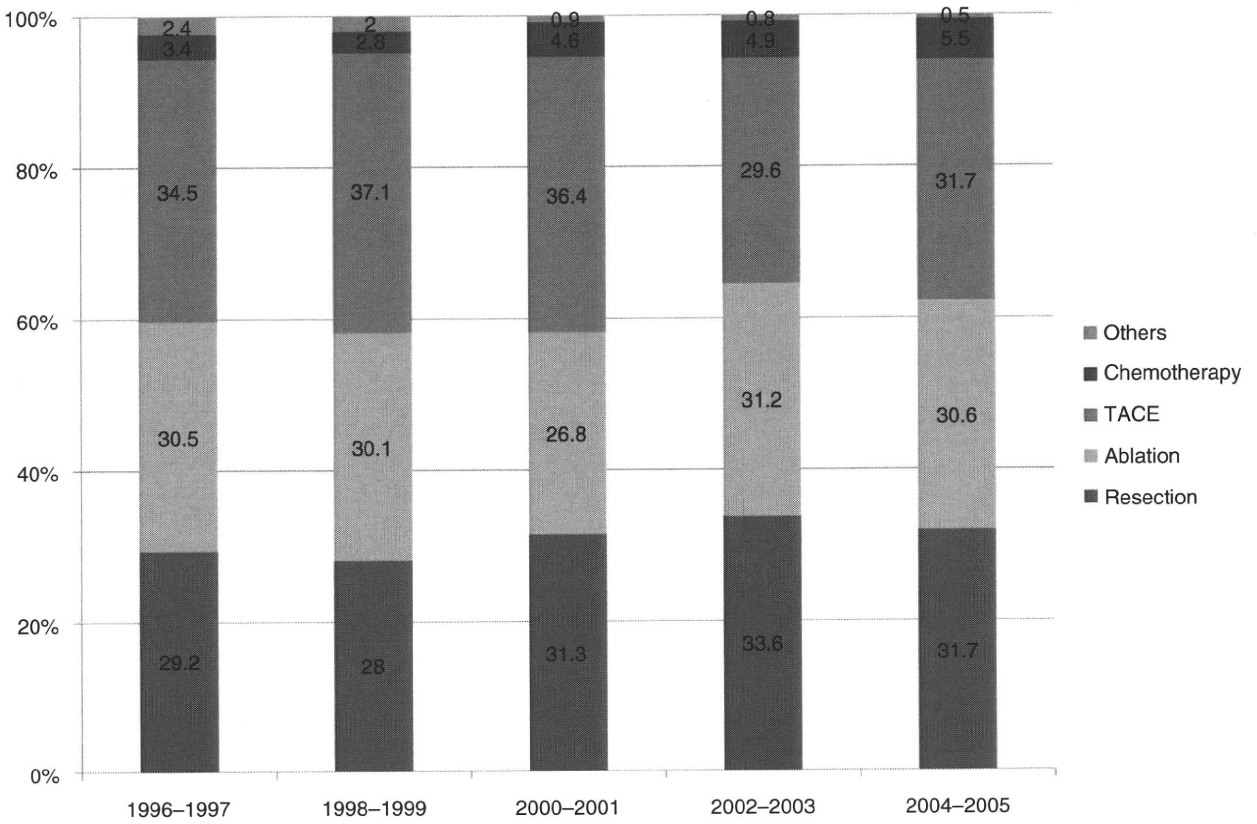

Figure 2 Change of treatment method for hepatocellular carcinoma in Japan. TACE, transcatheter arterial chemoembolization.

48.4% and 29.7%, respectively, for single tumors, and 46.4%, 37.3% and 23.0%, respectively, for two tumors.[90]

In contrast, in a large prospective cohort study of 8510 patients who received TACE for unresectable HCC, according to the LCSGJ, the median survival was 34 months with 1-, 2-, 3-, 5- and 7-year survival rates of 82%, 63%, 47%, 26% and 16%, respectively.[91] In patients with early stage HCC, single tumors of 2 cm or more and preserved liver function (clinical stage I and liver damage A according to the LCSGJ),[92] the median survival was 62 months with 1-, 2-, 3-, 5- and 7-year survival rates of 98%, 92%, 73%, 52% and 38%, respectively.[91] These results for TACE with early stage HCC seem comparable with those for surgery or ablation. Thus, although curative therapies are highly recommended for patients with early stage HCC, TACE can be applied in these patients contraindicated for curative therapies.

Transcatheter arterial chemoembolization can be used in combination with percutaneous ablation, including RFA. A meta-analysis of four RCT comparing combination therapy (TACE plus percutaneous ethanol injection [PE]) or RFA) versus monotherapy (TACE alone, PEI or RFA alone) showed a significant decrease in mortality favoring combination therapy versus monotherapy in patients with small (<3 cm) or large (>3 cm) HCC (OR = 0.534; 95% CI = 0.288–0.990; $P = 0.046$).[93]

In RFA treatment, as the tumor size increases, the therapeutic response decreases because of the limited volume of coagulation necrosis induced by the electrode. Blood flow also promotes heat loss to result in insufficient necrosis; therefore, reducing blood flow during RFA increases the ablation volume. Therefore, it seems to be reasonable to perform RFA after reducing blood flow by preceding RFA with TACE. Several cohort studies have shown that performing TACE before RFA is feasible and safe, and offers a useful treatment in compensated cirrhosis (Child–Pugh A or B) with relatively small HCC nodules (20–50 mm).[94–97] RFA in combination with preceding TACE is already recommended in the consensus-based treatment algorithm proposed by the JSH[89].

In the current consensus meeting, for hypervascular HCC of 2 cm in size, 51% of the experts used TACE

before RFA treatment. By contrast, for hypervascular HCC of 3 cm in size, 81% of the experts performed TACE before RFA. This is theoretically reasonable because the possibility of incomplete ablation is greater for tumors of 2–3 cm in size, compared with tumors of less than 2 cm in size, based on the limited volume possible with a single ablation procedure. Additionally, the accumulation of lipiodol in the tumor should facilitate the decision on whether additional RFA treatment is required following the response evaluation by dynamic CT scan. However, the survival benefit of TACE in combination with RFA should be verified by well-designed RCT.

Transcatheter arterial chemoembolization is performed in various stages in the clinical management of HCC, not only for the initially detected HCC, but also for recurrent HCC. TACE has been shown to be valuable for improving the overall survival of HCC patients, although it is difficult to assess its clinical efficacy as second- or third-line therapy.

Informative Statement 3. TACE performed before RFA is favorable for the curative treatment of hypervascular HCC of 2–3 cm in size.

Recommendation 15. TACE performed before RFA is recommended for curative treatment of hypervascular HCC larger than 3 cm in size.

Chemotherapy

Chemotherapy for HCC is divided into two types according to the route of administration; the first is systemic chemotherapy and the second is hepatic arterial infusion chemotherapy (HAIC). Systemic chemotherapy can also divided into two types: intravenous and oral chemotherapy.

