Table 2 Results of the Asia–Pacific and SHARP studies

End point	Asia–Pacific		SHARP	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
OS	0.68 (0.50–0.93)	0.014	0.69 (0.55–0.87)	<0.001
TTSP	0.90 (0.67–1.22)	0.498	1.08 (0.88–1.31)	0.768
TTP	0.57 (0.42–0.79)	<0.001	0.58 (0.45–0.74)	<0.001
PFS	0.62 (0.46–0.82)	<0.001	0.65 (0.52–0.79)	<0.001

sorafenib versus sorafenib plus BIIB022, and phase I/II studies of AVE1642 as monotherapy or in combination with sorafenib or erlotinib are ongoing.

Sorafenib: trial results and clinical experience

Clinical results for sorafenib in HCC

As described above, sorafenib is a multi-kinase inhibitor of tumor growth and angiogenesis, and has a strong inhibitory effect on C-Raf and B-Raf serine/threonine kinases (comprising the Raf/MEK/ERK pathway), VEGFR and PDGFR tyrosine kinases, and FLT-3 and c-kit [20]. To date, sorafenib is the only molecular-targeted agent approved for treatment of HCC, on the basis of the results of two large-scale clinical trials, namely the SHARP (Sorafenib HCC assessment Randomized Protocol) study [53] and the Asia–Pacific study [54]. The median OSs for the sorafenib group in the SHARP and Asia–Pacific studies were 10.7 months (vs. 7.9 months for the placebo group, $P < 0.001$; HR: 0.69) and 6.5 months (vs. 4.2 months for the placebo group, $P = 0.014$; HR: 0.68), respectively, indicating that sorafenib prolongs survival by approximately 50% (Table 2). These data should compel HCC specialists to challenge their preconception that systemic anticancer drug therapy is not effective for HCC.

Current status regarding the use of sorafenib in Japan

Sorafenib was approved in Japan in May, 2009. A survey has confirmed that, at the time of writing (March, 2010), over 3,700 patients have been prescribed sorafenib. Across several centers, 15 Japanese patients have achieved CR, which was not observed in the SHARP or Asia–Pacific trials. This suggests that some Japanese patients may be very sensitive to sorafenib [55]. The reason for this, and predictive biomarkers, are now actively under investigation.

On the other hand, it has been reported that hand–foot syndrome occurs early after sorafenib administration [56] more often than was noted in the SHARP and Asia–Pacific studies, and the drug is often discontinued because of the adverse effects in many patients [56]. As demonstrated in the SHARP and Asia–Pacific studies, sorafenib is only used to achieve stable disease; it is, therefore, important to improve drug efficacy by extending the period of administration for as long as possible. Therefore, it is no exaggeration to say that, in the case of sorafenib, the "successful management of side effects" is equal to "successful treatment." According to "post-TACE phase III clinical study [56]" performed in Japan and Korea, it is strongly speculated that physicians who are unaccustomed to prescribing molecular-targeted agents and who fail to see marked efficacy, as induced by conventional chemotherapeutic agents, often do not understand the properties of this drug, and they (and the patients) do not fully comprehend therapeutic efficacy. Moreover, they feel too anxious about side effects that have not been encountered before. These circumstances may result in treatment discontinuation in many patients. Clearly, greater awareness among physicians for therapeutic efficacy and approaches to manage adverse effects is needed to improve treatment outcomes.

Experience of sorafenib use at our institute

Since the approval of sorafenib on May 20, 2009, we have treated 90 patients with sorafenib, and few have discontinued therapy because of adverse effects or patient refusal to continue. Of these 90 patients, two achieved CR [55]. These two CR patients, in whom pulmonary and adrenal metastases and intrahepatic lesions all disappeared, survived free of recurrence for more than 2 years and 1 year, respectively, at the time of writing (March, 2010), i.e., they are still alive at present. In other patients who apparently achieved SD, the tumor marker levels reached a plateau after sorafenib administration, when their levels were rising rapidly before sorafenib administration. Even if hepatic lesions do not show a clear tendency to undergo necrosis or regression on CT images, three tumor markers (AFP, PIVKA-II, and AFP-L3) are widely considered to serve as surrogate markers. In fact, there are very few data on serum tumor markers, except for AFP, outside Japan. Nevertheless, Japanese researchers have demonstrated the value of changes in these markers and the antitumor efficacy of sorafenib [55].

Interestingly, it has previously been demonstrated that the levels of PIVKA-II or DCP tend to be increased by inducing hypoxia [57]. Therefore, PIVKA-II or DCP may be a good predictive marker for evaluating the hypoxic response to antiangiogenic therapy for HCC.

Only 17 of the 90 patients showed PD on computed tomography (CT) images although follow-up period is still short (less than 10 months). However, because the speed with which the patient develops progressive disease may slow down due to tumor growth inhibition, it is very difficult to determine when to discontinue treatment because of tumor refraction. Important issues for future studies include:

1. identification of biomarkers that can be used to predict therapeutic responses, including CR or PR, in patient groups;
2. evaluation of the role of tumor markers in the determination of therapeutic responses;
3. establishing response evaluation criteria that can determine the therapeutic responses to molecular-targeted agents; and
4. development of effective second-line therapies after sorafenib failure (Figs. 2, 3).

In the treatment algorithm (Figs. 2, 3) approved by the Consensus Meeting of the 2009 Annual Meeting of the Japan Society of Hepatology (Congress chair: Professor Masatoshi Kudo), sorafenib is indicated for treatment of patients with Child-Pugh A HCC with extrahepatic metastasis, vascular invasion, or refractoriness to TACE or arterial infusion chemotherapy.

In addition to the pharmaceutical-sponsored clinical trials of sunitinib and brivanib as first and second-line therapy in sorafenib-refractory patients, investigator-initiated trials (IIT) of sorafenib in combination with hepatic arterial infusion chemotherapy (SILIUS trial), pharmaceutical and IIT trials of sorafenib in combination with TACE (SPACE, TACICS and BRISK-TA trials), and a trial to test the inhibitory effect of sorafenib on tumor recurrence after curative treatment (STORM trial) are ongoing, and the results of these trials are eagerly awaited (Figs. 2, 3). The working hypotheses in these studies can be deduced by extrapolating the MST and hazard ratios in overall survival (OS) calculated in a subanalysis of the SHARP study (Table 3). The results obtained suggest that starting treatment with molecular-targeted drugs at an earlier tumor stage in combination with standard treatment options such as resection, ablation, TACE, or hepatic arterial infusion chemotherapy can improve the prognosis of HCC. Thus, sorafenib has the potential to induce a change of emphasis in the treatment of HCC. For example, in a subanalysis of the SHARP trial, the hazard ratios for OS and MST ratio in intermediate stage HCC without vascular invasion or extrahepatic spread were 0.52 and 1.50, respectively (Table 4). This suggests that survival of early stage HCC and intermediate stage HCC may be prolonged from 5 years to 7.5–10 years by using sorafenib in an adjuvant setting after curative treatment, and from 3 years to 4.5–6 years by using sorafenib in combination with TACE (Fig. 4).

