cluded that a resection provided some advantages.[48] Furthermore, with regard to cases of HCC which are not suitable candidates for liver transplantation, a Markov model was used to compare the life-adjusted survival between resection and RFA. The survival rate in the resection group was 5.33 years, while in the RFA group it was 3.91 years. It was concluded therefore, that patients treated by a resection would have a better survival rates.[49] In another study, 79 cases of resection and 79 cases of RFA treated at two different institutions were compared. The result showed that resection would be better than RFA for tumors of 3 cm and larger in diameter with Child A score, but that the overall survival would be the same for surgery and RFA in the case of Child B score.[50]

Comparison between RFA and other ablations

A comparison between microwave coagulation and RFA for HCC, 2 cm or less in tumor diameter demonstrated that RFA was superior because it created a larger necrotic area, resulting in a lower local recurrence rate; this conferred better cumulative survival, while bile duct injury and pleural effusion occurred less frequently.[51]

Another study compared percutaneous ethanol injection (PEI) and RFA. This randomized controlled trial (RCT) conducted in Taiwan demonstrated that RFA required fewer treatment sessions to achieve complete tumor necrosis, and provided better overall survival.[52] Another RCT between PEI and RFA was conducted in Japan. The 4-year survival rates were 74% for RFA versus 57% for PEI, resulting in RFA treatment being associated with a lower risk of death and recurrence. There was no difference in frequency of adverse events.[53] Although it was not RCT, another study compared PEI and RFA and found that local recurrence rates after RFA were lower.[54] An RCT conducted in Italy compared RFA with PEI and found that complete response of RFA after one year was associated with a better outcome, though no survival advantage was observed.[55]

There have been three meta-analyses, based on RCT comparing the effects and complications between RFA and PEI. Each found that RFA had better overall survival, while PEI had a higher local recurrence rate; thus RFA was superior in cancer-free survival rates.[56–58] No difference was observed in the complications between the two.

RCT was conducted to identify whether a combination of RFA and PEI would produce a better outcome than RFA alone. For tumors measuring between 3.1 cm and 5 cm in size, RFA + PEI improved patient survival, and overall recurrence was lower with combination treatment.[59]

Combined TACE and RFA treatment

The combination of transarterial embolization (TAE) and RFA or PEI was compared with TACE alone, and it was found that TACE + RFA had a better prognosis.[60] The results of a case-control comparison between RFA combined with TACE and RFA alone demonstrated that there was no difference in cases of single HCC $\leq$ 5 cm, but that the TACE + RFA combined treatment had a higher survival rate in cases of single HCC > 5 cm or multiple tumors.[61] The combination of TACE and RFA was technically successful in 88% of cases; such patients, complete the therapy after a single treatment session.[62] In addition, the combination of TACE and RFA produced high local control rates.[63] TACE and RFA has been performed for HCC immediately below the diaphragm, and found to be effective.[64] The combination of bland arterial embolization with RFA and a resection has also been compared; the overall survival was found to be similar in patients with single HCC measuring up to 7 cm in diameter.[65]

The extent of necrosis resulting from RFA increases when combined with hepatic arterial balloon occlusion.[66] Furthermore, combined treatment with balloon occlusion after transcatheter arterial infusion chemotherapy (TAI) is effective in expanding the necrotic area.[67] However, some researchers argue that this combination is not necessary because the effects of the combined therapy involving TACE and RFA, and that of RFA alone, for small HCC $\leq$ 3 cm, are the same.[68]

Complications

Data from 3891 cases were collected in a joint study conducted in Osaka, Japan. Complications were observed in 207 cases (7.9%), with 9 patients dying within 3 months. The causes of death in these cases were: liver failure in 3 cases, rapid progression in 3 cases, biliary injury in 1 case, gastrointestinal bleeding in 1 case, and myocardial infarction in 1 case.[69] Data for 255 cases in China have also been reported, with major complications observed in 31 cases (10%) as follows: 13 cases of liver failure, 10 cases of hydrothorax, 2 cases of tumor seeding, 1 case of upper gastrointestinal bleeding, and one each of intrahepatic abscess, bile duct injury, and cardiac arrest, 5 cases of hyperglycemia, and 11 cases of death due to liver failure.[70] A report from the United States noted that complications had been observed in 7 out of 91 cases as follows: 2 cases of hepatic abscess and one each of skin burn, hemorrhage, myocardial infarction, and liver failure.[71] According to the results of a multicenter survey conducted in Korea, liver abscess (0.66%), peritoneal hemorrhage (0.46%), biloma (0.20%), ground pad burn (0.20%) and pneumothorax (0.20%) were reported as complications.[72]

Liver abscess and bile duct injury

Liver abscess is the most common complication—de Raere *et al.* observed 7 cases out of 350 sessions and a high risk of this complication among patients with a revious bilioenteroc anasomosis.[73] Likewise, Choi *et al.*[74] and Elias *et al.*[75] also reported that liver abscess was seen more often in cases of biliary abnormality, as well as after TACE treatment. In one report, cholangitis and liver abscess occurred simultaneously.[76] Attention should therefore be paid to the fact that the risk for liver abscess complication is high in cases of complicated anastomosis of the bile duct to the intestinal tract.

Biliary stricture was observed in 7 cases after the RFA procedure, with liver abscess as a complication in 3 cases.[77] It was reported that intraductal chilled saline perfusion by endoscope had been effective in preventing bile duct injury.[78]

Bleeding

A total of 4133 RFA treatments were performed in 2154 cases, with hemorrhagic complications occurring in 63 treatments (1.5%)

as follows: hemoperitoneum (0.7%), hemothorax (0.3%) and hemobilia (0.5%). In addition, there were two deaths due to hemoperitoneum.[79] Poggi *et al.* reported only one case of bleeding that required surgery.[80] Attention has also been focused on bleeding which occurred in one case of subcapsular liver tumor, but there were no complications such as seeding.[81,82]

Intestinal injury

Two cases were reported in which colonic perforation occurred as a complication on the 8th day after RFA. Attention should be paid to the fact that intestinal injury was indolently present.[83,84] Another report indicated the occurrence of duodenopleural fistula formation as a complication.[85]

Hepatic infarction

Hepatic infarction has been observed after RFA; the frequency is 1.8%.[86] The use of internally cooled electrodes is a risk. In addition, portal thrombosis has also been reported to occur.[73,87]

Seeding

A report given by Llovet *et al.* in 2001 on the high rate of seeding after RFA has received much attention. The risk factors included: subcapsular tumor localization, a high degree of poor differentiation, and a high baseline AFP.[88] Since then the risk of seeding after RFA, has been attiributed to subcapsular location, poorly differentiated tumors and high AFP levels.[89,90] However, a discrepancy exists between institutions, with some arguing that, in reality, seeding is exceptionally rare.[91,92] In order to prevent seeding, tract ablation should therefore be properly performed.

Other complications

In another report, pneumothorax occurred after RFA, and so careful attention is required for tumors adjacent to the diaphragm.[93] It has been reported that myoglobinuria occurs as a complication after RFA and that the serum creatinin level rises, making it necessary for attention to be paid thereto.[94] Another case was reported in which hemolysis occurred, thus inducing hemogeobinuria as a complication.[95] There have also been reports that rapid tumor progression occurred after RFA;[96,97] however, the actual frequency was low and it is therefore necessary to investigate whether or not it was indeed a complication associated with RFA.

We have done 1440 sessions of RFA to patients with early stage HCC from July, 1999 to December 2009. The complications have been analyzed as shown in Table 2. The complication rates were 1.8% and 1.9% when the patients were treated by laparoscopic or percutaneous RFA, respectively.

Table 2 Complications by laparoscopic or percutaneous RFA in Musashino Red-Cross hospital (from July, 1999 to December, 2009)

	Laparoscopic RFA ($n = 107$)	Percutaneous RFA ($n = 1333$)
Bile duct damage	0 (%)	4 (0.4%)
Liver abscess	1 (0.9%)	4 (0.3%)
Inter-costal arterial injury	0 (0%)	3 (0.3%)
Hemothorax	0 (0%)	4 (0.3%)
Hepatic infarction	0 (0%)	3 (0.3%)
Hepatic dysfunction	0 (0%)	2 (0.3%)
Skin burn	0 (0%)	2 (0.2%)
Subcutaneous hematoma	1 (0.9%)	0 (0%)
Peumothorax	0 (0%)	2 (0.1%)
Gastrointestinal perforation	0 (0)	1 (0.1%)
Total	2 (1.8%)	26 (1.9%)

Conclusion

RFA is promising for improving patient survival with early stage of HCC when performed skillfully to avoid serious complication. To prevent the recurrence of HCC is the most important issue for achieving better survival.

References

1 Lin SM, Lin CC, Chen WT, Chen YC, Hsu CW. Radiofrequency ablation for hepatocelular carcinoma: a prospective comparison of four radiofrequency devices. *J. Vasc. Interv. Radiol.* 2007; **18**: 1118–25.

2 Tateishi R, Shiina S, Teratani T *et al.* Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. *Cancer* 2005; **103**: 1201–9.

3 Yan K, Chen MH, Yang W *et al.* Radiofrequency ablation of hepatocellular carcinoma: long-term outcome and prognostic factors. *Eur. J. Radiol.* 2008; **67**: 334–47.

4 Teratani T, Yoshida H, Shiina S *et al.* Radiofrequency ablation for hepatocellular carcinoma in so-called high-risk locations. *Hepatology* 2006; **43**: 1101–8.

5 Song I, Rhim H, Lim HK, Kim YS, Choi D. Percutaneous radiofrequency ablation of hepatocellular carcinoma abutting the diaphragm and gastrointestinal tract with the use of artificial ascites: safety and technical efficacy in 143 patients. *Eur. Radiol.* 2009; **19**: 2630–40.

6 De Baere T, Rehim MA, Teriitheau C *et al.* Usefulness of guiding needles for radiofrequency ablative treatment of liver tumors. *Cardiovasc. Intervent. Radiol.* 2006; **29**: 650–4.

7 Hirooka M, Kisaka Y, Uehara T *et al.* Efficacy of laparoscopic radiofrequency ablation for hepatocellular carcinoma to percutaneous radiofrequency ablation with artificial ascites. *Dig. Endosc.* 2009; **21**: 82–6.

8 Asahina Y, Nakanishi Y, Izumi N. Laparoscopic radiofrequency ablation for hepatocellular carcinoma. *Dig. Endosc.* 2009; **21**: 67–72.