According to the Nationwide Follow-up Survey of Primary Liver Cancer by the LCSGJ, chemotherapy is used in 3.4–5.5% of primary HCC patients (Fig. 2). HAIC is theoretically more favorable for HCC than systemic chemotherapy because hepatic arterial infusion of anticancer drugs enables the delivery of high doses of drugs directly to the hypervascular HCC. In addition, HAIC provides a lower systemic level of the drugs than systemic administration, because the first-pass effect in the liver, and thus reduces toxicity and side-effects. Because of these advantages, HAIC is frequently used in Japan for intrahepatic advanced HCC with portal vein tumor thrombosis and/or intrahepatic multiple HCC. A recent report from the Japanese Nationwide Survey revealed that almost 90% of the chemotherapeutic regimens for HCC are done by hepatic arterial infusion. Thus, HAIC has become widely used in Japan, despite there being no solid evidence for a survival benefit of HAIC compared with systemic chemotherapy or best supportive care (Fig. 3).

Recommendation 16. HAIC is recommended for advanced HCC with major portal vein tumor thrombi with preserved liver function.

Various anticancer drugs and treatment regimens are used for HAIC in Japan. Two regimens in particular are widely used for HAIC. The first is interferon (IFN) in combination with 5-fluorouracil (5-FU); the second is low-dose cisplatin (CDDP) in combination with 5-FU. For IFN plus 5-FU, the response rate was reported to be 52.6%, with 16.4% achieving complete response (CR) and 36.2% achieving partial response (PR) among 116 patients with tumor thrombosis of the major portal vein or first branches of the portal vein. The survival rates at 6, 12 and 24 months were 53%, 34% and 18%, respectively, with a median survival of 6.9 months, compared with survival rates of 40%, 15% and 5%, respectively, in the historical control group.[98] The survival was significantly different between the two groups ($P < 0.01$). For low-dose CDDP plus 5-FU, the response rate was 48%, including 8% with CR and 40% with PR among 48 patients with portal vein tumor thrombosis. The 1-, 2-, 3- and 5-year cumulative survival rates were 45%, 31%, 25% and 11%, respectively, with a median survival of 10.2 months.[99]

In a review of previously reported small-size phase II studies of HAIC for advanced HCC,[10,17,98–108] the response rate varied from 14% to 71%. The mean survival duration also varied from 2.6 months to 32.4 months. However, few reports have compared systemic chemotherapy or HAIC using cytotoxic agents with placebo or best supportive care (Table 2).

The results of a randomized placebo-controlled double-blind phase III study with the multikinase inhibitor sorafenib were recently reported, representing a breakthrough in the chemotherapy for advanced HCC. Sorafenib is an oral drug that inhibits the platelet-derived growth factor (PDGF)-R, vascular endothelial growth factor (VEGF)-R, c-Kit-R and raf signaling pathways in tumor cells and in surrounding endothelial cells. In that study, 602 patients with advanced HCC, who were not indicated for other loco-regional treatments such as hepatic resection, who had not received prior systemic treatment and who had good liver functional reserve (Child–Pugh A) were randomized to sorafenib (400 mg b.i.d.) or placebo. Sorafenib was well tolerated and yielded a statistically significant improvement (44%) in overall survival. The median survival increased from 7.9 to 10.7 months (hazard ratio, 0.69;