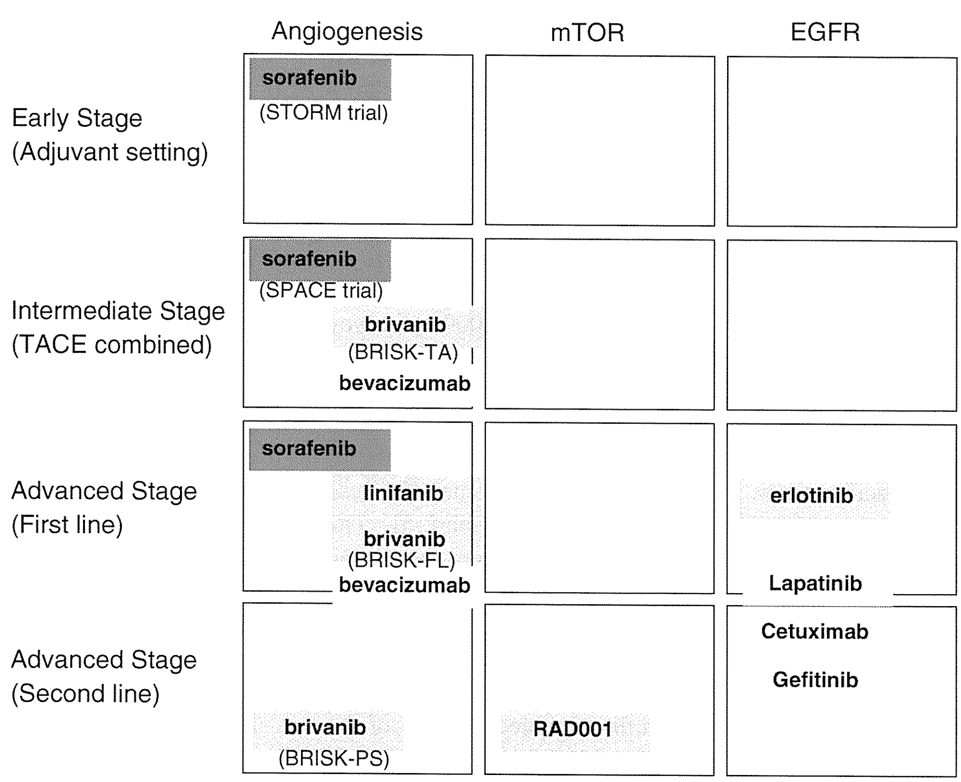

Fig. 2 Molecular targeted agents: ongoing trials in each stage of HCC

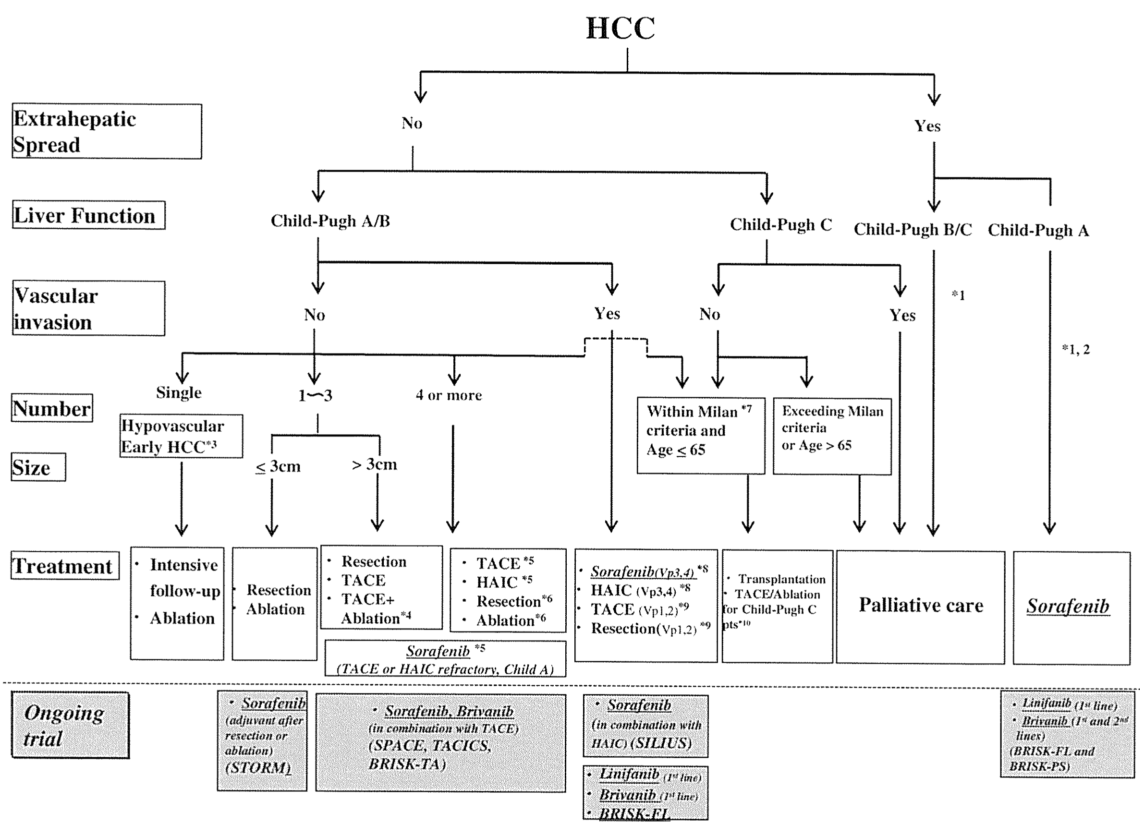

Fig. 3 Consensus-based treatment algorithm for HCC proposed by the Japan Society of Hepatology (JSH) revised in 2010. *1 Treatment should be performed as if extrahepatic spread is negative, when extrahepatic spread is not considered as a prognostic factor in Child-Pugh class A/B patients, *2 sorafenib 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: (1) when the nodule is diagnosed pathologically as early HCC; (2) when the nodules show decreased uptake on Gd-EOB-MRI; or (3) when the nodules show decreased portal flow by CTAP, since these nodules frequently progress to advanced HCC, *4 even for HCC nodules exceeding 3 cm in diameter, transcatheter arterial chemoembolization (TACE) in combination with 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 (5FU+CDDP) or intra-arterial 5FU infusion combined with systemic interferon therapy. Sorafenib is also recommended for TACE- or HAIC-refractory patients with Child-Pugh class A liver function, *6 resection is sometimes performed when more than four nodules are detected. Ablation is sometimes performed in combination with TACE, *7 Milan criteria: tumor size ≤3 cm and tumor number ≤3, or solitary tumor ≤5 cm. Even when liver function is good (Child-Pugh A/B), transplantation is sometimes considered for patients with frequently recurring HCC, *8 sorafenib and HAIC are recommended for HCC patients with major portal invasion such as Vp3 (portal invasion in the first portal branch) or Vp4 (portal invasion in the main portal branch), *9 resection and TACE are frequently performed when portal invasion is minor, such as Vp1 (portal invasion in the third or more peripheral portal branch) or Vp2 (portal invasion in the second 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 because there is no evidence of a survival benefit in Child-Pugh C patients. A prospective study is necessary to clarify this issue

Table 3 Subanalysis data of the SHARP study

		Advanced HCC with vascular invasion and extrahepatic spread	Advanced HCC without vascular invasion or extrahepatic spread
Hazard ratio		0.77 (95% CI: 0.60–0.99)	0.52 (95% CI: 0.32–0.85)
Median OS (MST)	Sorafenib	8.9 M (n = 209) (95% CI: 7.6–10.3 M)	14.5 M (n = 90) (95% CI: 14.0 M–N/E)
	Placebo	6.7 M (n = 212) (95% CI: 5.2–8.0 M)	10.2 M (n = 91) (95% CI: 8.6–15.5 M)

M, month

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Table 4 Results of studies of molecular-targeted agents for HCC

Agent	Type	Target	Number of patients	RR (%)	PFS (month)	TTP (month)	OS (month)	Reference
Phase III								
Sorafenib	s.m.	C-Raf, B-Raf,	602 (299[a])	2	–	5.5	10.7	Llovet [5, 53]
		PDGFR, VEGFR	271 (150[a])	3.3	–	2.8	6.5	Cheng [54]
Phase II								
Sorafenib	s.m.	C-Raf, B-Raf, PDGFR, VEGFR	137	2.2	–	5.5	9.2	Abou-Alfa [58]
Sunitinib	s.m.	VEGFR, PDGFR,	37	2.7	3.7	5.3	8	Faivre [33]
		SCFR, FLT3	34	2.9	3.9	4.1	9.8	Zhu [34]
Brivanib	s.m.	VEGFR, FGFR	55	n.r.	–	2.8	10	Raoul [36]
Linifanib	s.m.	VEGFR, PDGFR	44	6.8	–	5.7	9.3	Toh [59]
Bevacizumab	MoAb	VEGF	46	13	6.9	–	12.4	Siegel [60]
Erlotinib	s.m.	EGFR	38	9	–	3.2	13	Philip [40]
			40	0	–	–	10.7	Thomas [41]
Gefitinib	s.m.	EGFR	31	3.2	2.8	–	6.5	O'Dwyer [61]
Lapatinib	s.m.	EGFR	40	5	2.3	–	6.2	Ramanathan [62]
			26	0	1.9	–	12.6	Bekaii-Saab [48]
Cetuximab	MoAb	EGFR	30	0	1.4	–	9.6	Zhu [49]

[a] Sorafenib arm

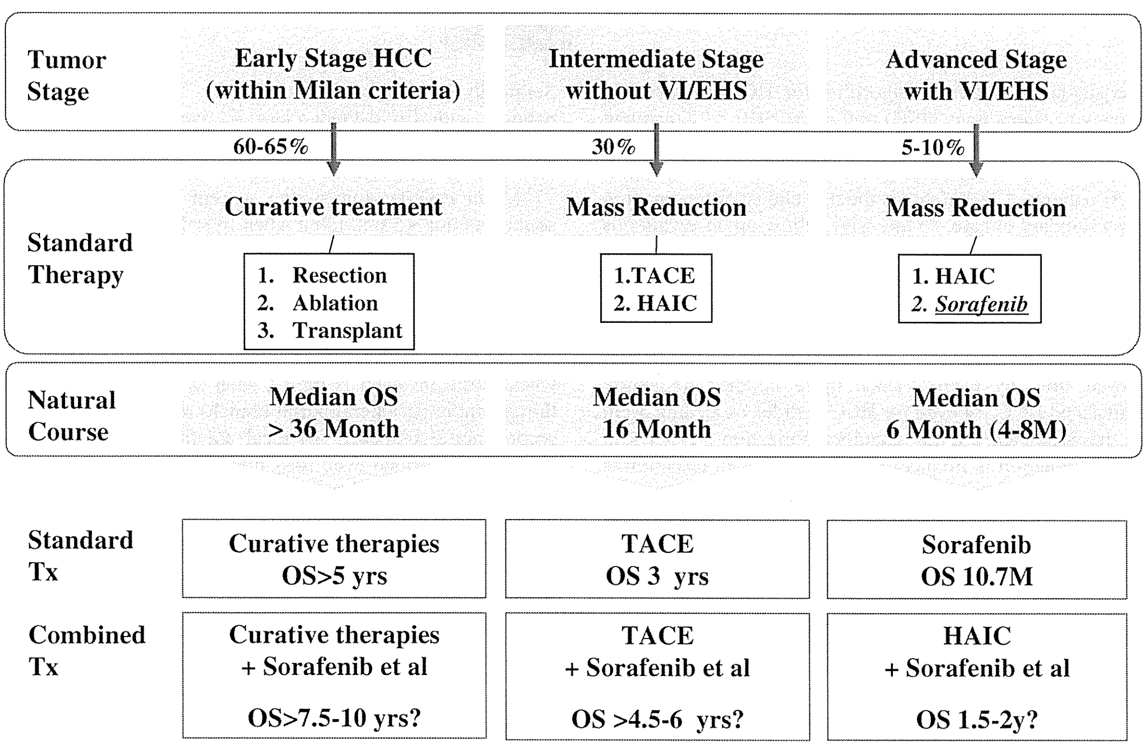

Fig. 4 Outcomes of standard treatment modalities and expected effects of combination therapy with molecular-targeted agents

Summary and future prospects

The results of clinical trials [33, 34, 36, 40, 41, 49, 58–62] of the molecular-targeted agents described above are summarized in Table 4. Angiogenesis-inhibiting drugs, particularly sorafenib, have been evaluated for HCC, and drugs targeting EGFR and mTOR are being developed. The results (numerical values) of phase II clinical trials show no marked differences in the therapeutic efficacy evaluated by time to progression (TTP) or progression-free survival

(RFS). However, results from phase II studies may be subject to patient selection bias and cannot be compared with results from other trials. Thus, when determining the therapeutic efficacy of drugs, we should review the efficacy of the respective drugs, and consider where the theoretical target molecules are present and what combinations of drugs have a theoretical rationale, and thus evaluate options for monotherapy and combination therapy based on the efficacy and safety data obtained from phase III clinical trials.