9 Norimiya T, Seo Y, Yano Y *et al.* Evaluation of the therapeutic effects using MD-CT immediately after RFA for HCC. *Hepatogastroenterology* 2006; **53**: 558–60.

10 Gallotti A, D'Onofrio M, Ruzzenente A *et al.* Contrast-enhanced ultrasonography (CEUS) immediately after percutaneous ablation of hepatocellular carcinoma. *Radiol. Med.* 2009; **114**: 1094–105.

11 Kisaka Y, Hirooka M, Koizumi Y *et al.* Contrast-enhanced sonography with abdominal virtual sonography in monitoring radiofrequency ablation of hepatocellular carcinoma. *J. Clin. Ultrasound* 2010; **38**: 138–44.

12 N'Kontchou G, Mahamoudi A, Aout M *et al.* Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology* 2009; **50**: 1475–83.

13 Livraghi T, Meloni F, Di Stasi M *et al.* Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? *Hepatology* 2008; **47**: 82–9.
14 Peng ZW, Zhang YJ, Chen MS, Liang HH, Li JQ, Lau WY. Risk factors of survival after percutaneous radiofrequency ablation of hepatocellular carcinoma. *Surg. Oncol.* 2008; **17**: 23–31.
15 Choi D, Lim HK, Rhim H *et al.* Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: long-term results and prognostic factors in a large single-institution series. *Eur. Radiol.* 2007; **17**: 684–92.
16 Kobayashi M, Ikeda K, Kawamura Y *et al.* High serum des-gamma-carboxy prothrombin level predicts poor prognosis after radiofrequency ablation of hepatocellular carcinoma. *Cancer* 2009; **115**: 571–80.
17 Takahashi S, Kudo M, Chung H *et al.* PIVKA-II is the best prognostic predictor in patients with hepatocellular carcinoma after radiofrequency ablation therapy. *Oncology* 2008; **75S**: 91–8.
18 Ogawa C, Kudo M, Minami Y, Chung H, Kawasaki T. Tumor markers after radiofrequency ablation therapy for hepatocellular carcinoma. *Hepatogastroenterology* 2008; **55**: 1454–7.
19 Du XL, Ma QJ, Wu T, Baqo GQ, Lu JG, Chu YK. Significance of alpha-fetoprotein mRNA level in hepatocellular carcinoma patients treated with radiofrequency ablation. *Hepatobiliary Pancreat. Dis. Int.* 2007; **6**: 172–5.
20 Poon RT, Lau C, Pang R, Ng KK, Yuen J, Fan ST. High serum vascular endothelial growth factor levels predict poor prognosis after radiofrequency ablation of hepatocellular carcinoma: importance of tumor biomarker in ablative therapies. *Ann. Surg. Oncol.* 2007; **14**: 1835–45.
21 Grieco A, Pompili M, Camitiniti G *et al.* Prognostic factors for survival in patients with early-intermediate hepatocellular carcinoma undergoing non-surgical therapy: comparison of Okuda, CLIP, and BCLC staging systems in a single Italian centre. *Gut* 2005; **54**: 411–8.
22 Yamagiwa K, Shiraki K, Yamamoto K *et al.* Survival rates according to the cancer of the Italian program score of 345 hepatocellular carcinoma patients after multimodality treatments during a 10-year period in a retrospective study. *J. Gastroenterol. Hepatol.* 2008; **23**: 482–90.
23 Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). *J. Gastroenterol.* 2003; **38**: 207–15.
24 Kudo M, Chung H, Haji S *et al.* Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. *Hepatology* 2004; **40**: 1396–405.
25 Lee JH, Han SY, Jo JH *et al.* Prognostic factors for survival in patients with hepatocellular carcinoma after radiofrequency ablation. *Korean J. Gastroenterol.* 2007; **49**: 17–23.
26 Takahashi S, Kudo M, Chung H *et al.* Initial treatment response is essential to improve survival in patients with hepatocllular carcinoma who underwent curative radiofrequency ablation therapy. *Oncology* 2007; **72S**: 98–103.
27 Liu CH, Arellano RS, Uppot RN, Samir AE, Gervais DA, Mueller PR. Radiofrequency ablation of hepatic tumours: effect of post-ablation margin on local tumour progression. *Eur. Radiol.* 2010; **20**: 877–85.
28 Lam VW, Ng KK, Chok KS *et al.* Risk factors and prognostic factors of local recurrence after radiofrequency ablation of hepatocellular carcinoma. *J. Am. Coll. Surg.* 2008; **207**: 20–9.
29 Lam VW, Ng KK, Chok KS *et al.* Imcomplete ablation after radiofrequency ablation of hepatocellular carcinoma: analysis of risk factors and prognostic factors. *Ann. Surg. Oncol.* 2008; **15**: 782–90.
30 Pitton MB, Herber S, Raab P *et al.* Percutaneous radiofrequency ablation of liver tumors using the LeVeen 4 cm array probe. *Rofo* 2003; **175**: 1525–31.
31 Okuwaki Y, Nakazawa T, Shibuya A *et al.* Intrahepatic distant recurrence after radiofrequency ablation for a single small hepatocellular carcinoma: risk factors and patterns. *J. Gastroenterol.* 2008; **43**: 71–8.
32 Izumi N, Asahina Y, Noguchi O *et al.* Risk factors for distant recurrence of hepatocellular carcinoma in the liver after complete coagulation by microwave or radiofrequency ablation. *Cancer* 2001; **91**: 949–56.
33 Ng KK, Poon RT, Lo CM, Yuen J, Tso WK, Fan ST. Analysis of recurrence pattern and its influence on survival outcome after radiofrequency ablation of hepatocellular carcinoma. *J. Gstrointest. Surg.* 2009; **12**: 183–91.
34 Izumi N, Asahina Y, Tsuchiya K *et al.* Repeated radiofrequency ablation for the distant recurrence in the liver in patients with chronic hepatitis C virus infection achieving long-term survival. *Hepatol. Res.* 2007; **37S2**: S254–63.
35 Yamashiki N, Yoshida H, Tateishi R *et al.* Recurrent hepatocellular carcinoma has an increased risk of subsequent recurrence after curative treatment. *J. Gastroenterol. Heapatol.* 2007; **22**: 2155–60.
36 Kim SH, Lim HK, Choi D *et al.* Percutaneous radiofrequency ablation of hepatocellular carcinoma: effect of histologic grade on therapeutic results. *Am. J. Roentgenol.* 2006; **186**: S327–33.
37 Kudo M, Sakaguchi Y, Chung H *et al.* Long-term interferon maintenance therapy improves survival in patients with HCV-related hepatocellular carcinoma after curative radiofrequency ablation. A matched case-control study. *Oncology* 2007; **72S**: 132–8.
38 Kuzuya T, Katano Y, Kumada T *et al.* Efficacy of antiviral therapy with lamivudine after initial treatment for hepatitis B virus-related hepatocellular carcinoma. *J. Gastroenterol. Hepatol.* 2007; **22**: 1929–35.
39 Yoshida H, Yoshida H, Goto E *et al.* Safety and efficacy of lamivudine after radiofrequency ablation in patients with hepatits B viru-related hepatocellular carcinoma. *Hepatol. Int.* 2008; **2**: 89–94.
40 Kakizaki S, Sohara N, Sato K *et al.* Preventive effects of vitamin K on recurrent disease in patients with hepatocellular carcinoma arising from hepatitis C viral infection. *J. Gastroenterol. Hepatol.* 2007; **22**: 518–22.
41 Ishikawa T, Michitaka I, Kamimura H *et al.* Oral branched-chain amino acids administration improves impaired liver dysfunction after radiofrequency ablation therapy for hepatocellular carcinoma. *Hepatogastroenterology* 2009; **56**: 1491–5.
42 Lu MD, Kuang M, Liang LJ *et al.* Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: a randomized clinical trail. *Zhonghua Yi Xue Za Zhi* 2006; **28**: 801–5.
43 Chen MS, Li JQ, Zheng Y *et al.* A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann. Surg.* 2006; **243**: 321–8.
44 Guglielmi A, Ruzzenente A, Valdgegamberi A *et al.* Radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma in cirrhosis. *J. Gastrointest. Surg.* 2008; **12**: 192–8.
45 Hong SN, Lee SY, Choi MS *et al.* Comparing the outcomes of radiofrequency ablation and surgery in patients with a single small hepatocellular carcinoma and well-preserved hepatic function. *J. Clin. Gastroenterol.* 2005; **39**: 247–52.
46 Santambrogio R, Opocher E, Zuin M *et al.* Surgical resection versus laparoscopic radiofrequency ablation in patients with hepatocelllar carcinoma and child-pugh class A liver cirrhosis. *Ann. Surg. Oncol.* 2009; **16**: 3289–98.