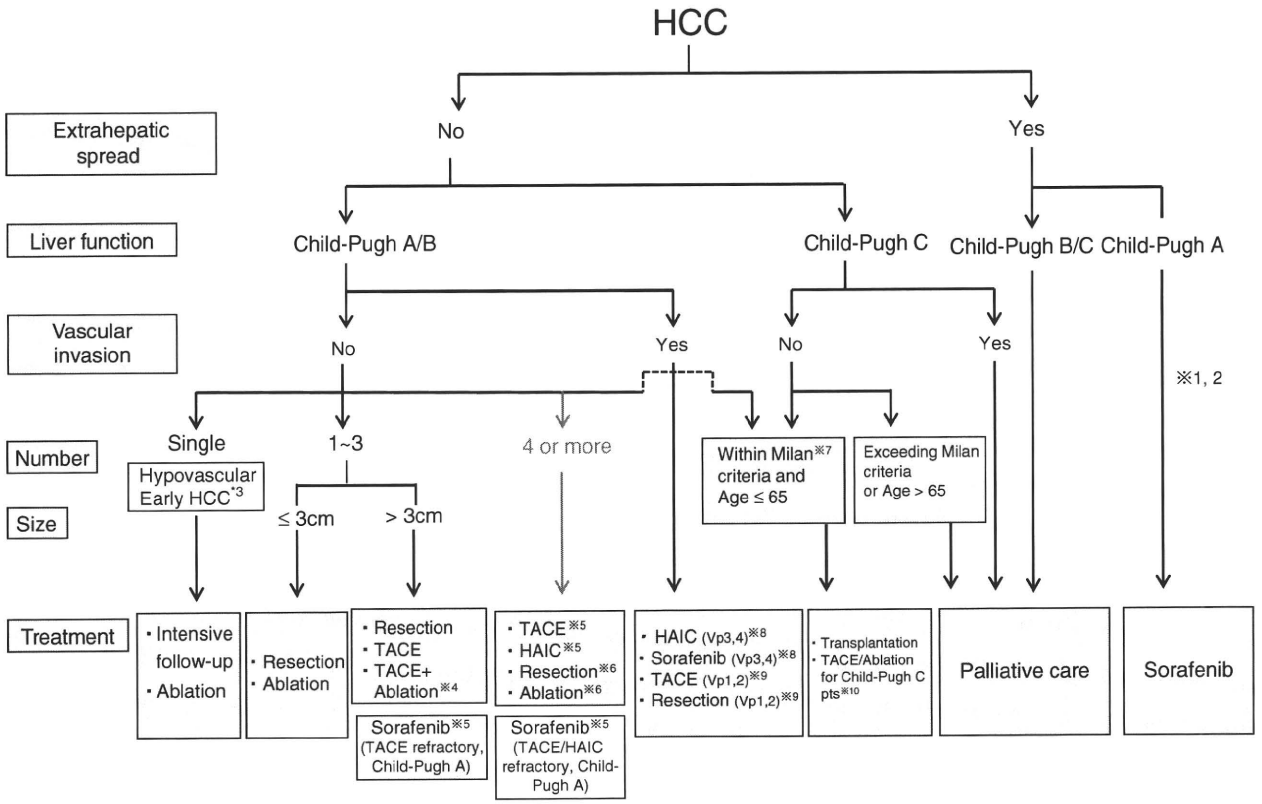

Figure 3 Consensus-based treatment algorithm for hepatocellular carcinoma proposed by the Japan Society of Hepatology (JSH) revised in 2010. (1) Treatment should be performed as if extrahepatic spread is negative, when extrahepatic spread is not regarded as a prognostic factor. (2) Sorafenib is the first choice of treatment in this setting as a standard of care. (3) Intensive follow-up observation is recommended for hypovascular nodules by the Japanese Evidence-Based Clinical Practice Guidelines. However, local ablation therapy is frequently performed in the following cases: (i) when the nodule is diagnosed pathologically as early hepatocellular carcinoma (HCC); (ii) when the nodules show decreased uptake on gadolinium ethoxybenzyl magnetic resonance imaging (Gd-EOB-MRI); or (iii) when the nodules show decreased portal flow by computed tomography during arterial portography (CTAP), because these nodules are known to frequently progress to the typical advanced HCC. (4) Even for HCC nodules exceeding 3 cm in diameter, combination therapy of transcatheter arterial chemoembolization (TACE) and ablation is frequently performed when resection is not indicated. (5) TACE is the first choice of treatment in this setting. Hepatic arterial infusion chemotherapy (HAIC) using an implanted port is also recommended for TACE refractory patients. The regimen for this treatment is usually low-dose FP (5-fluorouracil [5-FU] + cisplatin [CDDP]) or intra-arterial 5-FU in fusion combined with systemic interferon therapy. Sorafenib is also a treatment of choice for TACE/HAIC refractory patients with Child–Pugh A liver function. (6) Resection is sometimes performed even when numbers of nodules are over 4. Furthermore, ablation is sometimes performed in combination with TACE. (7) Milan criteria: tumor size ≤ 3 cm and tumor numbers ≤ 3; or solitary tumor ≤ 5 cm. Even when liver function is good (Child–Pugh A/B), transplantation is sometimes considered for relatively younger patients with frequently or early recurring HCC after curative treatments. (8) HAIC or sorafenib is recommended for HCC patients with Vp3 (portal invasion at the 1st portal branch) or Vp4 (portal invasion at the main portal branch). Sorafenib is only recommended for HCC patients with Child–Pugh A liver function. (9) Resection and TACE is frequently performed when portal invasion is minimal such as Vp1 (portal invasion at the 3rd or more peripheral portal branch) or Vp2 (portal invasion at the 2nd portal branch). (10) Local ablation therapy or subsegmental TACE is performed even for Child–Pugh C patients when transplantation is not indicated when there is no hepatic encephalopathy, no uncontrollable ascites and a low bilirubin level (<3.0 mg/dL). However, it is regarded as an experimental treatment since there is no evidence of its survival benefit in Child–Pugh C patients. A prospective study is necessary to clarify this issue. Even in Child–Pugh A/B patients, transplantation is sometimes performed for relatively younger patients with frequently or early recurring HCC after curative treatments.

Table 2 Response rates and survival periods in studies of intrahepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma

	Drugs	No. of Patients	Response rate (CR + PR, %)	Median survival time (months)	References
Single	Doxorubicin (IHAC)	72	60	7.0	Tzoracoleftherakis *et al.*[102]
	Doxorubicin (systemic)		44.1	6.5	
	CDDP	67	37	10.7	Court *et al.*[103]
Multiple	CDDP, 5-FU (low FP)	52	71	ND	Okuda *et al.*[104]
	CDDP, 5-FU (low FP)	48	48	10.2	Ando *et al.*[99]
	CDDP, 5-FU (low FP)	37	56.3	32.4	Sumie *et al.*[101]
	CDDP, 5-FU (low FP)	38	47	6.2	Tanioka *et al.*[105]
	CDDP, 5-FU	41	22	12.0	Park *et al.*[106]
	CDDP, Mitomycin C, 5-FU, LV	53	28.3	13.2	Lin *et al.*[100]
	IFN, CDDP	68	33	4.4	Chung *et al.*[107]
	CDDP		14	2.6	
	BSC			1.2	
	IFN, CDDP, 5-FU, MTX, LV	34	45	ND	Kaneko *et al.*[108]
	IFN, 5-FU	116	52	6.9	Obi *et al.*[98]

IHAC, intrahepatic arterial chemotherapy; CDDP, cisplatin; 5-FU, 5-fluorouracil; low FP, 5-fluorouracil + cisplatin. BSC, best support care; IFN, interferon; LV, leucovorin; MTX, methotrexate.

95% CI = 0.55–0.87). Side-effects included hand–foot skin reaction, diarrhea and fatigue, but sorafenib was not found to be toxic to the liver.[109] Similar findings were reported in a subsequent Asia–Pacific RCT.[110]

Based on the results of these RCT, sorafenib has become the first-line therapy for advanced HCC worldwide. Some Japanese experts for HCC are claiming low response rates, although the survival was significantly prolonged compared with placebo. This phenomenon could be explained by a longer period with stable disease with sorafenib than with placebo, or the necrotic change in the tumor is present without size reduction.

In Japan, sorafenib was approved for the treatment of HCC on 20 May 2009. In the consensus meeting held in June, 35% of the Japanese experts agreed that sorafenib should be selected as the first-line therapy for advanced HCC considered unsuitable for resection, RFA or TACE. A further 36% of the experts were undecided because they did not have enough experience with using sorafenib.

Informative Statement 4. Sorafenib is the first-line therapy for advanced HCC with major vascular invasion and/or extrahepatic spread and good liver function. However, further studies are needed to compare the overall efficacy of HAIC and sorafenib.

TREATMENT ALGORITHM

TO TREAT HCC, the most appropriate therapeutic option needs to be selected among the available treatment modalities, including resection, percutaneous ablation, TACE and transplantation, but few evidence-based guidelines have been developed to aid decision-making.[1,28,29,88,89,111] Recently, two treatment algorithms for HCC have been proposed in the Japanese guidelines. The profile of these algorithms is briefly described here, in addition to the results of two questions and answers at the JSH Consensus Meeting for HCC at Kobe.

Evidence-based treatment algorithm

The Clinical Practice Guidelines for HCC was established in 2005 based on evidence-based methodology, and covers six topics including prevention, diagnosis, surgery, chemotherapy, TACE and percutaneous ablation. To develop these guidelines, a systematic review of the English medical published work was performed and a total of 7118 articles on HCC were identified, mainly from MEDLINE (1966–2002), of which 334 were selected based on the evidence level to form 58 pairs of clinical questions and recommendations.[1,88] For convenience in clinical use, two algorithms were created for the surveillance and treatment of HCC. A full English version was uploaded to the website of the JSH (www.jsh.or.jp/) in 2006.

The treatment algorithm for HCC was made on the basis of three independent factors: degree of liver damage, tumor number and tumor size. For the resulting six patients' subgroups, the first- and second-line therapies were recommended as objectively as possible (Fig. 1). The degree of liver damage is a modified system based on the Child–Pugh classification: "encephalopathy" was replaced by $ICGR_{15}$, to provide an accurate evaluation of liver functional reserve, particularly in surgical candidates.

Patients with mild (class A) or moderate (class B) liver damage are subject to the following recommendations: (i) in patients with a single tumor, liver resection is recommended, irrespective of the tumor size (percutaneous ablation may be performed if liver damage is of class B and the tumor is no more than 2 cm in size); (ii) for patients with two or three tumors smaller than 3 cm, resection or ablation are recommended; (iii) for patients with two or three tumors larger than 3 cm, resection or TACE are recommended; and (iv) for patients with more than four tumors, TACE or HAIC is recommended. The recommendations for patients with severe (class C) liver damage are as follows: (v) in patients with tumor(s) meeting the Milan criteria, liver transplantation is recommended; and (vi) for patients with more than four tumors, palliative treatment is recommended. For patients with extrahepatic metastasis, chemotherapy may be performed.