Molecular-targeted agents that have been introduced into clinical use in recent years are approved for treatment of specific cancer and are then frequently used to treat other cancers. Although not discussed here, studies to identify predictors of efficacy (i.e., biomarkers) for angiogenesis inhibitors and EGFR tyrosine kinase inhibitors, and factors involved in drug resistance, are making steady progress, and the associated therapeutic strategies are undergoing major changes. Therefore, even in the treatment of HCC, it is necessary for HCC specialists to expand their knowledge of and techniques for applying existing treatment modalities (resection, ablation, TACE, arterial infusion chemotherapy) to physically remove, destroy, or necrotize the tumor, and to better understand clinical oncology, particularly the role and mechanisms of action of molecular-targeted agents. We are entering an era in which physicians treating HCC should pay close attention to the development of therapeutic agents not only for HCC but also for other cancers, and be aware of the use of molecular-targeted agents for treating cancers in clinical and basic research settings, and understand approaches to limit or control adverse effects associated with these drugs.

Although sorafenib was recently approved, many issues remain to be addressed, including:

1 how to determine and define refractoriness; and
2 whether to continue TACE or hepatic arterial infusion chemotherapy (a de facto standard in Japan) in patients with TACE-refractory tumors or portal tumor thrombi before starting sorafenib therapy.

For oncology, in particular, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has approved several drugs based on results from global clinical trials and on Japanese phase I study data alone. We strongly recommend that, on the basis of the molecular-targeted agents currently under development, clinical studies (including IITs) should be conducted aggressively, and therapeutic strategies should be devised to resolve the limitations of currently used therapeutic approaches and to improve therapeutic outcomes.

The introduction of sorafenib to treat HCC in 2007 in Western countries and in 2009 in Japan was undoubtedly the beginning of a change of emphasis, representing a significant breakthrough for HCC treatment not previously experienced for this unique tumor.

Conflict of interest statement M. Kudo has received honoraria for the lecture from Bayer HealthCare, Pfizer, and Bristol-Meyers.

References

1. Farazi PA, DePinho RA (2006) Hepatocellular carcinoma pathogenesis: from genes to environment. Nat Rev Cancer 6:674–687
2. Minguez B, Tovar V, Chiang D et al (2009) Pathogenesis of hepatocellular carcinoma and molecular therapies. Curr Opin Gastroenterol 25:186–194
3. Villanueva A, Newell P, Chiang DY et al (2007) Genomics and signaling pathways in hepatocellular carcinoma. Semin Liver Dis 27:55–76
4. Laurent-Puig P, Zucman-Rossi J (2006) Genetics of hepatocellular tumors. Oncogene 25:3778–3786
5. Llovet JM, Bruix J (2008) Molecular targeted therapies in hepatocellular carcinoma. Hepatology 48:1312–1327
6. Hopfner M, Shuppan D, Scherubl H (2008) Growth factor receptors and related signaling pathways as target for novel treatment strategies of hepatocellular cancer. World J Gastroenterol 14:1–14
7. Campbell JS, Hughes SD, Gilbertson DG et al (2005) Platelet-derived growth factor C induces liver fibrosis, steatosis, and hepatocellular carcinoma. Proc Natl Acad Sci 102:3389–3394
8. Ogasawara S, Yano H, Iemura A et al (1996) Expression of basic fibroblast growth factor and its receptors and their relationship to proliferation of human hepatocellular carcinoma cell lines. Hepatology 24:198–205
9. Kudo M (2008) Hepatocellular carcinoma 2009 and beyond: from the surveillance to molecular targeted therapy. Oncology 75:S1–S12
10. Roberts PJ, Der CJ (2007) Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene 26:3291–3310
11. Schmidt CM, McKillop IH, Cahill PA et al (1997) Increased MAPK expression and activity in primary human hepatocellular carcinoma. Biochem Biophys Res Commun 236:54–58
12. Huynh H, Nguen TTT, Chow KHP et al (2003) Over-expression of the mitogen-activated protein kinase (MAPK) kinase (MEK)-MAPK in hepatocellular carcinoma: its role in tumor progression and apoptosis. BMC Gastroenterology 3:19–30
13. Calvisi DF, Ladu S, Gorden A et al (2006) Ubiquitous activation of Ras and Jak/Stat pathways in human HCC. Gastroenterology 130:1117–1128
14. Bos JL (1989) ras Oncogenes in human cancer: review. Cancer Res 49:4682–4689
15. Beeram M, Patnaik A, Rowinsky EK (2005) Raf: a strategic target for therapeutic development against cancer. J Clin Oncol 23:6771–6790
16. Tannapfel A, Sommerer F, Benicke M et al (2003) Mutations of the BRAF gene in cholangiocarcinoma but not in hepatocellular carcinoma. Gut 52:706–712
17. Jenke HS, Deml E, Oesterle D (1994) C-raf expression in early ratliver tumorigenesis after promotion with polychlorinated biphenyls or Phenobarbital. Xenobiotica 24:569–580
18. Beer DG, Neveu MJ, Paul DL et al (1998) Expression of the c-raf protooncogene, gamma-glutamyltranspeptidase, and gap junction protein in rat liver neoplasms. Cancer Res 48:1610–1617
19. Hwang YH, Choi JY, Kim S et al (2004) Over-expression *c-raf*-1 proto-oncogene in liver cirrhosis and hepatocellular carcinoma. Hepatol Res 29:113–121