47 Montorsi M, Santambrogio R, Bianchi P *et al.* Survival and recurrences after hepatic resection or radiofrequency for hepatocellular carcinoma in cirrhotic patients: a multivariate analysis. *J. Gastrointest. Surg.* 2005; **9**: 62–7.
48 Abu-Hilal M, Primrose JN, Casaril A, McPhail MJ, Pearce NW, Nicoli N. Surgical resection versus radiofrequency ablation in the treatment of small unifocal hepatocellular carcinoma. *J. Gastroenterol. Surg.* 2008; **12**: 1521–6.
49 Molinari M, Helton S. Hepatic resection versus radiofrequency ablation for hepatocellular carcinoma in cirrhotic individuals not candidates for liver transplantation: a Markov model decision analysis. *Am. J. Surg.* 2009; **198**: 396–406.
50 Vivarelli M, Guglielmi A, Ruzzenente A *et al.* Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. *Ann. Surg.* 2004; **240**: 102–7.
51 Ohmoto K, Yoshioka N, Tomiyama Y *et al.* Radiofrequency ablation versus percutaneous microwave coagulation therapy for small hepatocellular carcinomas: a retrospective comparative study. *Hepatogastroenteology* 2007; **54**: 985–9.
52 Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma ≤ 4 cm. *Gastroenterology* 2004; **127**: 1714–23.
53 Shiina S, Teratani T, Obi S *et al.* A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005; **129**: 122–30.
54 Iwata K, Sohda T, Nishizawa S *et al.* Postoperative recurrence in hepatocellular carcinoma: comparison between percutanepus ethanol injection and radiofrequency ablation. *Hepatol. Res.* 2006; **36**: 143–8.
55 Brunello F, Veltri A, Carucci P *et al.* Radiofrequency ablation versusu ethanol injection for early hepatoclellular carcinoma: a randomized controlled trial. *Scand. J. Gastroenterol.* 2008; **43**: 727–35.
56 Cho YK, Kim JK, Kim MY, Rhim H, Han JK. Systemic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. *Hepatology* 2009; **49**: 453–9.
57 Bouza C, Lopez-Cuadrado T, Alcazar R, Saz-Parkinson Z, Amate JM. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. *BMC Gastroenterol.* 2009; **9**: 31.
58 Orlando A, Leandro G, Olivo M, Andriulli A, Cottone M. Radiofrequency thermal ablation vs. Percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: meta-analysis of randomized controlled trials. *Am. J. Gastroenterol.* 2009; **104**: 514–24.
59 Zhang YJ, Liang HH, Chen MS *et al.* Hepatocellular carcinoma treated with radiofrequency ablation with or without ethanol injection: a prospective randomized trial. *Radiology* 2007; **244**: 599–607.
60 Kirikoshi H, Saito S, Yoneda M *et al.* Outcome of transarterial chemoembolization monotherapy, and in combination with percutaneous ethanol injection, or radiofrequency ablation therapy for hepatocelllar carcinoma. *Hepatol. Res.* 2009; **39**: 553–62.
61 Peng ZW, Chen MS, Liang HH *et al.* A case-control study comparing percutaneous radiofrequency ablation alone or combined with transcatheter arterial chemoembolization for hepatocellular carcinoma. *Eur. J. Surg. Oncol.* 2010; **36**: 257–63.
62 Gadaleta C, Catino A, Ranieri G *et al.* Single-step therapy-feasibility and safety of simultaneous transarterial chemoembolization and radiofrequency ablation for hepatic malignancies. *In Vivo* 2009; **23**: 813–20.
63 Veltri A, Moretto P, Doriguzzi A, Pagano E, Carrara G, Gandini G. Radiofrequency thermal ablation (RFA) after transarterial chemoembolization (TACE) as a combined therapy for unresectable non-early hepatocellular carcinoma (HCC). *Eur. Radiol.* 2006; **16**: 661–9.
64 Yamakado K, Nakatsuka A, Takaki H *et al.* Subphrenic versus nonsubphrenic hepatocellular carcinoma: combined therapy with chemoembolization and radiofreqeuency ablation. *Am. J. Roentgenol.* 2010; **194**: 530–5.
65 Maluccio M, Covey AM, Gandhi R *et al.* Comparison of survival rates after bland arterilal embolization and ablation versus surgical resection for treating solitary hepatocellular carcinoma up to 7 cm. *J. Vasc. Interv. Radiol.* 2005; **16**: 955–61.
66 Yamazaki T, Kimura T, Kurokawa F *et al.* Percutaneous radiofrequency ablation with cooled electrodes combined with hepatic arterial balloon occlusion in hepatocellular carcinoma. *J. Gastroenterol.* 2005; **40**: 171–8.
67 Shiraishi R, Yamasaki T, Saeki I *et al.* Pilot study of combination therapy with transcatheter arterial infusion chemotherapy using iodized oil and percutaneous radiofrequency ablation during occlusion of hepatic blood flow for hepatocelluar carcinoma. *Am. J. Clin. Oncol.* 2008; **31**: 311–6.
68 Shibata T, Isoda H, Hirokawa Y, Arizono S, Shimada K, Togashi K. Small hepatocellular carcinoma: is radiofrequency ablation combined with transcatheter arterial chemoembolization more effective than radiofrequency ablation alone for treatment? *Radiology* 2009; **252**: 905–13.
69 Kasugai H, Osaki Y, Oka H, Kudo M, Seki T. Severe complications of radiofrequency ablation therapy for hepatocellular carcinoma: an analysis of 3891 ablations in 2614 patients. *Oncology* 2007; **72** (Suppl. 1): 72–5.
70 Kong WT, Zhang WW, Qui YD *et al.* Major complications after radiofrequency ablation for liver tumors: analysis of 255 patients. *World J. Gastroenterol.* 2009; **15**: 2651–6.
71 Wood TF, Rose DM, Chung M, Allegra DP, Foshag LJ, Bilchik AJ. Radiofrequency ablation of 231 unresectable hepatic tumors: indications, limitations, and complications. *Ann. Surg. Oncol.* 2000; **7**: 593–600.
72 Rhim H, Yoon KH, Lee JM *et al.* Major complications after radio-freqeuncy thermal ablation of hepatic tumors: a spectrum of imaging findings. *Radiographics* 2003; **23**: 123–34.
73 De Baere T, Risse O, Kuoch V *et al.* Adverse events during radiofrequency treatment of 582 hepatic tumors. *Am. J. Roentgenol.* 2003; **181**: 695–700.
74 Choi D, Lim HK, Kim MJ *et al.* Liver abscess after percutaneous radiofrequency ablation for hepatocellular carcinomas: frequency and risk factors. *Am. J. Roentgenol.* 2005; **184**: 1860–7.
75 Elias D, Pietroantonio D, Gachot B, Menegon P, Hakime A, De Baere T. Liver abscess after radiofrequency ablation of tumors in patients with a biliary tract procedure. *Gastroenterol. Clin. Biol.* 2006; **30**: 823–7.
76 Shibata T, Yamamoto Y, Yamamoto N *et al.* Cholangitis and liver abscess after percutaneous ablation therapy for liver tumors: incidence and risk factors. *J. Vasc. Interv. Radiol.* 2003; **14**: 1535–42.
77 Jensen MC, van Duijnhoven FH, van Hellegersberg R *et al.* Adverse effects of radiofrequency ablation of liver tumors in the Netherlands. *Br. J. Surg.* 2005; **92**: 1248–54.
78 Ohnishi T, Yasuda I, Nishigaki Y *et al.* Intraductal chilled saline perfusion to prevent bile duct injury during percutaneous radiofrequency ablation for hepatocellular carcinoma. *J. Gastrenterol. Hepatol.* 2008; **23**: 410–5.
79 Goto E, Tateishi R, Shiina S *et al.* Hemorrhagic complications of percutaneous radiofrequency ablation for liver tumors. *J. Clin. Gastroenterol.* 2010; **44**: 374–80.

80 Poggi G, Riccardi A, Quaretti P *et al.* Complications of percutaneous radiofrequency thermal ablation of primary and secondary lesions of the liver. *Anticancer Res.* 2007; **27**: 2911–6.
81 Sartori S, Tombesi P, Macario F *et al.* Subcapsular liver tumors treated with percutaneous radiofrequency ablation: a prospective comparison with nonsubcapsular liver tumors for safety and effectiveness. *Radiology* 2008; **248**: 670–9.
82 Kim YJ, Raman SS, Yu NC, Busuttil RW, Tong M, Lu DS. Radiofrequency ablation of hepatocellular carcinoma: can subcapsular tumors be safely ablated? *Am. J. Roentgenol.* 2008; **190**: 1029–34.
83 Yeung YP, Hui J, Yip WC. Delayed colonic perforation after percutaneous radiofrequency ablation of hepatocellular carcinoma. *Surg. Laparosc. Endosc. Percutan. Tech.* 2007; **17**: 342–4.
84 Meloni MF, Goldberg SN, Moser V, Piazza G, Livraghi T. Colonic perforation and abscess following radiofrequency ablation of hepatoma. *Eur. J. Ultrasound* 2002; **15**: 73–6.
85 Chan FS, Ng KK, Poon RT, Yuen J, Tso WK, Fan ST. Duodenopleural fistula formation after percutaneous radiofrequency ablation for recurrent hepatocellular carcinoma. *Asian J. Surg.* 2007; **30**: 278–82.
86 Kim YS, Rhim H, Lim HK, Choi D, Lee WJ, Kim SH. Hepatic infarction after radiofrequency ablation of hepatocellular carcinoma with an internally cooled electrode. *J. Vasc. Interv. Radiol.* 2007; **18**: 1126–33.
87 Zheng RQ, Kudo M, Inui K *et al.* Transient portal vein thrombosis caused by radiofrequency ablation for hepatocellular carcinoma. *J. Gastroenterol.* 2003; **38**: 101–3.
88 Llovet JM, Vilana R, Bru C *et al.* Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. *Hepatology* 2001; **33**: 1124–9.
89 Livraghi T, Lazzaroni S, Meloni F, Solbiati L. Risk of tumour seeding after percutaneous radiofrequency ablation for hepatocellular carcinoma. *Br. J. Surg.* 2005; **92**: 856–8.
90 Imamura J, Tateishi R, Shiina S *et al.* Neoplastic seeding after radiofrequency ablation for hepatocellular carcinoma. *Am. J. Gastroenterol.* 2008; **103**: 3057–62.
91 Giorgia A, Tarantino L, de Stafano G, Coppola C, Ferraioli G. Complications after percutaneous saline-enhanced radiofrequency ablation of liver tumors: 3-year experience with 336 patients at a sigle center. *Am. J. Roentgenol.* 2005; **184**: 207–11.
92 Latteri F, Sandonato L, Di Marco V *et al.* Seeding after radiofreqeuncy ablation of hepatocellular carcinoma in patients with cirrhosis: a prospective study. *Dig. Liver Dis.* 2008; **40**: 684–9.
93 Shankar S, van Sonnenberg E, Silverman SG, Tuncali K, Morrison PR. Management of pneumothorax during percutaneous radiofrequency ablation of a lung tumor: technical note. *J. Thorac. Imaging* 2003; **18**: 106–9.
94 Rodriguez J, Tellioglu G, Siperstein A, Berber E. Myoglobinuria after laparoscopic radiofrequency ablation of liver tumors. *J. Gastrointest. Surg.* 2010; **14**: 664–7.
95 Tsui SL, Lee AK, Lui SK, Poon RT, Fan ST. Acute intraoperative hemolysis and hemoglobinuria during radiofrequency ablation of hepatocellular carcinoma. *Hepatogastroenterology* 2003; **50**: 526–9.
96 Seki T, Tamai T, Ikeda K *et al.* Rapid progression of hepatocellular carcinoma after transcatheter arterial chemoembolization and percutaneous radiofrequency ablation in the primary tumour region. *Eur. J. Gastroenterol. Hepatol.* 2001; **13**: 291–4.
97 Zavaglia C, Corso R, Rampoldi A *et al.* Is percutaneous radiofrequency thermal ablation of hepatocellular carcinoma a safe procedure? *Eur. J. Gastroenterol. Hepatol.* 2008; **20**: 196–201.