The rationale for selecting resection or ablation in patients with class A or B liver damage is based on the outcome of the largest multicenter study involving 12 888 patients in Japan.[59] The recommendation for TACE is based on the findings of two RCT showing a significant improvement in the survival of patients with multiple tumors and class A or B liver damage.[84,85] The indication for liver transplantation is derived from a prospective cohort study using the Milan criteria,[71] and a nationwide survey of Japan justifying the criteria in living donor transplantation.[74]

Consensus-based treatment algorithm

An expert panel of the JSH established a consensus-based treatment algorithm based on the therapeutic policies that are widely used in Japan.[89,111] This algorithm categories the patients on five clinical variables (extrahepatic spread, liver function, vascular invasion, tumor number and tumor size), and it divides the treatment options into resection, ablation, TACE, HAIC, liver

transplantation and palliative treatment (Fig. 3).[89,111] Because of the recent introduction of sorafenib in Japan, this consensus-based treatment algorithm was further revised and approved by the experts at the consensus meeting.[111,112]

Essentially, the consensus-based algorithm follows the evidence-based algorithm, but the treatments widely used in Japan were included by consensus, even though the evidence may be weak. The major differences in the consensus-based algorithm include: (i) ablation is sometimes performed in patients with a single, hypovascular early HCC; (ii) sorafenib is recommended for use in Child–Pugh A patients with vascular invasion, TACE failure or extrahepatic spread of HCC;[109,112] and (iii) liver transplantation is recommended, even for Child–Pugh A/B patients, if the Milan criteria are met.

The consensus-based algorithm based on the consensus of a large number of specialists, and a treatment strategy for management of HCC in Japan is important, and should be revised based on prospective trials for aspects of the algorithm lacking sufficient evidence.[111,112]

Informative statement 5. RFA might be recommended as a first-line treatment option in patients with a single, hypervascular HCC of less than 2 cm in size and with preserved liver function (Child–Pugh A or Liver Damage Class A). However, there was a discrepancy between surgeons and non-surgeons for this statement. This statement is strongly supported by non-surgeons (68%), whereas 80% of the surgeons favor resection rather than RFA.

Recommendation 17. Resection should be considered as the first-line treatment option for patients with a single, hypervascular HCC of 3 cm or more in size and with preserved liver function (Child–Pugh A or Liver Damage Class A).

The revised version of the consensus-based treatment algorithm for HCC proposed by the JSH (Fig. 3) should aid decision-making at every stage in clinical practice. By sharing the information contained within the treatment algorithm chart, the physicians can offer recommended treatment options to the patient who can then choose one based on their preference (Fig. 3).

CONCLUSIONS

THIS CONSENSUS STATEMENT is a conclusion of the consensus meeting of HCC, which was held at the 45th JSH meeting, Kobe, Japan on 4–5 June 2009 (Congress President: Professor Masatoshi Kudo). This manuscript and recommendations largely reflect the daily practice in the real world carried out throughout Japan. The biggest difference of Japan's HCC practice from Western countries are pathological assessment issue, prognostic staging system, surveillance and diagnostic strategy, treatment strategy including role of HAIC, and method of RFA procedure, and treatment algorithm shown in Figure 3.

We believe every reader of this manuscript will well understand the real Japanese HCC practice much better than the other already published arterial articles. It is needless to say that consensus statements like this article should be regularly revised every 3–4 years because solid evidence or new diagnostic and treatment tool/drug or concept will be published and then established in clinical practice every year.

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Original Article

Recent progress in the management of hepatocellular carcinoma detected during a surveillance program in Japan

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Aim: This study explored recent improvements in the management of hepatocellular carcinoma (HCC) diagnosed during surveillance.

Methods: The subjects were 1074 patients with HCC, subdivided into three groups. Group A comprised 211 patients for whom HCC was detected during periodic follow-up examinations at Kurume University School of Medicine, Group B comprised 544 patients diagnosed with HCC during periodic follow-up examinations at other institutions, and, Group C comprised 319 patients with HCC detected incidentally or because of symptoms.

Results: In 1995–2000 and 2001–2006, 91% and 91% of group A, 68% and 70% of group B, and 27% and 26% of group C patients with HCC, respectively, met the Milan criteria. For groups A and B, the proportions of patients with Child–Pugh class A and use of promising treatment increased in the later periods compared to those diagnosed during the earlier periods (group A, Child–Pugh class A, 72% vs 58% [$P = 0.040$], receiving treatment, 90% vs 70% [$P < 0.0001$]; group B, Child–Pugh class A, 71% vs 62% [$P = 0.031$]; receiving treatment, 72% vs 52% [$P < 0.0001$], respectively). The cumulative survival rates of the 405 patients with HCC detected in the latter 6 years tended to be better than those for patients diagnosed in the former 6 years (350 patients) (4 years, 58% vs 50% [$P = 0.0349$]).

Conclusion: The use of promising treatment and prognosis have improved in the last 6 years for patients with HCC diagnosed through surveillance relative to those identified in 1995–2000.

Key words: carcinoma, cirrhosis, hepatocellular surveillance, prognosis.

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the most common malignancies worldwide[1] and is the leading cause of death in patients with cirrhosis.[2] HCC commonly occurs in patients with chronic liver diseases related to hepatitis C virus (HCV) or hepatitis B virus (HBV) infection, with a reported incidence of HCC in patients with HCV of 1–8% per annum.[3–7] Several cohort studies have shown that surveillance by abdominal ultrasonography (US) and α-fetoprotein (AFP) assay for patients with cirrhosis can detect early-stage HCC and thus have the potential to reduce mortality.[4–13] However, the results of surveillance are controversial including cost effectiveness[14,15] due to the high annual incidence of HCC, the target population and frequency of surveillance, available treatment for HCC, management of cirrhosis, and possibly the US equipment and skill of the US examiner.

The advent of new imaging techniques for tumor staging and improved criteria for selection of patients for liver transplantation (LT), hepatic resection (HR) and locoregional ablative therapies (LAT) has improved survival rates in patients with HCC.[2,16–23] Based on recent technological improvements in LAT, radiofrequency ablation therapy (RFA) has become more effective than percutaneous ethanol injection therapy (PEI) for patients with early-stage HCC.[22,23] Moreover, recent progress in managing complications related to cirrhosis has prolonged the life of many patients with cirrhosis.[2,24,25] These factors have contributed to the reported increase in survival of cirrhotic patients with HCC detected during surveillance over the three quinquennia (1987–2001).[7]

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We reported previously that surveillance for HCC at our Department of Liver Disease, Kurume University School of Medicine, successfully detected early-stage HCC, allowing a better chance of receiving promising treatment in 574 patients diagnosed from 1995–2001.[13] In addition, Kurume University School of Medicine recently introduced RFA for the treatment of early-stage HCC,[22,23] interferon (IFN) therapy for patients with cirrhosis, follow up after curative treatment of HCC[26,27] and management of cirrhosis-related complications by nutritional therapists.[24,25]

The present study explored the effects of recent improvements in managing HCC diagnosed through surveillance in Japanese hospitals.

METHODS

Patients

THE STUDY COMPRISED 1074 Japanese patients with HCC diagnosed at Kurume University School of Medicine from January 1995 to December 2006. The diagnosis of HCC was established by histopathology and/or imaging studies (US, computed tomography [CT], angiography, CT angiography, and magnetic resonance imaging [MRI]), and/or on high plasma levels of tumor markers such as AFP, lens culinaris agglutinin reactive AFP (AFP-L3), and des-γ-carboxy prothrombin (DCP). Patients were subdivided into three groups according to the manner of HCC detection: group A, 211 patients found to have HCC during periodic follow-up examination at Kurume University School of Medicine; group B, 544 patients found to have HCC during periodic follow-up examination in other institutions; and, group C, 319 patients found to have HCC incidentally or because of symptoms.