20. Wilhelm SM, Adnane L, Newell P et al (2008) Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther 7:3129–3140
21. Ohren JF, Chen H, Pavlovsky A et al (2004) Structures of human MAP kinase kinase 1(MEK1) and MEK2 describe novel non competitive kinase inhibition. Nat Struct Mol Biol 11:1192–1197
22. Huynh H, Nguyen TTT, Chow KHP et al (2003) Over-expression of the mitogen-activated protein kinase (MAPK) kinase (MEK)-MAPK in hepatocellular carcinoma: its role in tumor progression and apoptosis. BMC Gastroenterol 3:19–40
23. Engelma J (2009) Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer 9:550–562
24. Zhou L, Huang Y, Li J et al (2009) The mTOR pathway is associated with the poor prognosis of human hepatocellular carcinoma. Med Oncol (Epub ahead of print)
25. Chen J, Wang Q, Fu X et al (2009) Involvement of PI3K/PTEN/AKT/mTOR pathway in invasion and metastasis in hepatocellular carcinoma: association with MMP-9. Hepatol Res 39:177–186
26. Villanueva A, Chiang DY, Newell P et al (2008) Pivotal role of mTOR signaling in hepatocellular carcinoma. Gastroenterology 135:1972–1983
27. Treiber G (2009) mTOR inhibitors for hepatocellular carcinoma: a forward-moving target. Expert Rev Anticancer Ther 9:247–261
28. Ferrara N, Davis-Smyth T (1997) The biology of vascular endothelial growth factor. Endocr Rev 18:4–25
29. Griffioen AW, Molema G (2000) Angiogenesis: potentials for pharmacologic intervention in the treatment of cancer, cardiovascular diseases, and chronic inflammation. Pharmacol Rev 52:237–268
30. Harper SJ, Bates DO (2008) VEGF-A splicing: the key to anti-angiogenic therapeutics? Nat Rev Cancer 8:880–887
31. Fernandez M, Semela D, Bruix J et al (2009) Angiogenesis in liver disease. J Hepatol 50:604–620
32. Schoenleber SJ, Kurtzl DM, Talwalkar JA et al (2009) Prognostic role of vascular endothelial growth factor in hepatocellular carcinoma: systematic review and meta-analysis. Br J Cancer 100:1385–1392
33. Faivre S, Raymond E, Boucher E et al (2009) Safety and efficacy of Sunitinib in patients with advanced hepatocellular carcinoma: an open-label, multicenter, phase II study. Lancet Oncol 10:794–800
34. Zhu AX, Sahani DV, Duda DG et al (2009) Efficacy, safety, and potential biomarker of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. J Clin Oncol 27:3027–3035
35. Forner A, Llovet JM, Bruix J (2009) Sunitinib and the benefits of a negative study. Lancet Oncol 10:743–744
36. Raoul JL, Flinn RS, Kang YK et al (2009) An open-label phase II study of first- and second-line treatment with Brivanib in patients with hepatocellular carcinoma (HCC). J Clin Oncol 27:15S Suppl; Abstr 4577
37. Kanai F, Yoshida H, Tateishi R et al (2008) Final results of a phase I/II trial of the oral anti-angiogenesis inhibitor TSU-68 in patients with advanced hepatocellular carcinoma. J Clin Oncol 26 (abstract 4589)
38. Ciardiello F, Tortora G (2008) EGFR antagonists in cancer treatment. N Engl J Med 358:1160–1174
39. Buckley AF, Burgart LJ, Sahai V et al (2008) Epidermal growth factor receptor expression and gene copy number in conventional hepatocellular carcinoma. Am J Clin Pathol 129:245–251
40. Philip PA, Mahoney MR, Allmer C et al (2005) Phase II study of erlotinib (OSI-774) in patients with advanced hepatocellular cancer. J Clin Oncol 23:6657–6663
41. Thomas MB, Chadhal R, Glover K et al (2007) Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. Cancer 110:1059–1066
42. Thomas MB, Morris JS, Chadha R et al (2009) Phase II trial of the combination of bevacizumab and Erlotinib in patients who have advanced hepatocellular carcinoma. J Clin Oncol 27:843–850
43. Modified folfox7/bevacizumab or modified Xelox/bevacizumab with or without erlotinib in first-line metastatic colorectal cancer (MCRC): results of the feasibility phase of the DREAM-OPTIMOX3 study (GERCOR). J Clinical Oncol, 2007 ASCO Annual Meeting Proceedings Part I, vol 25, No. 18S: 4097
44. Tournigand B, Samson W, Scheithauer C et al (2009) mFOLFOX-bevacizumab or XELOX-bevacizumab then bevacizumab alone or with erlotinib in first-line treatment of patients with metastatic colorectal cancer (mCRC): interim safety analysis of DREAM study. J Clin Oncol 27:15S, ASCO Annual Meeting Abstract No:4077C
45. Hecht JR, Mitchell E, Chidiac T et al (2008) A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 27:672–680
46. Azad NS, Posadas EM, Kwitkowski VE et al (2008) Combination targeted therapy with sorafenib and bevacizumab results in enhanced toxicity and antitumor activity. J Clin Oncol 26:3709–3714
47. Burris HA III, Hurwitz HI, Dees EC et al (2005) Phase I safety, pharmacokinetics, and clinical activity of Lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. J Clin Oncol 23:5305–5313
48. Bekaii-Saab T, Markowitz J, Prescott N et al (2009) A multi-institutional phase II study of the efficacy and tolerability of Lapatinib in patients with advanced hepatocellular carcinomas. Clin Cancer Res 15:5895–5901
49. Zhu AX, Stuart K, Blaszkowsky LS et al (2007) Phase 2 study of cetuximab in patients with advanced hepatocellular carcinoma. Cancer 110:581–589
50. Comoglio PM, Giordano S, Trusolino L (2008) Drug development of MET inhibitors: targeting oncogene addiction and expedience. Nat Rev Drug Dis 7:501–516
51. Scharf JG, Braulke T (2003) The role of the IGF axis in hepatocarcinogenesis. Horm Metab Res 35:685–693
52. Chen YW, Boyartchuk V, Lewis BC (2009) Differential roles of insulin-like growth factor receptor–and insulin receptor–mediated signaling in the phenotypes of hepatocellular carcinoma cells. Neoplasia 11:835–845
53. Llovet JM, Ricci S, Mazzaferro V et al (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378–390
54. Cheng AL, Kang YK, Chen Z et al (2009) Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10:25–34
55. Kudo M (2010) Positioning of a molecular-targeted agent, sorafenib, in the treatment algorithm for hepatocellular carcinoma in Japan, including its impact on complete remission. Oncology (in press)
56. Okita K, Imanaka K, Chiba N et al (2010) Phase III study of sorafenib in patients in Japan and Korea with advanced hepatocellular carcinoma (HCC) treated after transarterial chemoembolization. ASCO Gastrointestinal Cancers Symposium Proceedings 2010: 89 (LBA128)
57. Murata K, Suzuki H, Okano H et al (2010) Hypoxia-induced des-γ-carboxy prothrombin production in hepatocellular carcinoma. Int J Clin Oncol 36:161–170
58. Abou-Alfa GK, Schwartz L, Ricci S et al (2006) Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 24:4293–4300
59. Toh H, Chen PJ, Carr BI et al (2009) A phase II study of ABT-869 in hepatocellular carcinoma (HCC) : Interim analysis. J Clin Oncol 27:15s (Suppl; Abstr 4581)

60. Siegel AB, Cohen EI, Ocean A et al (2008) Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. J Clin Oncol 26:2992–2998
61. O'Dwyer PJ, Giantonio BJ, Levy DE et al (2006) Gefitinib in advanced unresectable hepatocellular carcinoma: Results from the Eastern Cooperative Oncology Group's Study E1203. J Clin Oncol 24:18S (Suppl, Abstr 4143)
62. Ramanathan RK, Belani CP, Singh DA et al (2009) A phase II study of Lapatinib in patients with advanced biliary tree and hepatocellular cancer. Cancer Chemother Pharmacol 64:777–783

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Special Report

Management of hepatocellular carcinoma: Report of Consensus Meeting in the 45th Annual Meeting of the Japan Society of Hepatology (2009)

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Hepatocellular carcinoma (HCC) is responsible for approximately 600 000–700 000 deaths worldwide. It is highly prevalent in the Asia–Pacific region and Africa, and is increasing in Western countries. The evidence-based guideline for HCC in Japan was published in 2005 and revised in 2009. Apart from this guideline, a consensus-based practice manual proposed by the HCC expert panel of the Japan Society of Hepatology (JSH), which reflects widely accepted daily practice in Japan, was published in 2007. At the occasion of the 45th Annual meeting of the JSH in Kobe 4–5 June 2009, a consensus meeting of HCC was held. Consensus statements were created based on 67% agreement of 200 expert members.This article describes the up-to-date consensus statements which largely reflect the real world HCC practice in Japan. We believe readers of this article will gain the newest knowledge and deep insight on the management of HCC proposed by consensus of the HCC expert members of JSH.

Key words: hepatocellular carcinoma, Japan Society of Hepatology, staging system, surveillance, treatment algorithm, consensus-based guideline

INTRODUCTION

THE LAST EVIDENCE-BASED guideline for hepatocellular carcinoma (HCC) for Japan was published in 2005,[1] and has prevailed nationwide. This document was developed by a committee composed of 14 experts (Chairman: Professor Masatoshi Makuuchi) and was based on a critical review of 7118 English reports published between 1966 and 2002. This guideline includes 58 research questions regarding important issues for the prevention, diagnosis, surveillance and treatment of HCC. The utility of this guideline is recognized by many Japanese clinicians and has provided a great contribution to clinical practice. However, there are several issues in which solid evidence is still lacking; thus, clear recommendations for clinical practice cannot be stated. In fact, 45% of the research questions are of grade C recommendation level, representing a lack of adequate evidence. These issues are left to the clinician's discretion within the clinical setting. Furthermore, because the guidelines did not include the most up-to-date articles, no recommendation or statements were made regarding newly established evidence. In addition, the clinical practices that follow these guidelines are considered to account for 70–80% of general practice institutions.

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As mentioned above, Congress President, Professor Masatoshi Kudo, at the 45th Annual Meeting of the Japan Society of Hepatology organized the Consensus Meeting of Hepatocellular Carcinoma. The program was chaired by Professors M. Sata and S. Arii and covered the updated problems and clarified some controversial issues. Eight experts were selected to contribute to the meeting and they were assigned the following topics based on their specialties. Professor M. Sakamoto presented recommendations regarding diagnostic problems for small-sized HCC from the clinicopathological point of view. Professor M. Shimada discussed the utility of clinical staging and prognosis. Dr T. Kumada reviewed the current status of diagnostic imaging and tumor markers. Dr S. Shiina discussed important issues on ablative treatment. Dr Yamashita reviewed transarterial chemoembolization and chemotherapy. Professor N. Kokudo discussed surgical treatment, including liver transplantation. Dr M. Tanaka presented a treatment algorithm from the point-of-view of hepatologists. Finally, Professor T. Takayama comprehensively discussed the appropriateness of the present treatment algorithm.

In each presentation, the speakers raised clinical questions regarding the remaining problems that needed to be clarified in the present guidelines, and the HCC specialists (a total of 200 physicians: hepatologists, 70%; surgeons, 24%; radiologists, 2%; and pathologists, 4%) answered these questions using a question and answer analyzer system. Recommendations were approved when at least 67% of the HCC experts reached agreement. For instances where agreement was between 50% and 67%, the statements were considered informative, and are cited here as "informative statements".

In this consensus paper, each presenter has provided a summary of the recommendations and consensus. It is highly expected that this Consensus Statement established by the Japan Society of Hepatology (JSH)will provide valuable insight, and will greatly contribute to the future improvement of the guidelines and appropriate clinical practices for patients with HCC worldwide.

PATHOLOGICAL ASSESSMENT

PATHOLOGICAL ASSESSMENT OF HCC is described in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer.[2] It focuses on macroscopic typing and tumor grading based on tumor differentiation and reflects the aggressiveness of the tumors; differential diagnosis between multicentric development and intrahepatic metastasis of multiple tumors; and diagnosis of early HCC and precancerous lesions. Historically, careful and detailed histological evaluation of surgical specimens enabled us to understand the clinicopathological features of HCC development and extension, and to establish the above-mentioned diagnostic criteria. However, the recent increase in non-surgical treatments for HCC, such as radiofrequency ablation (RFA), is rapidly changing the role and position of pathological diagnosis. Thus, we discussed the indications for liver tumor biopsy for the diagnosis and treatment of HCC.