ISSN 1386-6346

Hepatology Research

Volume 40 Issue 4 April 2010

The Official Journal of the Japan Society of Hepatology

www.blackwellpublishing.com/hep

WILEY-BLACKWELL

Hepatology Research

Volume 40 Issue 4 April 2010

Hepatology Research 2010; 40: 347–368 doi: 10.1111/j.1872-034X.2010.00642.x

Special Report

Management of hepatitis C; Report of the Consensus Meeting at the 45th Annual Meeting of the Japan Society of Hepatology (2009)

Izumi Namiki,[1] Shuhei Nishiguchi,[2] Keisuke Hino,[3] Fumitaka Suzuki,[4] Hiromitsu Kumada,[4] Yoshihito Itoh,[5] Yusuhiro Asahina,[1] Akihiro Tamori,[6] Naoki Hiramatsu,[7] Norio Hayashi[7] and Masatoshi Kudo[8]

[1]Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Musashinoshi, Tokyo, [2]Department of Hepatobiliary and Pancreas Disease, Hyogo Medical University, Nishinomiya, [3]Department of Hepatobiliary and Pancreas Disease, Kawasaki Medical University, Kurashiki, [4]Department of Hepatology, Toranomon Hospital, Tokyo, [5]Molecular Gstroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, and [6]Department of Hepatology, Osaka City University Graduate School of Medicine, Report of Consensus Meeting in the 45th Annual Meeting of the Japan Society of Hepatology (2009), [7]Department of Gastroenterology, Osaka University and [8]Department of Gastroenterology, Kinki University, Osaka, Japan

The consensus meeting for the diagnosis, management and treatment for hepatitis C was held in 45th annual meeting for the Japan Society of Hepatology (JSH) in June 2009 where the recommendations and informative statements were discussed including organizers and presenters. The Several important informative statements and recommendations have been shown. This was the fourth JSH consensus meeting of hepatitis C, however, the recommendations have not been published in English previously. Thus, this is the first report of JSH consensus of hepatitis C. The rate of development of hepatocellular carcinoma (HCC) in HCV-infected patients in Japan is higher than in the USA, because the average age of the HCV-infected patients is greater and there are more patients with severe fibrosis of the liver than in the USA. In Japan, more than 60% of HCV-infected patients are genotype 1b infection, and they show lower response to perinterferon and ribavirin combination treatment. To improve the response rate is also an important issue in our country. To establish the original recommendations and informative statements to prevent the development of HCC is a very important issue in Japan.

Key words: chronic hepatitis C, peginterferon, ribavirin, fibrosis of the liver, hepatocellular carcinoma, HCV mutation

INTRODUCTION

HEPATITIS C VIRUS (HCV) infection is a major public health problem and a leading course of death from liver disease in Japan. Two million people are infected, and more than 30 000 patients die from hepatocellular carcinoma (HCC) and/or liver cirrhosis every year. HCC is the fourth leading cause of death from malignant neoplastic disease, and prevention of the development of HCC is an urgent issue in Japan. The purpose of this consensus is to provide clinicians with consensus-based approaches to diagnosis and treatment of HCV infection.

The consensus meeting for the diagnosis, management and treatment for hepatitis C was held during the 45th annual meeting of the Japan Society of Hepatology (JSH) in June 2009 (Congress President: M. Kudo), where the recommendations and informative statements were discussed and compared with AASLD practice guidelines which has been published in *Hepatology*.[1] This was the fourth JSH consensus meeting of hepatitis C, however, the recommendations have not been published in English previously. This is the first report of the JSH consensus of hepatitis C. Established information regarding the pathogenesis and contributing factors for disease

Correspondence: Mr Namiki Izumi, *Department of Gastroenterology and Hepatology, Musashino Red-Cross Hospital, 1-26-1 Kyonancho, Musashinoshi, Tokyo 180-8610, Japan. Email: nizumi@musashino.jrc.or.jp*

Disclaimer Statement: The view expressed in these consensus do not necessarily represent the view of the National Health Insurance of Japan, or the Japanese Government.

This article was previously published in Japanese in *Kanzo* 50:11, pp 665–677 (November 2009).

Received 24 September 2009; revision 1 December 2009; accepted 1 December 2009.

Table 1 Grading system for recommendations

	Description
Classification	
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Conditions for which there is no evidence and/or general agreement that a diagnostic evaluation, procedure/ treatment is not useful/effective and in some cases may be harmful
Level of evidence	
Level A	Data derived from multiple randomized clinical trials or meta-analysis
Level B	Data derived from a single randomized trial, or non-randomized studies
Level C	Only consensus opinion of experts, case studies or standard of care

progression which were agreed by the organizers and presenters are shown as informative statements, and clinically useful consensuses are shown as "Recommendations". The rate of development of HCC in HCV-infected patients in Japan is higher than that in the USA, because the average age of the patient is greater and there are more patients with severe fibrosis of the liver than in the USA. To establish original recommendations and informative statements to prevent the development of HCC is a very important issue in our country. The quality of recommendations or informative statements is required to show a "class" (reflecting benefit vs risk) and "level" (assessing strength or certainty) of evidence according to AASLD practice guidelines (Table 1).[1,2]

PATHOGENESIS OF HEPATITIS C

HEPATITIS C VIRUS infection causes acute and chronic hepatitis (CH), cirrhosis and HCC. The severity and rate of progression of the disease are highly variable and may reflect both host and viral factors, but the mechanisms of pathogenesis are incompletely understood. Thus, understanding the mechanisms of HCV pathogenesis is an important goal of HCV research.

Entry pathway of HCV

For the virus, the first step in propagation is enter into hepatocytes. A decade ago, the HCV envelop protein E2 was shown to bind human CD81, a tetraspanin expressed on various cell types including hepatocytes and B lymphocytes.[3] Next, two other essential proteins, scavenger receptor class B type I (SR-B1)[4] and claudin-1 (CLDN1),[5] and potentially additional accessory factors such as glycosaminoglycans and low-density protein receptors[6] were identified as receptors involved in HCV entry. Finally, the crucial factor was identified as the tight junction protein occludin (OCLN).[7] Interestingly, both CLDN1 and OCLN are components of tight junctions which are structures forming firm seals between adjacent cells. The initial adhesion of HCV to hepatocytes may be mediated by accessory factors and/or direct interaction with SR-B1 and CD81 proteins. On transfer to a tight junction complex, HCV may interact directly with CLDN1 and/or OCLN, allowing viral uptake into the cell.

Hepatitis C virus infects only humans and chimpanzees. Once these HCV entry factors were identified, the next concern was to determine which factors dictate species-specific tropism. CD81 proteins from other mammals, such as the mouse, are used inefficiently by HCV.[8] Although HCV does not discriminate between human and mouse SR-B1 and CLDN1, mouse OCLN like CD81 cannot substitute for the related human protein in aiding viral entry. These findings indicate that CD81 and OCLN represent minimal human-specific entry factors.

Informative statement: CLDN1 and OCLN in addition to CD81 and SR-B1 are required for entering of HCV into hepatocytes, and especially CD81 and OCLN represent minimal human-specific entry factors. (Grade A.)

Evasion of intracellular host defense by HCV

One of the mechanisms by which HCV infection is likely to lead to be persistent is evasion of intracellular host defense through a complex combination of processes that include interference of interferon (IFN) signaling, modulation of its effectors and continual viral genetic variation. The HCV genome contains pathogen-associated molecular pattern (PAMP) signatures which

are recognized by the retinoic-inducible gene I (*RIG-I*) and specific Toll-like receptors when introduced into naïve cells.[9–11] Viral signaling through *RIG-I* and its adaptor protein, IFN promoter-stimulator 1 (IPS-1), activates IFN regulatory factor-3 (IRF-3) and the host IFN-α/β response that limits virus infection.[12,13] HCV NS3/4A protease cleaves IPS-1, releasing IPS-1 from the mitochondrial membrane.[14] Cleavage results in subcellular redistribution of IPS-1 and loss of interaction with *RIG-I*, thereby preventing downstream activation of IRF-3 and induction of IFNβ.[15]

Secreted IFNβ engages the local tissue through the autocrine and paracrine processes of binding the IFN-α/β receptors. This results in activation of the Jak-signal transducer and activator of transcription (STAT) pathway, in which the receptor-associated Jak and Tyk1 protein kinases catalyze the phosphorylation of STAT proteins. The resulting IFN-stimulated gene factor-3 (ISGF3) transcription factor complex localizes in the cell nucleus, where it binds to the IFN-stimulated response element (ISRE) within the promoter/enhancer region of IFN-stimulated genes (ISG). Jak-STAT signaling leads to a second wave of transcriptional activity stimulating ISG expression in the infected cells. Expression of the HCV core protein has been associated with increased expression levels of suppressor of cytokine signaling (SOCS)-3.[16] The SOCS proteins are known for their role as negative regulators and inhibitors of Jak-STAT signaling, where they mediate a classic negative feedback loop on IFN-α/β receptor signaling events.[17] The HCV NS5A protein has been shown to induce interleukin (IL)-8 production leading to partial inhibition of the IFN-induced antiviral response, probably through the alteration of ISG expression.[18] The HCV NS5A and E2 proteins also bind double-strand RNA-activated protein kinase (PKR) and inhibit its catalytic activity,[19,20] which allows HCV to evade in part the translational-suppressive actions of IFN. Thus, HCV evasion of the host response includes various strategies directed by viral proteins to control IFN signaling, ISG expression or function.

Informative statement: HCV evades intracellular host defenses through a complex combination of processes that include IFN signaling, modulation of its effectors and continual viral genetic variation. These mechanisms include cleavage of IPS-1 by the NS3/4A protease, inhibition of Jak-STAT signaling by HCV-induced SOCS3, inhibition of the IFN-induced antiviral response by NS5A-induced IL-8, and/or inhibition of catalytic activity of PKR by the NS5A and E2 proteins. (Grade A.)

Oxidative stress induced by HCV

Oxidative stress is well known to be present in CH-C to a greater degree than in other inflammatory liver diseases. Although the mechanisms underlying oxidative stress induced by HCV have not been elucidated fully, there are several lines of evidence suggesting that HCV directly generates reactive oxygen species (ROS) *in vitro* and *in vivo*. Hepatic ROS production is significantly higher in HCV core transgenic mice than in normal control mice in the absence of hepatic inflammation.[21] HCV core protein also produces ROS in human hepatoma Huh-7 cells and HeLa cells.[22] Analysis of the interaction of HCV core protein with mitochondria in transgenic mice and direct interaction of recombinant core protein and isolated mitochondria indicated oxidation of the mitochondrial glutathione pool and an increase in ROS production by the mitochondrial electron transport complex I, suggesting that direct interaction of core protein with mitochondria is an important cause of the oxidative stress seen in CH-C.[23]

Informative statement: Mitochondrial dysfunction induced by HCV leads to ROS generation that causes the oxidative stress seen in CH-C. (Grade A.)