Surveillance program

Surveillance of 211 subjects in group A included patients of all ages, those with chronic hepatitis and cirrhosis, patients with a background of infection by HCV or HBV, and those suffering from alcoholism or other chronic liver diseases. The surveillance program was based on US examination and AFP determination every 3 months. The need for concomitant examination by CT, MRI and DCP was decided by the referring physician (hepatologist or gastroenterologist). During the subsequent surveillance period, imaging and tumor marker studies, together with physical examinations and routine biochemical testing, were repeated every 3 months. The 544 patients of group B showed nodular liver lesions or elevated AFP or DCP during periodic follow up in other institutions performed at approximately 6-month intervals. The classification of 319 patients into group C was based on a nodular liver lesion detected incidentally or at examination for symptoms and on patient interview, but not at periodic follow-up examination.

Treatment strategy

When a diagnosis of HCC was established at Kurume University School of Medicine, the following treatment options were assessed:

1 LT was only considered after 2003 and was based on HCC meeting the Milan criteria[20] with Child–Pugh class C cirrhosis, as set by the health insurance system in Japan.
2 HR was particularly assessed in patients with localized HCC and preserved hepatic reserve capacity.
3 Non-surgical treatments, such as PEI, microwave coagulation therapy (MCT), RFA, transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), systemic chemotherapy and radiotherapy were assessed when LT and HR were contraindicated or when the patient refused surgical treatment. The most appropriate therapeutic procedure was selected according to the tumor status and underlying cirrhosis. LAT such as PEI, MCT and RFA was considered in patients with one to three tumor nodules of 30 mm or less in diameter that were devoid of vascular invasion and not associated with extrahepatic metastasis. TACE, HAIC and systemic chemotherapy or radiotherapy were considered in patients with a maximum tumor size of 30 mm, more than three tumors, presence of vascular invasion and/or presence of extrahepatic metastasis.
4 Best supportive care was assessed when the patient had little hepatic reserve capacity or when the patient refused any treatment for the HCC.

Outcome measures

Outcome measures were compared between the two 6-year periods. In January 1995 to December 2000 and January 2001 to December 2006, 512 patients (79 of group A, 271 of group B, 162 of group C) and 562 patients (132 of group A, 273 of group B, 157 of group C), respectively, were diagnosed with HCC. In each group, we compared the following parameters between periods: (i) hepatic function tests and Child–Pugh class; (ii) tumor characteristics including size and number of HCC nodules, presence of vascular invasion and presence of extrahepatic metastasis; (iii) Milan criteria for

HCC (single nodule ≤50 mm in diameter or two to three tumor nodules, each measuring ≤30 mm in diameter), that were devoid of vascular invasion and not associated with extrahepatic metastasis);[20] (iv) treatment of HCC; and (v) cumulative survival of patients with HCC.

Statistical analysis

We used the χ^2-test,[2] Fisher's exact and Mann–Whitney *U*-tests, where appropriate, to evaluate differences in clinical features of patients and in tumor characteristics. Survival was analyzed by the Kaplan–Meier method and survival curves were compared by the log-rank test. Survival was confirmed up to 30 September 2007. Data were analyzed using the statistical software package SPSS for Windows ver. 10.0. $P < 0.05$ was considered significant.

RESULTS

Clinical features of patients

TABLE 1 SUMMARIZES the clinical profile of the 1074 patients with HCC. Child–Pugh class A was reported in 141 group A patients (67%), 363 of group B (67%) and 228 of group C (71%). Patients with cirrhosis numbered 174 in group A (82%), 427 in group B (78%) and 213 in group C (67%). The median tumor sizes in groups A–C were 18.0, 24.0 and 50.0 mm, respectively.

Of the 1074 patients, 650 (61%) with HCC met the Milan criteria, including 192 of group A (91%), 374 of group B (69%) and 84 of group C (28%). With regard to treatment, none of the patients received LT, while 27 (13%), 65 (12%) and 43 (13%) of group A, B and C patients, respectively, were treated with HR. Furthermore, 147 (69%), 265 (49%) and 46 (15%) patients in groups A, B and C, respectively, were treated by LAT, including PEI, MCT and RFA, while 31 (15%), 196 (36%) and 213 (67%) patients in groups A, B and C, respectively, were treated with interventional radiology (IVR) including TACE and HAIC, systemic chemotherapy or radiotherapy. Six (3%), 18 (3%) and 17 (5%) patients in groups A, B and C, respectively, were followed up conservatively without any specific treatment for HCC because of hepatic failure or patient refusal of treatment for HCC.

Comparison between 1995 and 2000 and 2001–2006

Tables 2–4 summarize the comparison of groups A–C patients between January 1995 and December 2000, and January 2001 and December 2006. For group A, male : female ratio, age, background liver disease, cirrhosis, serum levels of prothrombin activity, total bilirubin, AFP and DCP were not different between the two periods, while serum albumin levels and the frequency of Child–Pugh class A were significantly higher in

Table 1 Clinical profile of 1074 patients with hepatocellular carcinoma

	Group A	Group B	Group C
Number of patients	211	544	319
Sex (M/F)	124/87	373/171	270/49
Age (median [range])	67 (49–86)	67 (16–88)	64 (29–87)
Background (HCV/HBV/HCV[–] and HBV[–])	179/18/14	454/54/36	214/59/46
Prothrombin activity (%; median [range])	81 (35–130)	79 (24–130)	83 (30–130)
Total bilirubin (mg/dL; median [range])	1.0 (0.3–3.3)	1.0 (0.2–12.5)	1.0 (0.1–20.0)
Albumin (g/dL; median [range])	3.6 (1.8–5.1)	3.5 (1.8–4.8)	3.5 (2.1–4.6)
Child–Pugh class (A/B or C)	141/70	363/181	228/91
Cirrhosis (yes/no)	174/37	427/117	213/106
AFP (ng/mL; median [range])	17 (1–195741)	39 (1–883828)	72 (1–2397149)
DCP (<100/≥100 mAU/mL)	173/38	371/173	110/209
Tumor size (mm; median [range])	18.0 (7–99)	24.0 (8–140)	50.0 (9–300)
Tumor number (1/2–3/≥4)	137/61/13	275/166/103	81/87/151
Vascular invasion (yes/no)	4/207	37/507	87/232
Extrahepatic metastasis (yes/no)	1/210	7/537	36/283
Milan criteria (met Milan/outside Milan)	192/19	374/170	84/235
Treatment (HR or LAT/IVR or supportive care)	174/37	330/214	89/230

HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HR, hepatic resection; LAT, locoregional ablative therapies; IVR, interventional.