When we consider the indications for liver biopsy, the risk and benefit of this procedure must be considered.[3–8] The risk includes complications caused by the procedure itself, such as hemorrhage by needle insertion, and by tumor seeding. The incidence of tumor seeding has been reported in approximately 1–5% of cases. Certainly, we have to note that the incidence depends on the characteristics of the tumor such as tumor size and tumor differentiation. Liver biopsy is important in terms of tumor diagnosis, assessment of prognosis and decision making for treatment. For example, for a typical HCC larger than 2 cm in size with a typical vascular pattern on imaging, and elevated tumor markers such as α-fetoprotein (AFP) and/or des-γ-carboxy prothrombin (DCP), the benefit of performing tumor biopsy to confirm the diagnosis of HCC seems minimal. In contrast, only liver biopsy can be used to confirm the diagnosis of cancer in cases with suspected HCC or borderline lesions on clinical and imaging diagnosis. However, controversy remains because of the inconsistent treatment strategy for suspected lesions, particularly in cases with poor liver function.

Previous follow-up data of suspected HCC and borderline lesions showed that the tumors grow slowly during the precancerous or early HCC stages, but grow rapidly in some early HCC cases or in progressed HCC.[9] The transition from slow growing to rapidly growing tumors was supposed to take place once the tumor reaches approximately 1.5 cm in size. Therefore, the proposed recommendations for liver biopsy are as follows.

Recommendation 1. Liver biopsy should be discouraged in cases with a typical HCC over 1.5 cm in size, which shows typical pattern on imaging.

Recommendation 2. Liver biopsy should be considered in cases with a suspected HCC or borderline lesions/early HCC of 1.5 cm in size or less, which does not show typical pattern on imaging.

In addition to these recommendations, the requirement of liver biopsy should increase if the detection and diagnostic ability of imaging techniques increases for smaller lesions. The emergence of new contrast agents such as gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) are expected to reveal suspected HCC nodules, including early HCC at approximately 1 cm in size. Tumor biopsy should then be performed to confirm the diagnosis of early cancer before it can progress to overt HCC. It is also expected that the increase in therapeutic options will increase the need for more detailed information of the tumor characteristics, such as tumor differentiation and immunophenotype reflecting tumor aggressiveness, which can only be determined by tumor biopsy.

PROGNOSTIC STAGING SYSTEM

IN TERMS OF estimating the prognosis of HCC, there are currently insufficient evidence-based data; therefore, no definite recommendations can be made, unlike other fields of HCC management. It is well known that the prognosis of HCC is defined by the behavior of the HCC itself, and by host factors such as hepatic functional reserve. The major questions that still need to be answered in terms of estimating the prognosis of HCC are: (i) whether an integrated staging system is necessary for the management of HCC; (ii) what is the best integrated staging system; and (iii) should the integrated staging system be included in the algorithm for HCC treatment?

Tumor staging (TNM staging)

There are two major classifications used for tumor staging of HCC. One is the tumor–node–metastasis (TNM) stage, developed by the American Joint Committee on Cancer (AJCC). This classification can also be applied to liver transplant recipients. However, the cut-off value for tumor diameter of 5 cm is too large to define small HCC, which are frequently found in Japan.

The other is the TNM stage proposed by the Liver Cancer Study Group of Japan (LCSGJ). The cut-off of 2 cm is very appropriate for patients in countries such as Japan, where small HCC are often found in an established nationwide screening system. However, in this system, the weighting of the strongest prognostic factor, vascular invasion, is equal to that of other factors used to estimate prognosis, which might not be adequate.

Staging for hepatic functional reserve

There are two major classifications for estimating liver functional reserve. One is the Child–Pugh classification, which is widely used worldwide, but is difficult to apply for decision making for hepatectomy. The other is the Liver Damage Classification scheme proposed by the LCSGJ, which is useful for hepatectomy. However, this scheme is not widely accepted because of the need to perform the indocyanine green retention at 15 min test ($ICGR_{15}$).

Integrated staging system for HCC

The combined classification of TNM stage and liver function stage, namely, an integrated staging system, is extremely important to estimate patient prognosis and guide decision making for patient management. The integrated staging system contributes to: (i) estimate patient prognosis; (ii) select the best treatment option for each patient; (iii) compare different treatment modalities; and (iv) compare treatment outcomes among different institutions.

Since the Okuda classification in 1985,[10] several integrated staging systems have been reported, including the Cancer of the Liver Italian Program (CLIP) score,[11] the Barcelona Clinic Liver Cancer (BCLC) stage[12] and the Japan Integrated Staging (JIS) score.[13] The Okuda classification scheme is simple and has been found to be suitable in the past, but does not seem to be suitable at the present time, now that relatively small HCC can be detected. The CLIP score is popular in Western countries, but its discriminating power is weak for small HCC, particularly at higher scores of 4–6, and over 50% of Japanese HCC patients are classified as score 0. The BCLC staging is thought to be useful as an integrated staging system and for guiding treatment. Therefore, it is recommended as an integrated treatment algorithm by the European Association for the Study of the Liver and the American Association for the Study of Liver Disease (AASLD). However, it is not suitable for the estimation of patient prognosis, and a large number of variables are used. In contrast, the JIS score essentially consists of the Child–Pugh score and the LCSGJ TNM stage, and is widely accepted in Japan. The discriminating power for relatively small HCC is excellent, and is particularly suitable for countries such as Japan, where many small HCC are detected.

In terms of a comparison of these integrated staging systems, Cillo *et al.*[14] reported that the BCLC was the best system among the Okuda, CLIP, BCLC and French classifications. Meanwhile, Tateishi *et al.*[15] reported that the Tokyo score was superior to BCLC staging and comparable to the CLIP score in predicting prognosis after hepatectomy and ablation. Kudo *et al.*[16] reported that the JIS score was better than the CLIP score, particularly in terms of discriminating power for each subgroup. Similarly, Chung *et al.*[17] reported that the JIS score was the most excellent staging system among the BCLC, Tokyo and JIS staging systems. Therefore, JIS score is currently considered to be the best integrated staging system in Japan. Regarding other integrated staging systems, modified JIS score has been reported[13,18] to be useful for patients undergoing hepatectomy. Biomarker combined JIS score has also been reported to be useful in discrimination in patients with good prognosis.[19] However, the usefulness of these new staging systems will remain unclear until they are assessed in a range of patient sets with HCC.

Regarding the estimation of HCC prognosis, most hepatologists recognize the importance of an integrated staging system rather than applying the TNM stage and hepatic functional reserve scales individually. Furthermore, the JIS score is considered to be the best integrated staging system for current clinical practice. However, it is still difficult to incorporate the integrated staging systems, such as the JIS score, into algorithms for HCC treatment.

Recommendation 3. Integrated staging system should be used to assess the prognosis of patients with HCC, instead of individually applying scales for TNM stage and liver function stage.

Recommendation 4. The JIS score is the best staging system to estimate the prognosis of patients with HCC.

Informative Statement 1. Integrated staging systems, such as the JIS score, are not yet suitable for inclusion in algorithms for HCC treatment.

SURVEILLANCE AND DIAGNOSIS

Surveillance programs

IT IS WELL known that HCC mainly occurs in cases with chronic liver disease, particularly cirrhosis. Several cohort studies have shown that the surveillance of high-risk patients with hepatitis B virus (HBV)- or hepatitis C virus (HCV)-related chronic liver disease improves the rate of early detection and the rate of curative treatments.[20–27] For this reason, UK[28], European[29] and American[3] practice guidelines for HCC recommend routine surveillance of HCC among individuals with viral hepatitis or cirrhosis. Almost all gastroenterologists in Japan conduct surveillance programs using a combination of tumor markers such as AFP, the *lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3%) and DCP, and by ultrasound (US).[30] However, no consensus has been reached in terms of the optimal surveillance strategy. Thompson *et al.* calculated the number of people who need to be under surveillance to prevent either a single death from HCC or a single premature death (defined as death before the age 75 years) and showed the effectiveness of surveillance programs.[31] In the absence of surveillance, approximately 20% of the mixed etiology cohort died as a result of HCC.

Recommendation 5. Surveillance with US and three tumor markers including AFP, DCP and AFP-L3 should be performed for early detection of HCC in patients with HBV- and HCV-related chronic liver disease, particularly cirrhosis.

Tumor markers

In Japan, AFP, AFP-L3 and DCP are widely and routinely used as serological tumor markers for the surveillance, diagnosis and prognostic estimation of HCC. The Evidence-Based Clinical Practice Guidelines of HCC published in 2005[1] recommended that AFP, AFP-L3 and DCP should be measured at intervals of 3–4 months for very high-risk patients (defined as HBV- or HCV-related liver cirrhosis), and at 6-month intervals for high-risk patients (defined as HBV- or HCV-related chronic liver disease or other causes of liver cirrhosis).[32] Although AFP is the most widely used tumor marker for HCC, the levels of AFP are also increased in patients with liver diseases other than HCC, including viral hepatitis, with a prevalence of 10–42%.[33–35] In contrast, AFP-L3 and DCP are very specific for HCC, compared with AFP alone. The combination assay for AFP, AFP-L3 and DCP should be performed for the early detection of HCC.[36,37] The specificity and sensitivity of the combination assay of AFP and DCP were 83% and 84%, respectively, to detect small HCC of less than 3 cm in diameter.[38] The specificity and sensitivity of the combination assay of DCP and AFP-L3 were 41.7–66.7% and 89.5–89.8%, respectively, to detect small HCC of less than 3 cm in diameter.[39,40]

Recommendation 6. Periodical measurement of more than two kinds of tumor markers (particularly AFP and DCP) is recommended for the early detection of HCC in high-risk and very high-risk patients.