Metabolic disorders caused by HCV

Epidemiological studies have suggested a link between type 2 diabetes and chronic HCV infection, which implies HCV-induced insulin resistance. A high level of tumor necrosis factor (TNF)-α and disturbance of tyrosine phosphorylation of the insulin receptor substrate (IRS)1 by TNF-α has been demonstrated in HCV core transgenic mice.[24] Another possible mechanism is that HCV core-induced SOCS3 promotes proteosomal degradation of IRS1 and IRS2 through ubiquitination.[25] Hepatic steatosis is one of the histopathological features in CH-C. HCV core protein inhibits microsomal triglyceride transfer protein activity and secretion of very low density lipoprotein.[26] HCV core protein also upregulates the sterol regulatory element binding protein (SREBP)1c promoter activity through the enhanced binding of the LXRα/RXRα to LXR-response element,[27] which leads to an increase in transcription of genes involved in hepatic fatty acid synthesis. Hepatic iron accumulation is also a histopathological feature of CH-C, even though its levels are not extremely high. HCV-induced ROS down-regulates the transcriptional activity of hepcidin, a negative regulator in iron homeostasis, in transgenic mice expressing the HCV polyprotein[28] and in HCV replicon cells[29] (Fig. 1).

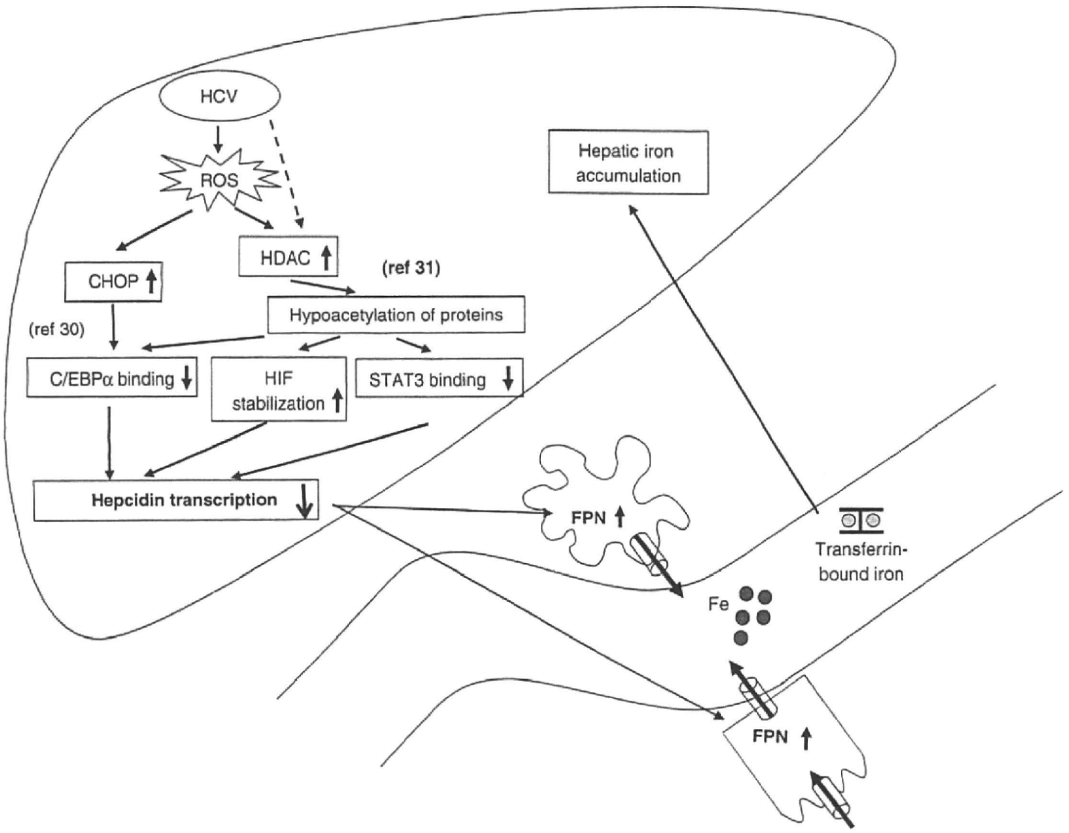

Figure 1 Schematic diagram depicting the mechanisms underlying the hepatic iron accumulation induced by HCV. HCV-induced ROS reduces hepcidin transcription through the inhibited binding of CHOP and/or STAt3 to the hepcidin promoter, and/or stabilization of HIF that is negative hepcidin regulator. C/EBP, CCAAT/enhancer-binding protein; CHOP, C/EBP homology protein; FPN, ferroportin; HCV, hepatitis C virus; HDAC, histone deacetylase; HIF, hypoxia inducible factor; ROS, reactive oxygen species; STAT, signal transducer and activation of transcription.

Metabolic disorders caused by HCV such as insulin resistance, hepatic steatosis and iron accumulation are clinically important in terms of amplification of oxidative stress and involvement in hepatocarcinogenesis in CH-C.[30–33] In addition, these metabolic disorders are related to the response to antiviral therapy. Insulin resistance[34] and hepatic steatosis[35] seem to be negatively correlated with response to antiviral therapy in CH-C.

Informative statement: HCV induces insulin resistance, hepatic steatosis, and/or hepatic iron accumulation, which is associated with hepatocarcinogenesis in CH-C. (Grade A.)

Recommendation 1: Insulin resistance and hepatic steatosis seem to be negatively correlated with response to antiviral therapy in CH-C, whereas it remains controversial whether hepatic iron accumulation is related to a poor response to therapy. (Level 2a, Grade C.)

Liver biopsy for evaluating pathogenesis of hepatitis C

Assessment of the extent of liver fibrosis is still of great importance in terms of predicting the response to antiviral therapy and hepatocarcinogenesis in CH-C. It is also apparent that as many as a quarter of CH-C patients with persistently normal aminotransferase values have significant fibrosis.[36] The recently developed transient elastography that uses ultrasound and low-frequency elastic waves to measure liver elasticity has

Table 2 Definitions of virological responses to interferon therapy

RVR (rapid virological response)	Undetectable HCV RNA at week 4
cEVR (complete early virological response)	Undetectable HCV RNA at week 12
pEVR (partial early virological response)	Two log drop of HCV RNA without undetectable level at week 12
LVR (late virological response)	Undetectable HCV RNA between week 13 and 24 week
NVR (null virological response)	Positive HCV RNA during treatment
Relapse	Undetectable HCV RNA at end of treatment followed by detectable level after treatment
SVR (sustained virological response)	Undetectable HCV RNA at 24 weeks after treatment

improved the ability to define the extent of fibrosis without a liver biopsy, particularly when combined with other non-invasive markers,[37] but it is not yet ready to replace liver biopsy. Among the pathological features, steatosis and excess hepatocellular iron that affect disease progression and possibly impede treatment response are difficult to diagnose without liver biopsy. Thus, a liver biopsy should be considered if it is desirable to determine the stage of fibrosis or presence of steatosis or excess hepatocellular iron for prognostic purposes or making a decision regarding treatment.

Recommendation 2: A liver biopsy should be considered if it is desirable to determine the stage of fibrosis or presence of steatosis or excess hepatocellular iron for prognostic purposes or making a decision regarding treatment. (Level 1, Grade C.)

VIRAL LOAD, GENOTYPE, VIRAL MUTATIONS

DEFINITIONS OF VIROLOGICAL responses to IFN therapy are summarized in Table 2.

HCV RNA assay and genotype

In clinical practice, the usual approach is to test initially for antibodies to HCV (anti-HCV), then to use HCV RNA to document viremia. The quantity of HCV RNA is useful to know before providing and monitoring HCV treatment. For HCV RNA determination, quantitative tests based on target amplification (reverse transcriptase polymerase chain reaction [RT–PCR]) and signal amplification (branched DNA [bDNA]) techniques with differing sensitivity and linear measuring ranges are commercially available. The COBAS Amplicor HCV Monitor Test v2.0 (Roche Molecular Systems, Branchburg, NJ, USA), however, requires sample dilutions for accurate quantification of high-titer specimens. In addition, the assay displays relatively low sensitivities of approximately 600 IU/mL. Recently, the COBAS AmpliPrep/COBAS TaqMan HCV test (Roche Molecular Systems) and AccuGene m-HCV (Abbott Molecular, Des Plaines, IL, USA) have become available. These meet the requirements for highly sensitive detection and reliable quantification of HCV in clinical samples.

There are six major HCV genotypes. Genotype specificity predicts the likelihood of treatment response and determines the duration of treatment. Therefore, HCV genotype should be determined in all HCV-infected persons prior to treatment in order to determine the duration of therapy and likelihood of response.[38]

Many reports showed that sustained virological response (SVR) rates in IFN monotherapy and IFN plus ribavirin (RBV) combination therapy were higher in patients who had lower pretreatment RNA levels and genotype 2 infections.[39–41]

Recommendation 3: HCV RNA level and genotype should be determined in all HCV-infected persons prior to treatment in order to predict the efficacy of response of therapy. SVR rate in IFN therapy are higher in patients who had lower pretreatment RNA levels and genotype 2 HCV infections in IFN therapy. (Level 1, Grade A.)

HCV mutation

IFN sensitivity determining region (ISDR)

Enomoto *et al.* were able to demonstrate a strong correlation between the number of mutations within the carboxy terminal region of the NS5A gene, the ISDR spanning codons 2209–2248, and response to IFN therapy.[42] Thus, no patient infected with HCV with a wild-type ISDR sequence (identical to the prototype Japanese HCV strain [HCV-J]) responded to IFN therapy whereas all patients infected with the "mutant type", defined by four or more amino acid substitutions in this region, showed an SVR.[43] These initial findings have been confirmed by other Japanese studies but controversial data were reported from other parts of the world, particularly from Europe and the

USA. This may indicate that geographical factors account for different sensitivities of HCV genotype 1b infection to antiviral therapy. Pascu *et al.* reported that the distribution of wild-, intermediate- and mutant-type ISDR sequences differed significantly between Japanese ($n = 655$) (44.1%, 37.6% and 18.3%, respectively) and European patients ($n = 525$) (24.8%, 63.4% and 11.8%, respectively; $P = 0.001$). However, there was a significant positive correlation between the number of ISDR mutations and SVR rate, irrespective of geographical region.[44]

Moreover, Shirakawa *et al.* reported that a logistic regression model that includes the sequence of ISDR of HCV, and other factors (T-helper cell [Th]1/Th2 ratio, bodyweight and neutrophil count) can be useful for accurately predicting accurately the SVR rate before pegylated (PEG)-IFN and RBV combination therapy.[45]

Recommendation 4: The ISDR should be evaluated before IFN treatment in order to predict the response to treatment. (Level 2b, Grade B.)