Table 2 Comparison of 1995–2000 and 2001–2006 data of 211 patients of group A

	1995–2000	2001–2006	*P*-value
Number of patients	79	132	
Sex (M/F)	44/35	80/52	$P = 0.483$
Age (median [range])	66 (49–80)	67 (49–86)	$P = 0.352$
Background (HCV/HBV/HCV[–] and HBV[–])	71/3/5	108/15/9	$P = 0.156$
Prothrombin activity (%; median [range])	79 (51–130)	82 (35–115)	$P = 0.090$
Total bilirubin (mg/dL; median [range])	1.1 (0.4–3.0)	0.9 (0.3–3.3)	$P = 0.089$
Albumin (g/dL; median [range])	3.4 (1.8–4.4)	3.7 (2.4–5.1)	$P = 0.004$
Child–Pugh class (A/B or C)	46/33	95/37	$P = 0.040$
Cirrhosis (yes/no)	69/10	105/27	$P = 0.191$
AFP (ng/mL; median [range])	20 (3–5765)	16 (1–195741)	$P = 0.129$
DCP (<100 /≥100 mAU/mL)	61/18	112/20	$P = 0.163$
Tumor size (mm; median [range])	18.0 (7–50)	18.5 (8–99)	$P = 0.406$
Tumor number (1/2–3/≥4)	48/25/6	89/36/7	$P = 0.581$
Vascular invasion (yes/no)	0/79	4/128	$P = 0.118$
Extrahepatic metastasis (yes/no)	0/79	1/131	$P = 0.438$
Milan criteria (met Milan/outside Milan)	72/7	120/12	$P = 0.955$
Treatment (HR or LAT/IVR or supportive care)	55/24	119/13	$P < 0.0001$

HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HR, hepatic resection; LAT, locoregional ablative therapies; IVR, interventional.

patients diagnosed during the latter period than in those detected earlier. Tumor characteristics including size, number, vascular invasion, extrahepatic metastasis and Milan criteria for HCC were comparable between the two periods. However, the frequency of receiving promising treatment was significantly higher in the latter 6 years than in the former 6 years (Table 2). For group B, significantly older age, higher frequency of HCV- and HBV-unrelated HCC and Child–Pugh class A, higher serum levels of prothrombin activity, albumin and DCP, and lower serum levels of total bilirubin and AFP were noted in the latter 6 years than in the former 6 years.

Table 3 Comparison of 1995–2000 and 2001–2006 data of 544 patients of group B

	1995–2000	2001–2006	*P* value
Number of patients	271	273	
Sex (M/F)	190/81	183/90	$P = 0.439$
Age (median [range])	66 (16–87)	69 (32–88)	$P = 0.001$
Background (HCV/HBV/HCV[–] and HBV[–])	232/29/10	222/25/26	$P = 0.022$
Prothrombin activity (%; median [range])	77 (24–130)	81 (36–122)	$P = 0.011$
Total bilirubin (mg/dL; median [range])	1.0 (0.2–7.8)	0.9 (0.3–12.5)	$P = 0.024$
Albumin (g/dL; median [range])	3.5 (2.1–4.6)	3.7 (1.8–4.8)	$P < 0.0001$
Child–Pugh class (A/B or C)	169/102	194/79	$P = 0.031$
Cirrhosis (yes/no)	222/49	205/68	$P = 0.060$
AFP (ng/mL; median [range])	52 (1–124714)	31 (2–883828)	$P = 0.001$
DCP (<100/≥100 mAU/mL)	196/75	175/98	$P = 0.040$
Tumor size (mm; median [range])	22.0 (8–105)	25.0 (9–140)	$P < 0.0001$
Tumor number (1/2–3/≥4)	122/86/63	153/80/40	$P = 0.012$
Vascular invasion (yes/no)	15/256	22/251	$P = 0.242$
Extrahepatic metastasis (yes/no)	2/269	5/268	$P = 0.258$
Milan criteria (met Milan/outside Milan)	184/87	190/83	$P = 0.669$
Treatment (HR or LAT/IVR or supportive care)	140/131	190/83	$P < 0.0001$

HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HR, hepatic resection; LAT, locoregional ablative therapies; IVR, interventional.

Table 4 Comparison of 1995–2000 and 2001–2006 data of 319 patients of group C

	1995–2000	2001–2006	*P* value
Number of patients	162	157	
Gender (M/F)	143/19	127/30	$P = 0.068$
Age (median [range])	65 (29–83)	64 (32–87)	$P = 0.760$
Background (HCV/HBV/HCV[–] and HBV[–])	118/28/16	96/31/30	$P = 0.037$
Prothrombin activity (%; median [range])	82 (32–130)	85 (30–120)	$P = 0.190$
Total bilirubin (mg/dL; median [range])	1.0 (0.3–7.9)	0.9 (0.1–20.0)	$P = 0.512$
Albumin (g/dL; median [range])	3.5 (2.1–4.4)	3.6 (2.1–4.6)	$P = 0.099$
Child–Pugh class (A/B or C)	112/50	116/41	$P = 0.348$
Cirrhosis (yes/no)	106/56	107/50	$P = 0.636$
AFP (ng/mL; median [range])	78 (2–976554)	72 (1–2397149)	$P = 0.877$
DCP (<100/≥100 mAU/mL)	53/109	57/100	$P = 0.500$
Tumor size (mm; median [range])	50.0 (9–180)	51.0 (10–300)	$P = 0.363$
Tumor number (1/2–3/≥4)	39/48/75	42/39/76	$P = 0.616$
Vascular invasion (yes/no)	38/124	49/108	$P = 0.120$
Extrahepatic metastasis (yes/no)	18/144	18/139	$P = 0.920$
Milan criteria (met Milan/outside Milan)	43/119	41/116	$P = 0.931$
Treatment (HR or LAT/IVR or supportive care)	43/119	46/111	$P = 0.583$

HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HR, hepatic resection; LAT, locoregional ablative therapies; IVR, interventional.

Tumor characteristics were contradictory, with significantly larger size tumors, but smaller numbers of HCC detected in the latter 6 years than in the former 6 years. The frequencies of vascular invasion, extrahepatic metastasis and Milan criteria for HCC were not different between the two periods. Finally, the frequency of receiving promising treatment was significantly higher in the latter 6 years than in the former 6 years (Table 3). For group C patients, liver function tests, Child–Pugh class, tumor characteristics, Milan criteria for HCC and treatment of HCC were comparable between the two periods; the only difference was a higher frequency of HCV- and HBV-unrelated HCC in the latter 6 years than in the former 6 years (Table 4).

Comparison of LAT between 1995 and 2000 and 2001–2006

Locoregional ablative therapies were used to treat 196 and 262 patients in 1995–2000 and 2001–2006, respectively. In the former 6 years, 140 (72%; 37 of group A, 85 of group B and 18 of group C), 32 (16%; six of group A, 24 of group B and two of group C) and 24 (12%; five of group A, 12 of group B and seven of group C) patients were treated with PEI, RFA and MCT, respectively. In the latter 6 years, none of the patients were treated with MCT, while 18 (7%; 11 of group A, six of group B and one of group C) and 244 (93%; 88 of group A, 138 of group B and 18 of group C) patients were treated with PEI and RFA, respectively. The frequency of receiving RFA was significantly higher in the latter 6 years than in the former 6 years.

Comparison of survival rates between 1995–2000 and 2001–2006

The cumulative survival rates between the two periods according to the manner of HCC detection are shown in Figures 1 and 2. For the surveillance (+) group (groups A and B, 755 patients), the 2-, 3- and 4-year cumulative survival rates were 83%, 71% and 58% for the latter 6 years (405 patients) and 75%, 61% and 50% for the former 6 years (350 patients), respectively (Fig. 1). The cumulative survival rates of those patients in whom HCC was detected in the latter 6 years tended to be better than those diagnosed during the former 6 years. For the surveillance (–) group (group C), the cumulative survival rates were not different between the two periods ($P = 0.5546$) (Fig. 2).