Recommendation 7. The surveillance interval needs to be shorter in very high-risk patients than in high-risk patients.

Imaging modalities

Periodic follow-up of chronic liver disease by US, multidetector row computed tomography (MDCT) and magnetic resonance imaging (MRI) allows relatively easy detection of small HCC.[41–43] However, it is sometimes difficult to characterize small hepatic nodular lesions detected by these imaging modalities. Definitive diagnosis requires invasive methods such as US-guided liver biopsy. Hemodynamic evaluation of the nodule is also important to assess the biological behavior of HCC. The recent advances in MRI and computed tomography (CT) procedures, such as CT during hepatic arteriography (CTHA) and CT during arterial portography (CTAP), have enabled the detailed hemodynamic evaluation of small hepatic nodules.

Recently, liver-specific contrast agents such as superparamagnetic iron oxide particles (SPIO), which are taken up by Kupffer cells, and Gd-EOB-DTPA, which is taken up by hepatocytes, are frequently used in MRI for early diagnosis of HCC. Gd-EOB-DTPA is a superb agent because it provides dynamic and liver-specific MR images.[44–46] This contrast agent is highly liver specific; approximately 50% of the injected dose is taken up by functioning hepatocytes and is excreted in bile, compared with just 3–5% for gadobenate dimeglumine.[46] Early studies comparing Gd-EOB-DTPA-enhanced dynamic MRI with dynamic MDCT showed that Gd-EOB-DTPA-enhanced MRI is significantly more accurate, sensitive and specific than dynamic MDCT for the diagnosis of HCC in patients with cirrhosis.[47,48] In addition, Gd-EOB-DTPA-enhanced MRI has a high detection rate for early stage HCC nodules that are not enhanced in dynamic studies. However, although the differentiation of early HCC from dysplastic nodule by hepatobiliary phase images of Gd-EOB-DTPA MRI is promising, more data are still needed.

Informative statement 2. Gd-EOB-DTPA-enhanced MRI provides dynamic and hepatocyte-specific images and is more accurate than dynamic MDCT or SPIO-MRI for the detection and characterization of small HCC, including early HCC.

ABLATION THERAPIES

IMAGE-GUIDED PERCUTANEOUS ablation therapies have long played important roles in the treatment of HCC. Percutaneous ethanol injection has been used for unresectable, small HCC since the early 1980s[49–51] and offers us the potential to treat HCC using non-surgical means. Percutaneous microwave coagulation therapy became popular in Japan in the late 1990s.[52] However, since the introduction of radiofrequency ablation (RFA) into clinical practice around 1999, there has been a dramatic shift from ethanol injection or microwave coagulation to RFA.[53] RFA for HCC has been covered by public health insurance since April 2004 in Japan. Although more than 1700 institutions have experienced RFA in Japan, RFA is estimated to be performed routinely in approximately 1000 institutions throughout Japan at the present.

Radiofrequency ablation often seems to be performed with less than adequate treatment planning or preparation compared with surgical resection. RFA appears to be a very simple procedure. Thus, some physicians may perform RFA without adequate training or experience. In addition, RFA does not require expensive equipment. Thus, several hospitals have introduced RFA into clinical practice without high-performance US and CT.

However, RFA is indicated for malignant tumors and inadequate outcome should be avoided. Thus, only physicians with sufficient experience and appropriate skill should perform the procedure. Furthermore, only well-equipped hospitals should perform RFA because the outcomes of RFA are strongly influenced by the performance of the CT and US equipment available at each institution. It is crucial to offer consistent outcomes for RFA at all institutions and for all operators.

More importantly, before commencing RFA, the tumors should be evaluated by US, contrast-enhanced CT or MRI to determine tumor size, shape, number, presence or absence of extracapsular invasion, presence or absence of satellite lesions, location relative to Glisson's capsule or other critical structures, and to determine the optimal route to approach the tumor.

Within 1–3 days after RFA, contrast-enhanced CT or MRI is essential to objectively assess the treatment response. If the tumor is completely ablated with a sufficient safety margin, the treatment may be considered complete. However, if there is any residual cancer tissue or an insufficient safety margin, RFA should be repeated until complete tumor destruction with a sufficient ablative margin is achieved. The following recommendation was supported by 94% of the experts.

Recommendation 8. Imaging should be performed within 1–3 days after RFA to evaluate treatment response. It is essential that RFA is repeated until entire tumor destruction with a sufficient ablative margin is achieved.

For accurate tumor evaluation, CT and MRI performed before and after RFA should be done using a thin slice interval. The following recommendation was agreed by 94% of the experts.

Recommendation 9. CT and MRI before and after RFA should be done using a slice thickness and interval of 5 mm or less; slice thickness and interval of 10 mm or more is not adequate.

A histopathological study has revealed that, in cases with incomplete necrosis, viable cancer tissue remains around the main tumor, in portions isolated by the septa, or along the edge of the tumor after ablation therapies.[54] There may also be extranodular growth, satellite nodules or portal vein invasion, which cannot be detected by imaging modalities.[55,56] The incidence of satellite nodules and portal vein invasion is associated with the gross appearance of the main tumor. The single nodular type with extranodular growth and the confluent multinodular type both show satellite lesions more frequently than early HCC (vaguely nodular-type HCC showing preservation of the preexisting liver structure) and the single nodular type. Thus, it is important to determine the gross appearance of the tumor by imaging. It is also essential to ablate beyond the tumor border to achieve complete tumor necrosis and prevent local tumor progression (ablative margin or safety margin). Sonazoid-enhanced US in the Kupffer phase is useful to determine the gross tumor appearance.[57] The width of the safety margin should be modified based on the gross appearance of the tumor, the number of tumors, the initial tumor or recurrent tumor, the duration of time between the previous treatment and recurrence in recurrent cases, tumor location (particularly in relation to the Glisson's capsule), liver function, comorbid conditions and the patient's age.

Furthermore, the accuracy of contrast-enhanced CT or MRI for evaluating the extent of necrosis is limited because of the partial volume effect.[58] The following recommendation was agreed by 94% of the experts.

Recommendation 10. A safety margin completely surrounding the lesion should be achieved in cases in which RFA is performed as a locally curative treatment (level 6, grade A).

Ablation therapies, including RFA, are widely accepted as the preferred treatment for unresectable small HCC. On the other hand, it has been strongly debated whether ablation therapies can provide a treatment option for resectable HCC since the introduction of ethanol injection. Although the number of patients treated by RFA has steadily increased, the Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan recommends surgery rather than ablation.[1] Their scientific statement recommends the following: "(i) if only one tumor is present, liver resection is recommended irrespective of the diameter of the tumor. Ablation therapy may also be selected if the severity of liver damage is class B and the diameter of the tumor is no more than 2 cm; (ii) if two to three tumors with diameters of no more than 3 cm are present, liver resection or local ablation therapy is recommended". This scientific statement is based on a cohort study of patients at clinical stage I (fair liver function), with a solitary tumor of less than 2 cm in diameter, patients across all clinical stages with a solitary tumor greater than 2 cm, and patients of clinical stage II (moderately impaired liver function) with two tumors greater than 2 cm. In that cohort, those who underwent hepatic resection showed higher survival rates than those who received non-surgical interventions.[59]

However, those findings were not based on randomized controlled trials (RCT) and the different survival rates may be subject to bias arising from the background characteristics of the patients. Of note, the hepatic resection group was younger than the ethanol injection group. Furthermore, even among patients at clinical stage I, most patients with normal liver or chronic hepatitis seemed to undergo resection while many with cirrhosis seemed to receive ethanol injection. This might reduce the recurrence rate because of multicentric carcinogenesis and less frequent development of liver failure in the resection group. Moreover, the trend that patients with severe comorbid conditions, such as cardiopulmonary diseases and others, received ethanol injection rather than resection might explain some of the disparity in survival. By contrast, in one RCT the recurrence and survival rates were comparable between surgical resection and ethanol injection.[60] In addition, other non-randomized trials have reported similar or better overall survival after ethanol injection than after resection.[61–63]

In addition, the findings described above only compared resection with ethanol injection. For example, our RCT showed that RFA had higher survival and lower recurrence rates than ethanol injection while the adverse events were similar between the two therapies.[64] Similarly, other RCT have shown that RFA is superior to ethanol injection in terms of treatment outcomes for HCC.[65–67] Another RCT has shown that there was no difference between resection and RFA in terms of overall and disease-free survival, while post-treatment complications occurred more frequently and were more severe after surgery.[68]

Hence, it is inappropriate to generalize the findings for ethanol injection to other percutaneous local ablation therapies such as RFA, and it should not be concluded that hepatectomy is recommended over percutaneous local ablation.

Further trials are needed to determine whether RFA can become a preferred treatment for "resectable HCC". In such trials, the primary end-point should be overall survival.[69] The AASLD practice guideline clearly states the following: "although a treatment might be less active against the tumor than another treatment and thus result in a higher recurrence rate after initial treatment, the overall survival might not differ or may even be better".[3]

Recurrence-free survival can be misleading and should not be considered as a surrogate end-point for overall survival. In HCC, unlike other solid tumors, recurrence can still be treated, and the first recurrence does not cause death in most cases. Furthermore, surgery theoretically offers better disease-free survival than RFA because it removes larger liver tissue. However, the better curability associated with hepatectomy could be cancelled out by the surgical invasion and the potential deterioration in liver function. The following recommendation was agreed by 84% of the experts.

Recommendation 11. Overall survival should be the end-point to compare results between ablation and hepatectomy.