IFN/RBV resistance-determining region (IRRDR)

El-Shamy *et al.* have reported recently that a high degree of sequence variation in the V3 and the pre-V3 regions (amino acid [aa]2334-2355) of NS5A, which they refer to collectively as the IRRDR (aa2334-2379), was closely correlated with virological response in HCV-1b-infected patients treated with PEG-IFN and RBV.[46] A high degree (>6 aa substitutions) of sequence variation in the IRRDR should be a useful marker for predicting SVR, whereas a less diverse (<5) IRRDR sequence predicts non-SVR.

Amino acid substitutions in the HCV core region

Akuta *et al.* identified pretreatment substitutions of aa70 and aa91 in the core region as independent and significant pretreatment factors associated with virological non-response, based on 48-week combination therapy of IFN plus RBV.[47] Moreover, they identified aa70 and aa91 substitutions in the core region as predictors of response to PEG-IFN-RBV therapy in Japanese patients infected with HCV genotype 1b[48] (Table 3). Donlin *et al.* reported sequencing the complete pretreatment genotype 1 HCV open reading frame using samples from 94 participants in the Virahep-C study to assess the effects of viral diversity on response to therapy.[49] Genotype 1b sequences from patients with more than 3.5 log declines in viral RNA levels by day 28 (marked responders) were more variable than those from patients with declines of less than 1.4 log (poor responders) in core and NS3. Moreover, arginine (R) at aa70 in the core region was related to a marked response.

Recently evaluations were made of the impact of aa substitutions in HCV core region on hepatocarcinogenesis. Akuta *et al.* reported that cumulative hepatocarcinogenesis rates in double wild-type (arginine at aa70/leucine at aa91) of the HCV core region were significantly lower than those in the non-double wild type in CH-C patients.[50] Moreover, another report showed that a logistic regression model developed

Table 3 Factors associated with sustained virological response to 48-week pegylated interferon plus ribavirin combination therapy in patients infected with hepatitis C virus genotype 1b, identified by multivariate analysis ($n = 114$) 52)

Factor	Category	Risk ratio (95% confidence interval)	*P*
Amino acid substitution in core region	1: double wild	1	
	2: non-double wild	0.102 (0.022–0.474)	0.004
Low-density lipoprotein cholesterol (mg/dL)	1: <86	1	
	2: ≥86	12.87 (2.177–76.09)	0.005
Sex	1: male	1	
	2: female	0.091 (0.017–0.486)	0.005
ICG R15 (%)	1: <10	1	
	2: ≥10	0.107 (0.017–0.678)	0.018
γ-Glutamyltransferase	1: <109	1	
	2: ≥109	0.096 (0.0011–0.819)	0.032
Ribavirin dose (mg/kg)	1: <11.0	1	
	2: ≥11.0	5.173 (1.152–23.22)	0.032

through analysis of full-length core gene sequences identified seven polymorphisms significantly associated with increased HCC risk (36G/C [aaK12N], 209A [aaR70Q], 271U/C [aaL91M], 309A/C, 435A/C, 481A and 546A/C).[51] HCV core gene sequence data might provide useful information about HCC risk.

Recommendation 5: Amino acid substitutions in the HCV core region (aa70 and aa91) should be determined before IFN treatment in order to predict the response to treatment. (Level 2b, Grade B.)

NS3 protein secondary structure

Recently, Ogata *et al.* reported that HCV-1b strains can be classified into different groups based on the secondary structure of an amino-terminal portion of the NS3 protein and that specific strains are more prevalent among patients with HCC.[52] Moreover, the cumulative incidence of HCC was highest among patients infected with specific group HCV-1b, in whom the risk of HCC significantly increased compared with that among patients infected with another group (hazard ratio = 4.95 [95% confidence interval = 1.43–17.11]) after adjustment for age and histological stage.[53]

Informative statement: NS3 protein secondary structure may be related to hepatocarcinogenesis. (Grade B.)

NATURAL HISTORY OF CH-C

Progression to cirrhosis and HCC

PREVIOUS PUBLICATIONS REPORTED that approximately 60–80% of patients with acute hepatitis C develop chronic infection in the natural course.[54–57] Because it is difficult to ascertain precisely when the HCV infection occurred except for patients who had blood transfusions, and because chronic infection progresses slowly and asymptomatically, the natural entity of the disease has not been elucidated fully. Seeff *et al.* compared the long-term prognosis of HCV antibody-positive and -negative young men and reported that liver disease-related death was very rare in HCV antibody-positive patients.[58,59] Kenny-Walsh studied the liver histology of 363 young women 17 years after HCV infection and showed that 83% had no or mild hepatic fibrosis whilst 2% had liver cirrhosis.[60] These results demonstrate that progression to serious liver disease is a rare event two decades after infection of young people with HCV.

On the other hand, in blood transfusion-associated CH-C patients the mean interval to liver cirrhosis is estimated to be approximately 20–30 years and that to HCC approximately 30–40 years.[61,62] Because HCC is the most serious complication of HCV-infected people, it is desirable to predict the overall incidence of HCC in each patient. Up to now, many investigators have reported a close relationship between the stage of hepatic fibrosis and incidence of HCC. According to reports from Japan, the annual incidence of new HCC in liver cirrhosis is estimated to be approximately 5–8%.[63–65]

Informative statement: The natural history of CH-C is highly variable. HCV infection does not have much impact on the overall mortality of all the infected people, whereas progression to liver cirrhosis is observed 20–30 years and to HCC 30–40 years after infection. In Japan, the annual incidence of HCC in liver cirrhosis is estimated to be 5–8%. (Level 2b, Grade B.)

Recommendation 6: Treatment of HCV-infected people should be determined in consideration of the higher annual incidence of HCC in patients with liver cirrhosis in Japan as compared to Western countries. (Level 2b/3, Grade B.)

Progression of fibrosis

The rate of progression of fibrosis varies among patients with CH-C. Poynard *et al.*[66] calculated the average progression rate of hepatic fibrosis in CH-C to be 0.133 fibrosis units/year. In Japan, Shiratori *et al.*[67] reported this to be 0.10 fibrosis units/year. In HCV carriers with persistently normal aminotransferase levels (PNALT), progression of hepatic fibrosis is slower. Persico *et al.*[68] reported that median histological scores did not differ after 5 years of follow up in PNALT and Okanoue *et al.*[69] calculated the average progression rate of hepatic fibrosis in PNALT to be 0.05 fibrosis units/year.

Informative statement: On average, progression of hepatic fibrosis in CH-C is 0.10–0.13 fibrosis score units/year. The hepatic stage/grade score of HCV carriers with PNALT *are generally low and the progression of hepatic fibrosis is slow. Excessive alcohol intake, insulin resistance and hepatic steatosis are the major factors which induce the progression of hepatic fibrosis. (Level 2b, Grade B.)*

Alanine aminotransferase (ALT) levels

Alanine aminotransferase is an easy tool to evaluate hepatocellular damage in liver diseases. In the past, a higher incidence of HCC was reported in liver cirrhotic patients with elevated ALT levels.[70] The normal range of serum ALT level varies according to the institutions or hospitals, but it is likely to be located between 30 IU/L

and 40 IU/L. Recently, Kumada *et al.*[71,72] demonstrated that the cumulative incidence of hepatocarcinogenesis increased in parallel with the increase in ALT average integration value in CH-C even in patients with normal ALT levels. In a community-based study, an elevated ALT level (>35 IU/l) was shown to be a significant risk factor of HCC development.[73]

Recommendation 7: To prevent the occurrence of HCC, levels of serum ALT should be controlled at below 30 IU/l. (Level 3, Grade A.)

IFN administration

More than two decades have passed since IFN began to be used to treat CH-C patients. Nowadays, more than 70% of HCV-infected people can be cured by the combination therapy of PEG-IFN plus RBV. However, even in patients who were cured of HCV infection and attained an SVR, the occurrence of HCC may be reported long after completion of IFN therapy. The risk factor of HCC occurrence after IFN therapy is a combination of advanced hepatic fibrosis score before therapy, older age and male sex.[74–76] Bruno *et al.*[75] reported that annual incidence of HCC occurrence in liver cirrhosis after attaining SVR was 0.66%, which was one-third of the incidence of HCC in liver cirrhosis without a virological response (non-SVR).

Recommendation 8: Surveillance is required for the occurrence of HCC in patients with CH-C and liver cirrhosis. Even if IFN-based therapy is successful in attaining SVR, screening for the detection of HCC by computed tomography (CT), magnetic resonance imaging or ultrasonography and measurement of the serum tumor markers should be carried out routinely, especially for patients with advanced hepatic fibrosis, older age and male sex, because they are at high risk for the occurrence of HCC. (Level 2b, Grade A.)

Indication of IFN therapy for CH-C

Interferon-based therapy is used to treat chronic HCV-infected patients worldwide and PEG-IFN plus RBV is the first choice indication for CH-C patients. Because IFN and RBV have a variety of adverse effects including depression and thyroid dysfunction, "who and how" to treat should be determined with caution. The AALSD practice guideline advocates that treatment decision should be individualized based on the severity of liver disease, the potential for serious side-effects, the likelihood of treatment response, the presence of comorbid condition and the patient's readiness for treatment.[1]

Recommendation 9: Treatment decision of IFN therapy for CH-C should be individualized based on the body/mental condition, probability of successful therapy and prolonged survival, and likelihood of provoking serious adverse effects. Scores of hepatic stage/grade should be considered as well. For aged patients, in whom HCV infection is regarded as the major determinant of survival, IFN-based therapy should be considered with caution. (Level 3, Grade A.)

PEG-IFN AND RBV COMBINATION THERAPY

Factors associated with virological response to PEG-IFN and RBV combination therapy

TREATMENT WITH PEG-IFN-α-2A or -2b together with RBV has been evaluated in two nationwide phase III registration trials in Japan.[77,78] In one trial, which determined efficacy of PEG-IFNα-2b and RBV,[79] the SVR rate to 48-week combination therapy was 48% (121/254) in patients with HCV genotype 1b and a high viral load (≥100 KIU/mL). Another trial using PEG-IFN-α-2a and RBV demonstrated an SVR rate to 48-week combination therapy of 59% (57/96) in patients with HCV genotype 1b and a high viral load (≥100 KIU/mL).[80] Based on these results, the currently recommended standard therapy for the patients with CH-C in Japan is the combination of a PEG-IFN together with RBV, except for the treatment naïve patients with a low viral load for whom a PEG-IFN monotherapy is recommended.