DISCUSSION

OUR STUDY WAS designed to evaluate the effect of recent improvement in management of HCC according to the method applied for detection of HCC (group A, surveillance at Kurume University School of Medicine; group B, surveillance at other institutions; group C, control group).

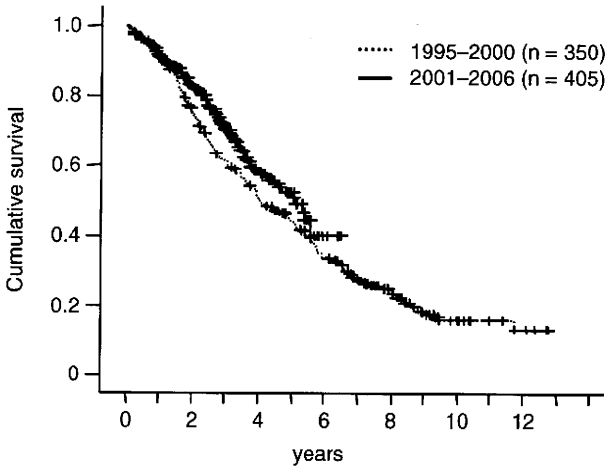

Figure 1 Kaplan–Meier survival curves of 755 patients with hepatocellular carcinoma detected by surveillance (groups A and B) in 1995–2000 and 2001–2006. The cumulative survival rate of those patients diagnosed in the latter 6 years (2001–2006) was significantly better than those diagnosed during the former 6 years (1995–2000) ($P = 0.0349$).

Sangiovanni *et al.*[7] reported that in the last quinquennium of 1987–2001, survival of HCC patients during surveillance increased as a consequence of improved early detection of the cancers,[4–13] wider application of radical therapies to accurately selected patients[2,16–23] and efficient management of liver-disease complications.[2,24,25] In the present study, improvement of surveillance did not translate into early detection of HCC in the latter 6 years (2000–2006) compared with the former 6 years (1995–2000) in either surveillance group (A or B; Tables 2,3). Surveillance for HCC based on US and AFP determination may have limited value in early detection of HCC despite the intense surveillance program in Japan. However, the frequency of patients with Child-Pugh class A and those receiving promising treatment increased more in the latter 6 years than in the former 6 years. Furthermore, the cumulative survival rates in surveillance groups in the latter 6 years tended to be better than those for patients from the former period (4-year, 58% vs 50%; Fig. 1). In Group C (control group), hepatic reserve capacity, tumor characteristics, receiving promising treatment and cumulative survival were not different between the two periods (Table 4, Fig. 2).

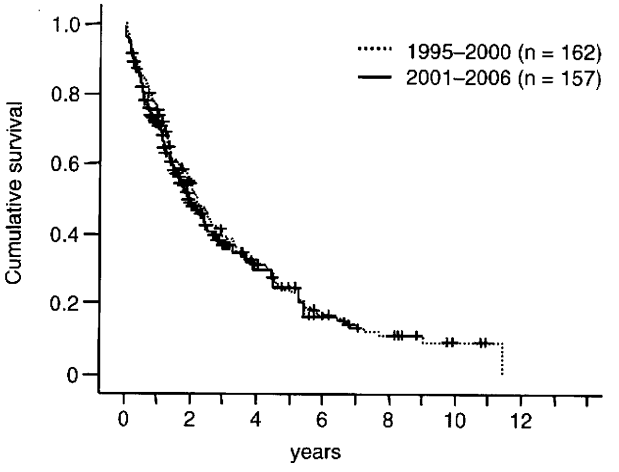

Figure 2 Kaplan–Meier survival curves of 319 patients with hepatocellular carcinoma detected incidentally or because of symptoms. The cumulative survival rates were comparable between the two periods ($P = 0.5546$).

Based on recent technological improvements in LAT, RFA is superior to PEI with regard to the achievement of complete tumor necrosis and increase in the survival chance of patients with early-stage HCC.[22,23] In the present study, the proportion of patients receiving RFA was significantly higher in the latter period compared to the earlier one. The change from PEI to RFA in the LAT treatment contributed to this improved survival in patients with HCC detected during surveillance. Moreover, Kurume University School of Medicine provided IFN therapy for patients with cirrhosis, in addition to follow up after curative treatment of HCC, and management of cirrhosis-related complications by nutritional therapists in the latter 6 years. Proper management of cirrhosis complications including IFN therapy for patients with cirrhosis and patients with HCC following promising treatment[26,27] and nutrition therapy provided by nutritional therapists[24,25] could have contributed to the increased hepatic reserve capacity and possibly survival of patients with HCC detected during surveillance.

Ultrasonography and AFP determination every 6 months for cirrhotic patients is a convenient and cost-effective surveillance program.[7–12,14–16] In the present study, US and AFP determinations were performed every 3 months for patients with chronic liver disease (including chronic hepatitis and cirrhosis). The surveillance program in the present study may be too intensive and not as cost effective. However, the median tumor size of group A was only 18.0 mm and 192 of the 211 patients (91%) met the Milan criteria for HCC. Recent progress in available treatments for early-stage HCC and in the management of cirrhosis have made such surveillance programs more important for the early detection of HCC. Randomized prospective trials are needed to determine whether surveillance for HCC can improve survival of patients with chronic liver disease.

In conclusion, patients with HCC detected in the last 6 years through surveillance were more likely to receive promising treatment and to have better prognoses than similar patients identified in 1995–2000.

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APPENDIX

Table A1 Clinical profile of 1074 patients with hepatocellular carcinoma

	Group A	Group B	Group C	Kruskal–Wallis test
Number of patients	211	544	319	
Sex (M/F)	124/87	373/171 $P = 0.011$	270/49 $P < 0.0001$ $P < 0.0001$†	
Age (median [range])	67 (49–86)	67 (16–88) $P > 0.05$	64 (29–87) $P < 0.05$ $P < 0.05$†	$P < 0.0001$
Background (HCV/HBV/HCV[−] and HBV[−])	179/18/14	454/54/36 $P = 0.842$	214/59/46 $P < 0.0001$ $P < 0.0001$†	
Prothrombin activity (%; median [range])	81 (35–130)	79 (24–130) $P > 0.05$	83 (30–130) $P > 0.05$ $P < 0.05$†	$P = 0.005$
Total bilirubin (mg/dL; median [range])	1.0 (0.3–3.3)	1.0 (0.2–12.5) $P > 0.05$	1.0 (0.1–20.0) $P > 0.05$ $P > 0.05$†	$P = 0.761$
Albumin (g/dL; median [range])	3.6 (1.8–5.1)	3.5 (1.8–4.8) $P > 0.05$	3.5 (2.1–4.6) $P > 0.05$ $P > 0.05$†	$P = 0.953$
Child–Pugh class (A/B or C)	141/70	363/181 $P = 0.980$	228/91 $P = 0.255$ $P = 0.147$†	
Cirrhosis (yes/no)	174/37	427/117 $P = 0.224$	213/106 $P < 0.0001$ $P < 0.0001$†	
AFP (ng/mL; median [range])	17 (1–195741)	39 (1–883828) $P < 0.05$	72 (1–2397149) $P < 0.05$ $P < 0.05$†	$P < 0.0001$
DCP (<100/≥100 mAU/mL)	173/38	371/173 $P < 0.0001$	110/209 $P < 0.0001$ $P < 0.0001$†	
Tumor size (mm; median [range])	18.0 (7–99)	24.0 (8–140) $P < 0.05$	50.0 (9–300) $P < 0.05$ $P < 0.05$†	$P < 0.0001$
Tumor number (1/2–3/≥4)	137/61/13	275/166/103 $P < 0.0001$	81/87/151 $P < 0.0001$ $P < 0.0001$†	
Vascular invasion (yes/no)	4/207	37/507 $P = 0.008$	87/232 $P < 0.0001$ $P < 0.0001$†	
Extrahepatic metastasis (yes/no)	1/210	7/537 $P = 0.328$	36/283 $P < 0.0001$ $P < 0.0001$†	
Milan criteria (met Milan/outside Milan)	192/19	374/170 $P < 0.0001$	84/235 $P < 0.0001$ $P < 0.0001$†	
Treatment (HR or LAT/IVR or Supportive care)	174/37	330/214 $P < 0.0001$	89/230 $P < 0.0001$ $P < 0.0001$†	

