Clinical Practice Guidelines for Liver Cancer

List of Clinical Questions and Recommendations

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Chapter	CQ No.	Clinical Question
1. Diagnosis and Surveillance	1	Is surveillance recommended?
	2	What patient groups are targeted and what methods are used in surveillance?
	3	What tumor markers are useful for diagnosising HCC?
	4	Is measuring the levels of 2 or more tumor markers useful for diagnosing HCC?
	5	Are tumor markers effective indicators of treatment response in patients with HCC?
	6	What imaging modalities help to accurately diagnose typical HCC in high-risk patients?
	7	What size (cm) of liver nodules showing an atypical enhancement pattern on dynamic CT or dynamic MRI warrants further examination?
	8	What imaging modalities help to accurately diagnose early-stage HCC in patients with cirrhosis?
	9	What imaging modalities effectively detect liver cancer in patients with decreased kidney or liver function?
	10	Are head MRI, thoracic CT, bone scintigraphy, and FDG-PET required for staging HCC?
2. Treatment Algorithm	11	What treatment modalities are recommended for solitary HCC?
	12	What treatment modalities are recommended for 2 or 3 HCCs?
	13	What treatment modalities are recommended for 4 or more HCCs?
	14	What treatment modalities are recommended for HCC in patients with liver damage grade C (Child-Pugh C liver function)?
	15-1	Is radiation therapy effective against bone and brain metastasis from HCC?
	15-2	What treatment modalities are effective against extrahepatic metastasis (e.g., lung, adrenal, and lymph node metastasis and dissemination) from HCC?
	16	What treatment modalities are effective against HCC accompanied by vascular invasion?
3. Prevention	17	What treatment modalities are recommended as preventive measures against liver cancer associated with chronic hepatitis B liver disease?
	18	What treatment modalities are recommended as preventive measures against liver cancer associated with chronic hepatitis C liver disease?

Recommendations	Strength	Page
Regular screening enables the early detection and curative treatment of HCC, likely improving prognosis. Therefore, surveillance is recommended.	Strong	53
Patients with chronic hepatitis B or C liver disease or nonviral cirrhosis should undergo regular HCC surveillance consisting of abdominal US as the primary measure and tumor marker testing every 3-6 months. Additionally, dynamic CT or dynamic MRI should be performed in extremely high-risk patients such as those with cirrhosis.	Strong	55
It is recommended to measure AFP, PIVKA-II, and AFP-L3 fraction awhen diagnosing HCC.	Strong	58
Measuring the levels of 2 or more tumor markers is recommended in the diagnosis of small HCC.	Strong	62
Post-treatment tumor marker levels are effective indicators of clinical response in patients with high tumor marker levels prior to treatment.	Strong	65
Dynamic CT, dynamic MRI, and contrast-enhanced US are recommended when diagnosing typical HCC.	Strong	67
Further examination is recommended for hypervascular lesions ≥ 1 cm.	Strong	74
Gd-EOB-DTPA-enhanced MRI has a high detection rate for early-stage HCC.	Strong	78
Contrast-enhanced CT or MRI may be performed in patients with decreased kidney function in accordance with the following criteria: Gd-EOB-DTPA-enhanced MRI with estimated glomerular filtration rate (eGFR) 30–60 mL/min/1.73 m^2; SPIO-enhanced MRA with eGFR < 30 mL/min/1.73 m^2; and SPIO-enhanced MRI or dynamic CT when undergoing dialysis.	Weak	83
Noncontrast-enhanced MRI (including diffusion-weighted MRI) and US (including Sonazoid®-enhanced US) are safe and effective in patients with kidney failure for whom contrast-enhanced CT or MRI is contraindicated.	Weak	
(Only a few studies have investigated the effect of contrast-enhanced CT or MRI and appropriate contrast agents for use in patients with decreased liver function regarded as Child-Pugh C liver function.)	Supplementary note	
Thoracic CT and FDG-PET are recommended for HCC patients with risk factors for extrahepatic metastasis.	Weak	87
Bone scintigraphy may be performed when the patient's condition is unfavorable for FDG-PET.	Weak	
Head CT or MRI may be used as a screening modality for brain metastasis in HCC patients with neurological findings or lung metastasis.	Weak	
Hepatectomy is recommended as first-line therapy. For HCC ≤ 3 cm, percutaneous ablation is recommended as second-line therapy.	Strong	96
Hepatectomy or percutaneous ablation is recommended for HCCs ≤ 3 cm. For HCCs > 3 cm, hepatectomy is recommended as first-line therapy and embolization as second-line therapy.	Strong	98
Embolization is recommended as first-line therapy. TAI or molecular-targeted therapy is recommended as second-line therapy.	Strong	100