These clinical trials identified the following factors that are associated with non-SVR in patients with HCV genotype 1b and a high viral load: (i) older patients; (ii) non-responders to previous IFN therapy; (iii) advanced fibrosis; (iv) female sex; and (v) poor adherence below 80%. In marked contrast to the data from Europe and the USA, the SVR rate in Japanese female patients is lower than that in the male patients. Several community-based retrospective studies in Japan also demonstrated that female patients, especially older female patients, are more difficult to treat compared with other patients.[81,82] Other factors associated with virological response reported from Japan include the low-density lipoprotein cholesterol level,[83] α-fetoprotein (AFP) level,[83] whole-body insulin sensitivity index,[84] single nucleotide polymorphisms of MAP-KAPK3,[85] *RIG-I*/IPS-1 ratio,[86] Th1/Th2 ratio[45] and PKR response.[87] Association between viral mutations and treatment response is discussed in depth above.

Recommendation 10: Predictors associated with a non-SVR to PEG-IFN and RBV include: (i) age older than 60 years, particularly older women; (ii) advanced fibro-

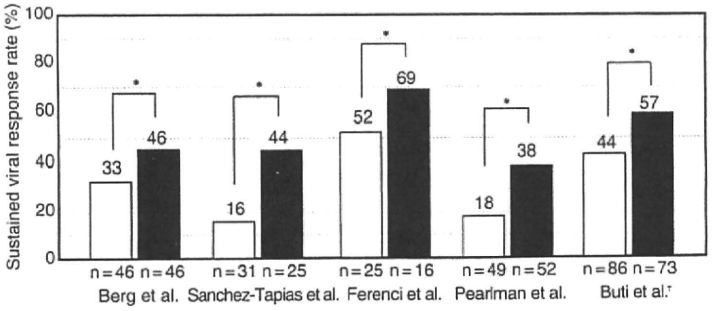

Figure 2 Comparison of sustained virological response rate between 48-week (open column) and 72-week (closed column) treatment with pegylated interferon and ribavirin in patients with partial early virological responder, which is defined as ≥2 log reduction in hepatitis C virus (HCV) RNA level compared to baseline HCV RNA level but detectable HCV RNA at treatment week 12. *Statistical significance between two treatment groups. †Comparison in patients with ≥80% adherence is shown.

sis; (iii) non-responder to previous IFN therapy; and (iv) poor adherence below 80%. (Level 2a, Grade B.)

Response-guided therapy for patients with HCV genotype 1

Measuring the rate of viral clearance from serum is helpful in predicting the likelihood of a response to PEG-IFN and RBV, and useful for determining the optimal duration of therapy. In two nationwide registration trials conducted in Japan,[77,78] the SVR rate was high, from 76–100% in patients whose HCV RNA was cleared rapidly from serum by week 4, and 71–73% in patients who achieved undetectable HCV RNA from week 5 to week 12. In contrast, the SVR rate in patients with late clearance of HCV RNA from week 13 to week 24 was low at 29–36%. No patients without clearance of HCV RNA by week 24 achieved SVR. It should be noted that time point of HCV clearance was determined by measurement of serum HCV RNA utilizing the Ampricor HCV method in these trials.

Recommendation 11: Measuring the time of viral clearance from serum is helpful in predicting the likelihood of a response to PEG-IFN and RBV. Measurement of HCV RNA is recommended at weeks 4, 12 and 24. (Level 1, Grade A.)

As mentioned above, patients whose HCV RNA measured by Amplicor HCV had not cleared by week 24 were unable to achieve SVR with 48-week standard PEG-IFN and RBV therapy. However, in a retrospective study conducted in 52 patients without HCV RNA clearance from serum by week 24, the rate of ALT normalization 6 months after the completion of therapy (so-called biochemical response) was 56% (5/9) and 62% (8/13) of patients achieved ALT normalization up to 2 years after the completion of therapy (sustained biochemical response).[88] Therefore, the proposal that recommends a continuation of PEG-IFN and RBV therapy for 48 weeks in biochemical responders at week 24 even without HCV clearance has been accepted widely in Japan. This proposal is in marked contrast to the AASLD practice guideline,[1] in which treatment discontinuation is strongly recommended in patients whose HCV RNA remains positive at week 24.

Recommendation 12: It is impossible to achieve SVR in patients without HCV RNA clearance by week 24 measured by Amplicor HCV. (Level 1, Grade A.) However, it is recommended to continue the therapy for 48 weeks even in patients without HCV RNA clearance by week 24 if ALT normalizes at week 24, because a sustained biochemical response can be obtained in these patients. (Level 4, Grade C.)

The strategy of extending therapy in patients with delayed virological responses, defined as clearance of HCV RNA between weeks 12 and 24, was evaluated in five studies.[89–93] These results cannot be compared directly with each other because of the heterogeneous study populations, differences in the baseline characteristics and the different regimens utilized amongst them. Nevertheless, the results showed a trend toward a higher SVR rate by extending therapy from 48 to 72 weeks in patients with delayed virological response (Fig. 2).[89–93]

In Japan, a randomized controlled trial was conducted in 113 patients with HCV genotype 1b and a high viral load, comparing a 48-week treatment group and extended treatment group where patients were treated for an additional 44 weeks after clearance of

HCV RNA from serum. In this trial, the SVR rate was 36% in the 48-week treatment group and 53% in the extended treatment group, and the SVR rate was significantly higher in patients in the extended treatment group who became HCV RNA-negative during the period week 16–24 (9% vs 78%, $P = 0.005$).[94] In addition, in a case–control study matched for age, sex and the timing of HCV RNA clearance from serum, the SVR rate was high at 62% in the 72-week treatment group ($n = 65$) compared to 33% in the 48-week treatment group ($n = 130$), and the extended treatment was particularly effective in patients with HCV core mutations at aa70 and aa91 as well as patients a with wild type of ISDR sequence.[79] Accordingly, 72-week extended treatment is recommended for patients who are slow to clear of HCV RNA between weeks 12 and 24.

Currently, HCV RNA clearance from serum is determined by real-time PCR detection, although most of former studies utilized the Amplicor HCV method for this purpose. Because real-time PCR is highly sensitive, it should be reevaluated in terms of who gains benefit from extended therapy. Currently, there is no sufficient evidence to determine this. Nevertheless, substantial number of community-based Japanese study using real-time PCR detection suggested that SVR could be obtained by 72-week treatment if HCV RNA became undetectable by week 36. Accordingly, when determining the timing of HCV RNA clearance using real-time PCR detection, 72-week treatment could be recommended for patients who achieve HCV RNA clearance between weeks 12 and 36.

Recommendation 13: 72-week extended therapy should be considered for patients with HCV genotype 1 who have delayed HCV RNA clearance from serum between weeks 12 and 24. (Level 2a, Grade B.)

Recommendation 14: When using a real-time detection PCR method for measurement of HCV RNA, SVR can be obtained by 72-week extended treatment in patients who have achieved HCV RNA clearance by week 36. (Level 2b, Grade C.)

Response-guided therapy for patients with HCV genotype 2

Six trials have evaluated a shortening of the duration of therapy from 24 weeks to 12–16 weeks for patients with chronic HCV genotype 2 and 3.[80,95–99] Although the data from some of these trials suggest that patients with genotype 2 and 3 infection who achieve viral clearance from serum by week 4 can shorten their treatment duration to 12–16 week,[80,95,99] the benefit of a shortening the duration of therapy remains controversial.[96] In a recent study by Mangia *et al.*, the factors associated with relapse after shorter duration of therapy are identified as age over 45 years, pre-treatment platelet count of less than 140×10^9/L, and body mass index over 30 kg/m^2,[100] suggesting shortening the duration of therapy can be considered only in particular patients without predictors associated with relapse. Because most Japanese patients have risk factors for relapse such as older age and advanced fibrosis, shortening the duration of the therapy is not generally recommended for Japanese patients with genotype 2, even if they achieve viral clearance by week 4.

PEG-IFN and RBV combination therapy in patients with compensated cirrhosis

In the early Western registration trials, patients with HCV-related compensated cirrhosis did achieve SVR but at lower rates than did those without cirrhosis.[101–103] Subsequently, there was one treatment study that focused exclusively on patients with compensated cirrhosis.[104] In this study, 124 patients with compensated cirrhosis were assigned randomly to an RBV 1000/1200-mg (standard dose) group and 600/800-mg (low dose) group to determine the efficacy of PEG-IFN and RBV combination therapy. The SVR was achieved in 52% of patients who received the standard RBV dose and in 38% of those treated with the low dose. Serious adverse events developed in 14% and 18% of recipients of the standard and low RBV doses, respectively, while dose reduction was necessary in 78% and 57% of the two groups, respectively. HCV genotype 2/3 and platelet count over 150×10^9/L were identified as factors contributing to SVR. Thus, patients with HCV-related compensated cirrhosis can be treated successfully with PEG-IFN and RBV but careful observation is needed because of an anticipated higher rate of adverse effects. Although PEG-IFN and RBV for patients with compensated cirrhosis has not been approved yet in Japan, the following recommendation is reasonable.

Recommendation 15: Patients with HCV-related compensated cirrhosis can be treated successfully with PEG-IFN and RBV but careful observation is needed because of an anticipated higher rate of adverse effects. (Level 3, Grade B.)

Retreatment with PEG-IFN and RBV combination therapy for patients who failed to respond to previous IFN treatment

Seven randomized controlled trials have been reported so far that examine the efficacy of PEG-IFN and RBV

combination therapy in patients who failed to respond to previous standard IFN therapy with or without RBV.[105–111] The SVR rate varies among these trials ranging 6–45%, and was lower among non-responders to previous IFN therapy compared with relapsers. In a study using PEG-IFNα-2b and RBV at two different doses (1.5 μg/kg per week of PEG-IFNα-2b together with 800 mg/day of RBV or 1.0 μg/kg per week of PEG-IFN together with 1000–1200 mg/day of RBV), the SVR rate was low at 10% and 6% in non-responders to previous treatment, but was high at 50% and 32% in relapsers, respectively.[109] In a phase III clinical trial in Japan, the SVR rate was also low in non-responders but sufficiently high in relapsers.[77] Accordingly, PEG-IFN and RBV combination therapy is well indicated for patients who relapse after standard IFN therapy with or without RBV.