SURGICAL TREATMENT: RESECTION AND TRANSPLANTATION

A NATIONWIDE SURVEY by the Japanese Liver Transplantation Society found that a total of 4725 cases of living-donor liver transplantations (LDLT) were reported in Japan as of the end of 2007 since its initiation in 1989. By contrast, during the same period, only 46 cases of deceased-donor liver transplantation (DDLT) were documented. At the end of 2006, 778 patients with HCC had undergone an LDLT in Japan.[70] Because of the severe shortage of brain-dead donors and the extremely long waiting time for such organs, DDLT is not a realistic treatment option for HCC patients in Japan.

Algorithm for the treatment of patients with HCC in Japan

Figure 1 shows the treatment algorithm presented in the Japanese evidence-based guideline for the diagnosis and treatment of HCC.[1] Liver transplantation is recommended for HCC patients with liver damage C (similar to Child–Pugh C), but only when the patients meet the Milan criteria proposed by Mazzaferro.[71] In the revised version of the guidelines published at the end of 2009, an age limit of 65 years was added to the criteria for liver transplantation.

Can the indications for liver transplantation be expanded beyond the Milan criteria?

Until the mid-1990s, HCC was considered a contraindication for liver transplantation because of the extremely poor outcome of early series.[72,73] This pessimistic view was reversed by Mazzaferro *et al.* who conducted a prospective cohort study to identify subgroups of HCC patients who may benefit from DDLT. They presented clear eligibility criteria for transplantation, as follows: the presence of a solitary tumor of 5 cm or less in diameter and no more than three tumor nodules, each 3 cm or less in diameter, in patients with multiple tumors, and the absence of vascular invasion or extrahepatic disease. In their series, the overall and recurrence-free survival rates

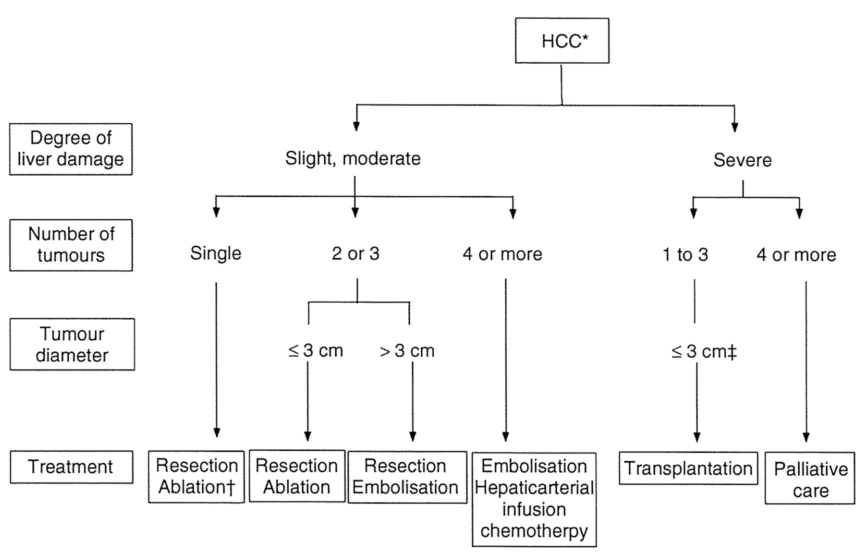

Figure 1 Japanese evidence-based treatment algorithm. HCC, hepatocellular carcinoma.

at 4 years for 35 patients who met the above criteria were as high as 85% and 92%, respectively. These criteria were named the "Milan criteria" and became the gold standard for patient selection for liver transplantation. The Milan criteria were also validated for LDLT using data from a nationwide survey in Japan.[74] Since 2004, LDLT for HCC has been covered by social medical insurance in Japan when the preoperative imaging studies indicate that the patient's condition meets the Milan criteria.

The Milan criteria have encouraged transplant surgeons to increase the number of liver transplantations performed in HCC patients, and the United Network for Organ Sharing (UNOS) has incorporated the Milan criteria as conditions for listing HCC patients. During the extensive application of liver transplantation for HCC, transplant surgeons have noticed that the outcomes of some patients who slightly exceeded the Milan criteria were also favorable. To expand the indications for liver transplantation, several groups from different countries have challenged these restrictive criteria (Table 1).[75–79] Yao *et al.* at the University of California at San Francisco (UCSF) proposed criteria consisting of a single tumor of less than 6.5 cm in diameter or two lesions of less than 4.5 cm in diameter, with a total tumor diameter of less than 8 cm; these criteria are known as the "UCSF criteria".[76] The utility of the UCSF criteria was subsequently confirmed by the University of California at Los Angeles.[80]

Regarding the indications for LDLT in HCC patients, several proposals from Asian centers have extended the eligibility criteria (Table 1). For example, a group at the University of Tokyo proposed the "5-5 rule", which allows up to five nodules with a maximum diameter of 5 cm.[77] The 3-year recurrence-free rate of 72 patients who met the Tokyo 5-5 rule was as high as 94%, which was comparable with that of patients within the Milan criteria. A group at the University of Kyoto subsequently proposed a further expansion of the criteria, increasing the upper limit of the number of tumors to 10.[79]

Because LDLT is not governed by an organ-sharing system, some authors have argued that the indications for LDLT in patients with HCC could be further extended. One might say that "If the patient (recipient) and his/her family (donor) strongly wish to undergo LDLT even in cases of very advanced HCC with full knowledge of potential for poor outcomes, there is no reason for transplant surgeons to reject their wish. The family members may accept the poor outcome after LDLT without doing any harm to the community." However, we should always remember that, while LDLT does not require a donor from the community, it does require extensive medical resources, including a large workload for surgeons and other hospital staff members, medical supplies, drugs and blood products. Furthermore, the premature death of the recipient is well known to cause severe emotional trauma to the living donors and their family members.

Based on an answer-pad vote at the consensus meeting of 45th JSH congress, 84% of the experts supported keeping the Milan criteria for DDLT, but only 25% supported keeping these criteria for LDLT. Although any expansion of the criteria should be modest, no consensus exists as to the extent to which the criteria can be extended.

Recommendation 12. For DDLT, the HCC status of the recipients should meet the Milan criteria.

Recommendation 13. For LDLT, the HCC status of the recipients does not need to be within the Milan criteria.

Which is better, liver resection or transplantation, for HCC patients who are eligible for either treatment?

Because liver transplantation replaces the whole liver, removing the highly carcinogenic background and the cirrhotic liver can avoid multicentric or de novo cancer recurrence.[80] In contrast, liver resection is associated with a very high risk of tumor recurrence. Even after curative liver resection in patients with good liver function, the 5-year recurrence rate is as high as 70–79%.[80] Roughly half of these recurrences are multicentric or de novo recurrences. For this reason, liver transplantation

Table 1 Summary of proposed criteria for indication of liver transplantation for HCC

Criteria	Conditions	References
Milan criteria	Up to 5 cm for single nodule or up to 3 nodules with a maximum diameter of 3 cm	70
UCSF criteria	Up to 6.5 cm for single nodule or up to 3 nodules with a maximum diameter of 4.5 cm	76
Tokyo 5-5 rule	Up to 5 nodules with a maximum diameter of 5 cm	77
Asan criteria	Up to 6 nodules with a maximum diameter of 5 cm	78
Kyoto criteria	Up to 10 nodules with a maximum diameter of 5 cm and PIVKA-II <400 mAU/mL	79
Up-to-seven criteria	Up to seven as the sum of the size of the largest tumor [in cm] and the number of tumors	75

may be recommended for HCC patients with good liver function who are also eligible for liver resection, as in Western countries.

Another issue is the operative risk of the two treatments. In Japan, the operative mortality rates for LDLT and liver resection are estimated to be 4–10% and 0.8–1.2%, respectively. This striking difference in operative mortality rates might preclude LDLT for patients with good liver function.

Using two databases at the National Cancer Center Hospital in Japan and the University of Pittsburgh Medical Center in the USA, Yamamoto *et al.* compared the long-term outcome of liver resection and transplantation in cirrhotic patients with HCC.[81] The overall survival of Child–Pugh A patients who underwent liver resection was similar to that of the patients without vascular invasion or lymph node metastases who underwent transplantation (most cases with Child-Pugh C). The recurrence rate was significantly lower in the transplantation group. For cases in which either treatment can be performed, the outcome of liver transplantation might be better than that of hepatic resection, particularly in cases with only a few small lesions.[81,82] In cases with large lesions, superior outcomes are achieved with hepatectomy. Because some patients may withdraw from treatment during the pre-transplantation period,[83] the outcomes with resection are better than those for liver transplantation based on intention-to-treat analysis of patients who meet the criteria for resection.

The evidence-based guideline[1] recommends the following: considering the occurrence of dropouts during the pre-transplantation period, the outcome of resection is better than that of liver transplantation among patients who meet the criteria for resection (grade B).

According to a question and answer-analyzer vote at this consensus meeting, 83% of the HCC experts selected LDLT for Child–Pugh C patients meeting the Milan criteria, whereas only 15–19% of the audience selected LDLT for Child–Pugh A or B patients.

Recommendation 14. LDLT should not be recommended for HCC patients with Child–Pugh A or B liver function.

PALLIATIVE TREATMENTS: TRANSARTERIAL CHEMOEMBOLIZATION AND CHEMOTHERAPY

PALLIATIVE TREATMENTS FOR HCC include transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC) and systemic chemotherapy.