Liver transplantation is recommended for HCC in patients with liver damage grade C (Child-Pugh C liver function) provided that the pathological condition is within the Milan criteria.	Strong	102
Radiation therapy is recommended for the management of painful bone metastasis.	Strong	105
Whole brain radiotherapy, stereotactic body radiotherapy, or combination therapy is recommended for brain metastasis.	Strong	
Molecular-targeted therapy is the standard treatment for advanced HCC accompanied by extrahepatic metastasis.	Strong	108
Locoregional therapies, including resection, may be selected for lung, adrenal, and lymph node metastasis and dissemination in HCC patients with no other intrahepatic lesions or well-managed intrahepatic lesions.	Weak	
Embolization, hepatectomy, TAI, and molecular-targeted therapy are recommended. Optimal treatment is selected considering each patient's pathological condition.	Strong	111
Nucleos(t)ide analogues are recommended as a preventive measure against liver cancer in patients with type B hepatitis positive for hepatitis B virus DNA and cirrhosis.	Strong	117
Antiviral therapy for eradication of hepatitis C virus is recommended as a preventive measure against liver cancer in patients with hepatitis C and compensated cirrhosis type C.	Strong	121

Chapter	CQ No.	Clinical Question
3. Prevention	19	What preventive measures are recommended for liver cancer associated with viral or nonviral chronic liver disease?
4. Surgery	20	Which patients are eligible for hepatectomy?
	21	What tests effectively evaluate liver function prior to hepatectomy?
	22	What procedures are considered safe and reasonable for liver resection?
	23	What are the indications for laparoscopic hepatectomy?
	24	What factors effectively predict prognosis after hepatectomy?
	25	Do resection margins affect prognosis?
	26	Does hepatic vascular occlusion or lowering of the central venous pressure reduce blood loss during hepatectomy?
	27	Is routine abdominal drainage necessary after hepatectomy?
	28	Is neoadjuvant therapy necessary in hepatectomy?
	29	What are the eligibility criteria for liver transplantation in patients with HCC?
	30	Does downstaging of HCC prior to liver transplantation improve prognosis after transplantation?
5. Percutaneous Ablation	31	Which patients are eligible for percutaneous ablation?
	32	How should suitable ablation therapy be chosen?
	33	Can the combination of percutaneous ablation and TACE improve the survival of HCC patients?
	34	Is contrast-enhanced US or fusion imaging useful for image-guided percutaneous ablation?
	35	What imaging modalities are useful for assessing treatment response to percutaneous ablation?
	36	What factors predict treatment response to percutaneous ablation?
6. Transcatheter Arterial Chemoembolization (TACE) and Transcatheter Arterial Embolization (TAC)	37	Which patients are eligible for TACE or TAE?
	38	What is the most appropriate method for selecting embolic agents and anticancer drugs for TACE or TAE?
	39	What factors determine the timing of re-embolization?
	40	What imaging modalities are useful for assessing treatment response to TACE?
	41	Is it appropriate to combine embolization and molecular-targeted therapy?
	42	What are the clinical features of TACE failure?

Recommendations	Strength	Page
Coffee consumption may decrease the risk of liver cancer.	Weak	125
Consumption of polyunsaturated fatty acids (PUFAs) may decrease the risk of HCC.	Weak	
It is desirable to perform hepatectomy in patients with up to 3 tumors located solely in the liver, regardless of tumor size. Tumor invasion up to the first branches of the portal vein (right and left portal veins) may be an indication for surgery.	Strong	131
It is recommended that the indocyanine green retention rate at 15 min (ICGR15) be measured in addition to regular liver function tests. It is appropriate to decide the indications for surgery based on the test results and estimated tumor resection size.	Strong	134
Anatomic resection of a small area or partial hepatectomy as cytoreductive surgery (especially in patients with impaired liver function) is recommended for small HCCs (≤ 5 cm); extended resection involving 2 or more segments (including hemi-hepatectomy) is recommended for large HCCs.	Strong	138
Solitary HCC ≤ 5 cm at the periphery of the anterior section (S2, 3, 4, 5, 6), where it is possible to perform partial hepatectomy and lateral segmentectomy, is a good indication for laparoscopic hepatectomy.	Strong	143
The main prognostic factors after hepatectomy are tumor size and number, vascular invasion, and liver function.	N/A	145
In hepatectomy for HCC, resection margins may be kept at minimum.	Strong	148
Hepatic vascular occlusion minimizes blood loss during hepatectomy.	Strong	150
Lowering of the central venous pressure minimizes blood loss during hepatectomy.	Strong	
Abdominal drainage is not always necessary after elective hepatectomy.	Strong	153
No therapy is recommended as neoadjuvant therapy aimed at improving prognosis after hepatectomy for HCC.	Weak	155
Liver transplantation should be considered for patients with HCC within the Milan criteria accompanied by decompensated cirrhosis.	Strong	157
There is insufficient scientific evidence to support that downstaging HCC prior to liver transplantation improves the prognosis of transplantation.	Weak	161
Percutaneous ablation is indicated for patients with Child-Pugh A or B liver function and up to 3 tumors, and tumor diameters ≤ 3 cm.	Strong	165
RFA is recommended as percutaneous ablation.	Strong	169
RFA and PEI with artificial ascites are options for patients who are at higher risk of gastrointestinal perforation.	Weak	
It is expected that combination therapy with percutaneous ablation and TACE can improve survival in patients with relatively large tumors.	Weak	172