Data on retreatment of patients who failed to respond to previous PEG-IFN plus RBV therapy have been evaluated in two trials.[112,113] In a randomized controlled trial that used two different doses of PEG-IFN-α-2a (360 or 180 μg/week) with two different durations of therapy (72- or 48-week),[112] an SVR was achieved in 7–14% of patients. It should be noted, however, that the SVR was favorable at 52% in patients who achieved HCV RNA clearance from serum by week 12 in the 72-week treatment arm.[112] In the other trial that used PEG-IFN-α-2b and RBV in 2333 patients who failed to respond to previous PEG or standard IFN together with RBV, an SVR was achieved in 56% of patients whose HCV RNA was cleared from serum by week 12 and in 48% of those with genotype 1.[113] Accordingly, it is reasonable to propose that SVR could be obtained by retreatment with PEG-IFN and RBV in patients who achieve HCV RNA clearance by week 12 of retreatment, even if they failed to respond to previous PEG-IFN and RBV combination therapy.[112,113] In contrast, in the AASLD practice guideline, retreatment with PEG-IFN and RBV is not recommended for patients who did not achieve an SVR after a prior full course of PEG-IFN and RBV. Because it is still unclear who is more likely to respond to retreatment with PEG-IFN and RBV, and new drugs such as protease inhibitors may be indicated in the near future for patients who failed to respond to previous PEG-IFN and RBV therapy, data with retreatment of PEG-IFN and RBV should be accumulated to enable a conclusive recommendation.

Recommendation 16: Retreatment with PEG-IFN and RBV can be considered for non-responders and relapsers who were treated previously with IFN-based therapy with or without RBV. An SVR could be obtained in these patients whose HCV RNA is cleared from serum by week 12 of retreatment with PEG-IFN and RBV. (Level 2b, Grade B.)

MONOTHERAPY WITH IFN OR PEG-IFN

IN JAPAN, IFN monotherapy has been used to treat HCV infection since 1992. Today, IFN monotherapy is used only in patients with specific characteristics because combination therapy with PEG-IFN and RBV has achieved a high rate of SVR. Recently, a large randomized control trial (RCT) of maintenance therapy with a low dose of PEG-IFN was reported.[114] There were no differences in progression of liver disease between a PEG-IFN group and a control group. However, Japanese studies of elderly patients or patients who received maintenance therapy for longer periods showed that IFN can improve outcomes in advanced hepatic fibrosis.

Naïve patients with low viral loads

Previous studies showed that 3 MIU of IFN monotherapy achieved SVR rates of 15–45% in patients with fewer than 2×10^6 copies of HCV.[115–118] Monotherapy with 180 μg/week of PEG-IFN-α-2a or 1.5 μg/kg per week of PEG-IFN-α-2b produced SVR rates of 16–46% in patients with fewer than 2×10^6 copies.[119–121] In Japanese patients with fewer than 1×10^5 copies of HCV, 6 MIU of IFN treatment for 24 weeks achieved an SVR rate of 86% (127/148).[122] PEG-IFN monotherapy for 48 weeks similarly achieved an SVR rate of 86% (106/123). A recent RCT showed that PEG-IFN monotherapy for 24 weeks produced the same SVR rate as similar treatment for 48 weeks in patients with fewer than 1×10^5 copies of HCV. On the basis of these results, monotherapy with IFN or PEG-IFN is considered to be an effective treatment for naïve patients with fewer than 5.0 log copies/mL of HCV.[123]

Recommendation 17: Monotherapy with IFN or PEG-IFN can be considered for naïve patients with low viral loads (<5.0 log copies/mL). (Level 2a, Grade B.)

Patients with chronic kidney disease

Patients with chronic kidney disease (CKD) who undergo hemodialysis have a high prevalence of HCV infection. In Japan, one study reported that HCV RNA was detected in 117 (22%) of 543 patients who underwent maintenance hemodialysis.[124] Hemodialysis patients infected with HCV have a higher mortality rate than uninfected hemodialysis patients.[125] This higher

mortality is attributed to the frequent progression to cirrhosis and/or HCC in HCV-infected patients who receive hemodialysis.

Because RBV is excreted renally, it is currently contraindicated in patients with CKD who have a creatinine clearance of less than 50 mL/min. In addition, pharmacokinetic studies have shown that the clearance of IFN is lower in patients who undergo hemodialysis than in patients who have normal renal function.[126]

Studies of antiviral therapy in patients who undergo hemodialysis suggest that IFN monotherapy is generally well tolerated and that SVR rates are higher than those in patients with normal renal function.[127] The overall SVR rate was reported to be 33–37% in hemodialysis patients.[128] However, the number of subjects in these trials was too low to support confident conclusions. Adverse events are common in this population, and many patients discontinue therapy prematurely because of such events. A recent RCT showed in EASL 2008 that 135 μg/week of PEG-IFN-α-2a for 48 weeks achieved an SVR rate of 39% (23/38), whereas a dose of 90 μg/week produced an SVR rate of 35% (16/43). In 74% of the patients, treatment was completed as scheduled.

Another important point is when to initiate antiviral therapy in hemodialysis patients. IFN might induce allograft rejection and renal failure.[129] Therefore, IFN therapy should be considered before renal transplantation. The next issue to be resolved is the efficacy and safety of low-dose RBV combination therapy in hemodialysis patients.

In 2008, KDIGO proposed guidelines for the treatment of patients with CKD.[130] In Japan, a committee including hepatologists and specialists for CKD is planning a clinical trial for HCV-infected patients with CKD.

Recommendation 18: 3 MIU of IFN thrice weekly or 90 or 135 μg of PEG-IFN-α-2a weekly is recommended for patients with CKD. (Level 2a, Grade B.)

Patients with acute HCV infection

Acute HCV infection progresses to chronic infection in approximately 70% of patients.[131] Antiviral treatment should therefore be considered for this group of patients. On the other hand, it is difficult to identify patients with self-limited disease not requiring therapy. The results of previous studies indicate that anti-HCV treatment should be initiated if HCV RNA is detected continuously for more than 12–16 weeks. If treatment is initiated within this period, monotherapy with IFN or PEG-IFN achieves an SVR rate of more than 80% in patients with acute HCV infection.[132] Reliable evidence showing that additional treatment with RBV improves the SVR rate in such patients is not available.

Recommendation 19: Patients with acute HCV infection should be considered as candidates for antiviral therapy. If HCV RNA is detected continuously for 12 or 16 weeks from the onset, treatment with 6 MIU of IFN or 180 μg of PEG-IFN monotherapy should be initiated. (Level 2a, Grade B.)

Patients who receive curative treatment for HCC

Hepatocellular carcinoma frequently recurs in HCV-infected patients, even after curative therapy for HCC. Prevention of the recurrence of HCC is essential in such patients. Several RCT showed that the incidence of HCC was low in an IFN-treated group, compared to a control group (Table 4).[133,134] For example, Kubo *et al.* reported that 3 MIU IFN monotherapy thrice weekly for 96 weeks inhibited the recurrence of HCC in patients who had undergone a curative resection.[134] Furthermore, Shiratori *et al.* performed an RCT in 74 patients who had received curative percutaneous ethanol injection therapy for HCC. They reported that second and third recurrences of HCC were less frequent in patients who received IFN.[135] In an Italian study of 150 patients who had undergone curative resection, the recurrence rate of HCC 2 years after operation was significantly lower among patients who received IFN.[136]

Japanese studies showed that the survival rate was also improved by IFN treatment owing to the suppression of HCC and/or the progression of hepatic failure.[137,138]

Recommendation 20: IFN therapy should be considered for patients after curative treatment for HCC. (Level 1, Grade A.)

Maintenance therapy for patients with advanced hepatic fibrosis

Previous studies of patients with advanced hepatic fibrosis, defined as a fibrosis score 3 or 4, showed that IFN monotherapy inhibited the occurrence of HCC, compared to patients who did not receive IFN.[64,139,140] In Japanese studies, IFN was effective not only in SVR patients, but also in non-SVR patients.[139,141] On the other hand, an Italian study showed that the incidence of HCC decreased only in cirrhotic patients in whom HCV was eradicated by IFN therapy.[75]

Case–control studies in patients older than 60 years showed that a low dose of IFN reduced ALT and AFP levels and decreased the incidence of HCC, compared to a control group.[142,143] RCT for IFN monotherapy non-

Table 4 Interferon monotherapy for patients after curative treatment for hepatocellular carcinoma

Author	Study design	No. of patients (IFN group vs non-IFN group)	Age (IFN group vs non-IFN group)	Interferon	Sustained virological response	Follow-up duration (months)	HCC recurrence (IFN group vs non-IFN group)	Survival (IFN group vs non-IFN group)
Ikeda *et al.*	RCT	10 vs 10	60 vs 65	beta	0	25	10% vs 70% $P = 0.0004$	
Kubo *et al.*	RCT	15 vs 15	62 vs 60	alpha	2 (13%)	54	60% vs 87% $P = 0.055$	80% vs 50% $P = 0.041$
Suou *et al.*	Pilot study	18 vs 22	61 vs 62	alpha	6 (33%)	60	28% vs 82% $P < 0.001$	100% vs 73% $P < 0.05$
Shiratori *et al.*	RCT	49 vs 25	61 vs 63	alpha	14 (29%)	60	80% vs 92%	68% vs 48%
Lin *et al.*	RCT	8 vs 6	61 vs 59	alpha	no data	27	63% vs 83% $P = 0.34$	
Jeong *et al.*	Prospective case–control study	16 vs 16	69 vs 68	alpha	2 (13%)	36	69% vs 80% $P = 0.157$	100% vs 88% $P = 0.45$
Sakaguchi *et al.*	Case–control study	24 vs 33	69 vs 67	alpha	1 (4%)	36	14% vs 73% $P = 0.011$	100% vs 94% $P = 0.25$
Mazzaferro *et al.*	RCT	76 vs 74	65 vs 67	alpha	2 (3%)	45	76% vs 94% $P = 0.49$	64% vs 52% $P = 0.47$
Akamatsu *et al.*	Retrospective study	53 vs 399	60 vs 68	no data	17 (32%)	72		88%, 71% vs 53.2% $P = 0.025$
Kudo *et al.*	Case–control study	43 vs 84	65 vs 66	alpha or pegylated IFN	2 (5%)	60	56% s 71% $P = 0.04$	86% vs 56% $P = 0.004$

IFN, interferon; HCC, hepatocellular carcinoma; RCT; randomized control study.