Transarterial embolization/TACE

Transcatheter arterial embolization (TAE)/TACE is one of the treatment options to treat hypervascular HCC. The theoretical basis of embolization is to induce ischemic tumor necrosis by acute arterial occlusion in hypervascular classical HCC. Embolization may be done alone (TAE) or in combination (TACE) with antineoplastic agents such as doxorubicin, epirubicin or cisplatin and a contrast agent, lipiodol. TACE is more effective and, thus, more widely used than embolization alone.

The technique for TACE is well established. The subsegmental artery or a peripheral artery near the target tumor is selected by a micro-catheter technique, followed by selective injection of antineoplastic agents mixed with lipiodol (lipiodol emulsion). The artery is then selectively obstructed with gelatin sponge particles. For bi-lobular multiple HCC with moderately impaired hepatic function (Child–Pugh B), TACE might need to be performed twice with an interval of several weeks to avoid hepatic decompensation.

The survival benefit of TAE/TACE was controversial until the publication of two RCT in 2002, which showed that TACE improved the survival of selected patients (Child–Pugh A with no vascular invasion) compared with conservative treatment.[84,85] A subsequent meta-analysis of seven RCT comparing TAE/TACE as a primary treatment for HCC in comparison with conservative management and/or suboptimal therapies showed a significant improvement in the 2-year survival, favoring TAE/TACE (odds ratio [OR] = 0.53; 95% confidence interval [CI] = 0.32–0.89, $P = 0.017$).[86,87]

According to the Nationwide Follow-up Survey of Primary Liver Cancer in Japan, one-third of all patients with primary HCC were treated by TAE/TACE (Fig. 2). Thus, TAE/TACE, hepatic resection and local ablation therapy are commonly used in Japan. TAE/TACE is the most widely used treatment for unresectable HCC.

In two Japanese treatment guidelines for HCC, evidence-based[1,30,88] and consensus-based guidelines,[89] TACE is recommended for patients with the severity of the liver damage categorized into A or B, in whom there are two or three tumors with a diameter greater than 3 cm, or four or more tumors.

In early stages of HCC, TACE is not indicated as first-line treatment because the outcome review of the Nationwide Follow-up Survey by the LCSGJ reported worse results for TACE than surgery or percutaneous ablation. This survey revealed that the 5-year survival rates for resection, ablation and TACE were 59.2%,

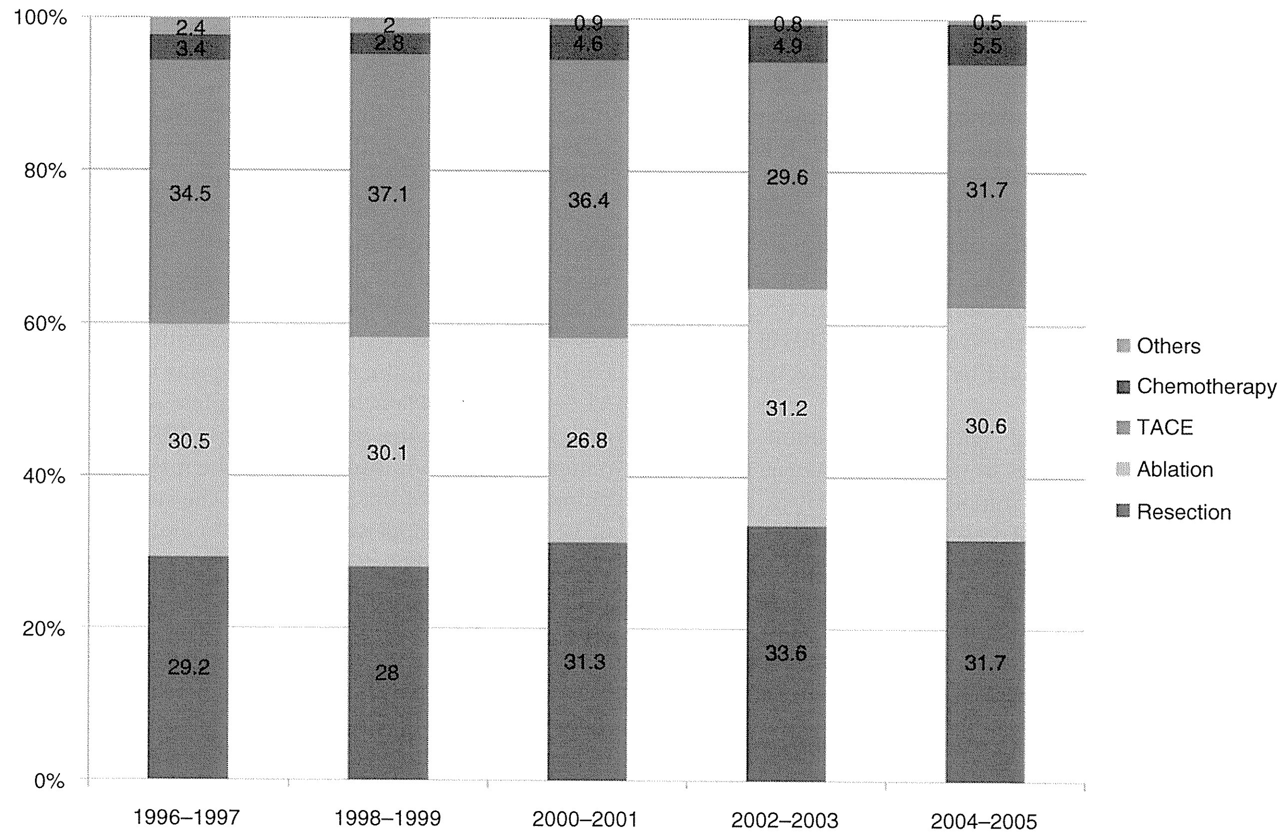

Figure 2 Change of treatment method for hepatocellular carcinoma in Japan. TACE, transcatheter arterial chemoembolization.

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 [PEI]) 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;

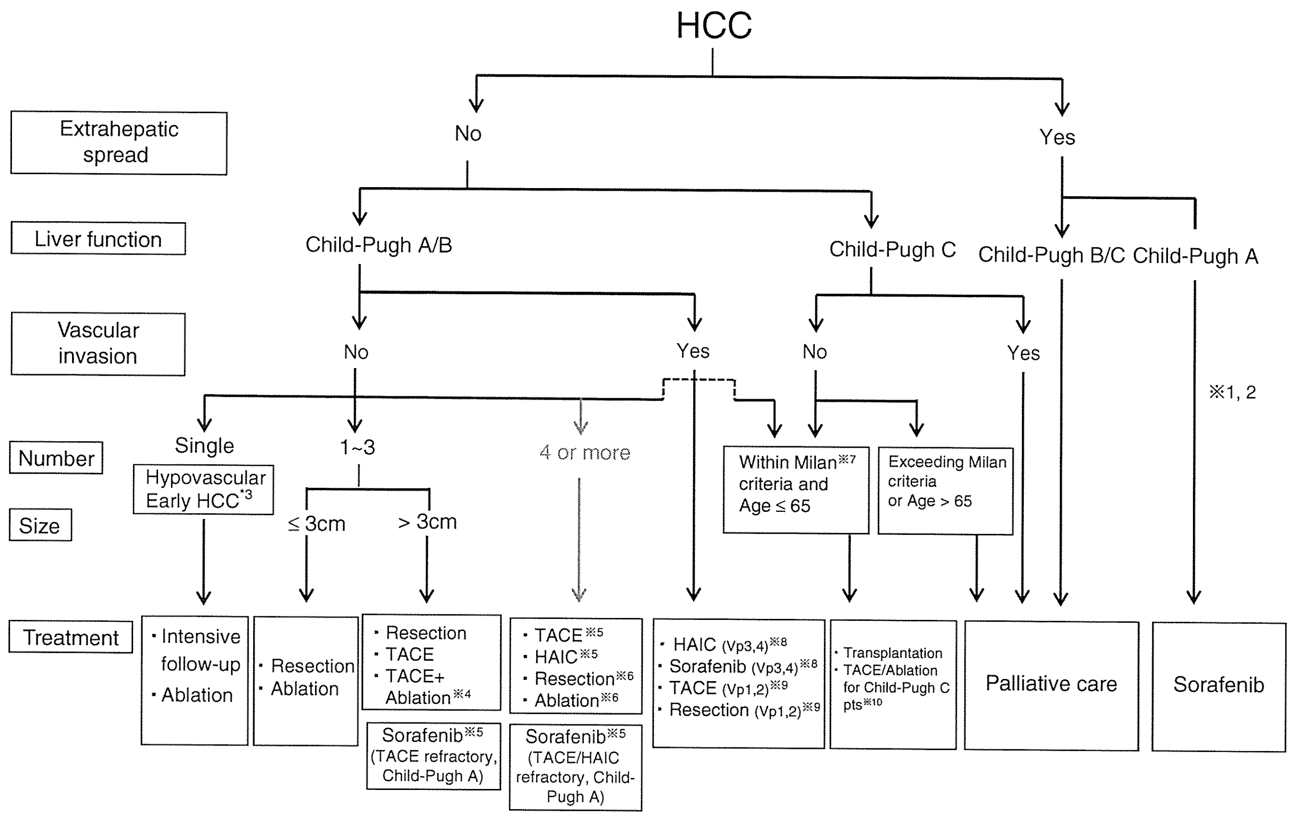

Figure 3 Consensus-based treatment algorithm for hepatocellular carcinoma proposed by the Japan Society of Hepatology (JSH) revised in 2010. (1) Treatment should be performed as if extrahepatic spread is negative, when extrahepatic spread is not regarded as a prognostic factor. (2) Sorafenib is the first 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.