†Group B vs group C.

HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HR, hepatic resection; LAT, locoregional ablative therapies; IVR, interventional.

AP&T Alimentary Pharmacology and Therapeutics

Intra-arterial therapy with cisplatin suspension in lipiodol and 5-fluorouracil for hepatocellular carcinoma with portal vein tumour thrombosis

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SUMMARY

Background
Portal vein tumour thrombosis is a negative prognostic factor for hepatocellular carcinoma (HCC).

Aim
To assess the efficacy of cisplatin in lipiodol emulsion combined with 5-fluorouracil (5-FU) for patients with HCC and portal vein tumour thrombosis.

Methods
The study subjects were 51 patients with the above-specified criteria who received injection of cisplatin suspension in lipiodol emulsion followed by intra-arterial infusion of 5-FU. The primary objective was to determine tumour response to the treatment, while the secondary objectives were safety and tolerability. Independent factors for survival were also assessed.

Results
Ten patients had complete response and 34 patients had partial response (response rate, 86.3%). The median survival for all 51 patients was 33 months, while that for 10 complete response patients and 21 patients who showed disappearance of HCC following additional therapies was 39 months. The single factor that significantly influenced survival was therapeutic effect. Treatment was well tolerated and severe toxicity was infrequent, with only grade 3 toxicity (thrombocytopenia) in one patient.

Conclusions
The present study demonstrated the efficacy of hepatic arterial infusion chemotherapy using cisplatin-lipiodol emulsion and 5-FU without serious adverse effects in patients with unresectable HCC and portal vein tumour thrombosis.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is increasing worldwide and is one of the most common malignant tumours in the tropics and the Far East, including Japan.[1] It is the sixth most common cancer worldwide with 626 000 new cases in 2002.[2] HCC develops multifocally in chronically damaged liver. Epidemiological studies from Japan indicate that approximately 75% of HCC are caused by hepatitis C virus (HCV) infection and 10% by hepatitis B virus (HBV) infection.[3]

The development of sophisticated diagnostic modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and abdominal ultrasonography (US), have allowed early diagnosis of HCC. Patients with small HCC are usually treated with surgical resection, liver transplantation, percutaneous ethanol injection therapy, microwave coagulation therapy, or percutaneous radiofrequency ablation. The prognosis of patients with small HCC has improved following the application of these therapeutic modalities.[4]

On the other hand, treatment of advanced HCC includes trans-hepatic arterial chemoembolization (TACE), trans-hepatic arterial infusion chemotherapy (HAIC), systemic chemotherapy, hormonal therapy and immunotherapy. However, only TACE has been confirmed to improve long-term survival.[5] In advanced HCC, tumour cells easily invade the portal vein.[6] Unfortunately, despite the progress in diagnostic techniques for HCC, portal vein tumour invasion is found in 12.5–39.7% of patients with HCC.[7–9] Portal vein tumour invasion is a crucial factor in the prognosis of patients with HCC.[10] Many clinical trials for advanced HCC with portal vein tumour thrombosis have been conducted. However, two systemic reviews confirmed negative outcome of these clinical trials.[6, 11] Two recent phase III clinical trials have shown that sorafenib, an orally available multikinase inhibitor, improves the median overall survival in patients with advanced HCC.[12, 13] Sorafenib has antivascular properties through targeting vascular endothelial growth factor (VEGF) receptor 2 and platelet-derived growth factor (PDGF) receptor and also blocks tumour cell proliferation by targeting the Raf/MEK/ERK signalling pathway.[14] However, patients with HCC and portal vein tumour thrombosis usually have very short survival and grave prognosis even when treated with sorafenib.[15] In Japan, such patients have been sometimes treated with HAIC with cisplatin and 5-fluorouracil (5-FU) or 5-FU and subcutaneous interferon-α injection.[16–19]

In the present study, we investigated the efficacy and safety of the new combination therapy of cisplatin-lipiodol suspension and 5-FU for HCC with portal vein tumour thrombosis.

PATIENTS AND METHODS

Criteria for treatment

The following criteria were used for the use of cisplatin-lipiodol suspension and 5-FU: (i) tumour thrombosis invading the portal vein (Vp2–4), (ii) absence of extrahepatic metastases, (iii) patients age >20 years, (iv) estimated life expectancy >3 months, (v) platelet count >50 000/μL and leucocyte count >2000/μL, (vi) Child-Pugh class A or class B, and (vii) performance status [Eastern Cooperative Oncology Group (ECOG)] level[20] of 0–2. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics review committees of Yame Republic Hospital and Kurume University, School of Medicine. Informed written consent was obtained from each patient before enrolment in the study.

Patients

From July 2004 to February 2009, 61 consecutive patients with non-resectable HCC and portal vein tumour thrombosis (Vp2–4) were referred to Yame Republic Hospital. All patients were classified as Barcelona Clinic Liver Cancer (BCLC) stage C.[21] Each patient underwent clinical examination, US, CT, MRI, and angiography. Extrahepatic metastases were found in seven patients and three patients were Child-Pugh class C. These 10 patients were excluded from the study. We investigated the efficacy and safety of cisplatin-lipiodol plus 5-FU therapy in the remaining 51 patients (men; 43, women; 8, age 57–85 years). All patients had liver cirrhosis (Child-Pugh class A; 26, class B; 25). Thirty-nine patients were HCV antibody-positive, six were HBs antigen-positive and six were HCV antibody-negative and HBs antigen-negative. The ECOG performance status of the 51 patients was 0 or 1. These patients were free of uncontrolled ascites and hepatic encephalopathy. Leucocyte and platelet counts were >3000/μL and 50 000/μL respectively. Serum creatinine level was <1.5 mg/dL (Table 1).

Catheter placement

After local anaesthesia, a J-shaped 4-French catheter through a 4-French introducer sheath was inserted through the femoral or brachial artery by the Seldinger method. The catheter was advanced into the target artery under fluoroscopic guidance, and visceral arteriography

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