Contrast-enhanced US and fusion imaging are useful for image-guided percutaneous ablation in patients with HCCs that are difficult to visualize on B-mode US.	Weak	175
Dynamic CT or dynamic MRI is recommended when assessing treatment response to percutaneous ablation.	Strong	178
The factors predicting treatment response to percutaneous ablation are tumor diameter, tumor marker levels, and sufficient ablative margins.	N/A	181
TACE or TAE is recommended for patients with BCLC stage B (intermediate stage; PS 0, Child-Pugh A/B, and 4 or more lesions) hypervascular HCCs that are inoperable and are not indications for percutaneous ablation.	Strong	186
TACE or TAE may be considered for patients with BCLC stage C (advanced stage) and inoperable hypervascular HCC accompanied by portal vein tumor thrombus.	Weak	
Conventional TACE (cTACE) with Lipiodol® and porous gelatin particles (Gelpart®, Astellas Pharma Inc., Japan) or TACE with drug-eluting beads is recommended.	Strong	190
No anticancer drug is recommended specifically for use in TACE or TAE	Weak	
Local recurrence of hypervascular HCC after embolization therapy and the occurrence of second primary hypervascular HCC in another part of the liver are the factors determining the timing of re-embolization.	Strong	197
Dynamic CT and dynamic MRI are recommended as useful imaging modalities for assessing treatment response to TACE.	Strong	200
Combination therapy with embolization and molecular-targeted drugs is not recommended because of insufficient scientific evidence to verify that the combination therapy improves survival.	Weak	204
HCC is empirically considered to be unresponsive to TACE when any of the following 3 conditions are met: (1) insufficient improvement of the primary lesion or the appearance of a new intrahepatic lesion after 2 TACE sessions, (2) vascular invasion or extrahepatic metastasis, or (3) persistent elevated levels of tumor markers.	Weak	207

Chapter	CQ No.	Clinical Question
7. Drug Therapy	43	Is molecular-targeted therapy recommended for unresectable advanced HCC?
	44	Is HAIC recommended for unresectable advanced HCC?
	45	What factors predict treatment response to drug therapy?
	46	How should treatment response to drug therapy be assessed?
	47	How should the side effects of drug therapy be managed?
8. Radiation therapy	48	Is stereotactic body radiotherapy recommended for HCC?
	49	Does particle therapy (proton therapy and heavy particle [carbon ion] therapy) effectively treat HCC?
	50	When is 3D conformal radiotherapy recommended for HCC?
9. Post-treatment Surveillance and Prevention and Treatment of Recurrent Cancer	51	How should patients be followed up after hepatectomy and percutaneous ablation?
	52	What methods are effective for preventing recurrence after hepatectomy and percutaneous ablation?
	53	What measures are effective for preventing recurrence after liver transplantation?
	54	What treatment modalities are effective against recurrence after hepatectomy and percutaneous ablation?
	55	What treatment modalities are effective against recurrence after liver transplantation?

Recommendations	Strength	Page
Sorafenib or lenvatinib therapy is recommended as first-line therapy for unresectable advanced HCCs that are not indicated for surgical resection, liver transplantation, locoregional therapy, or TACE in patients with Child-Pugh A liver function, good functional reserve, and good PS. * As of September 2017, lenvatinib is not approved for the treatment of HCC in Japan.	Strong	213
Regorafenib therapy is recommended as second-line therapy for patients with Child-Pugh A liver function who, during sorafenib therapy, show HCC disease progression on imaging study and tolerancy for sorafenib	Strong	
HAIC may be performed for advanced HCC accompanied by intrahepatic lesions, which are not indications for surgical resection, liver transplantation, locoregional therapy, or TACE.	Weak	217
There is insufficient scientific evidence that some factors effectively predict treatment response to drug therapy.	N/A	219
Treatment response to molecular-targeted therapy should be assessed using response evaluation criteria that reflect intratumoral blood flow, because accurate assessment of areas of necrosis and viable tumor is essential.	Strong	221
When using cytotoxic anticancer drugs, adequate attention must be paid to hematological toxicity because of a high incidence of pancytopenia. Because each drug used in molecular-targeted therapy is associated with specific severe side effects, it is important to follow up patients carefully and respond to adverse events properly, including reducing drug dosage and prescribing drug holidays.	Strong	223
Stereotactic body radiotherapy may be performed in HCCs that are not indications for other types of locoregional therapies and for recurrent HCCs after various locoregional therapies, including HCC unresponsive to TACE.	Weak	233
Particle therapy (proton therapy and heavy particle [carbon ion] therapy) may be performed for HCCs that are not indicated for other types of locoregional therapies.	Weak	237
Three-dimensional CRT may be performed when stereotactic body radiotherapy and particle therapy are difficult to perform in patients who are not candidates for other standard treatments due to portal vein tumor thrombus, unresectable HCC, or internal complications.	Weak	242
As in the surveillance of extremely high-risk patients at onset, follow-up with tumor marker tests and imaging-based screening are recommended.	Strong	249
In patients with HCC associated with viral hepatitis, antiviral therapy may effectively suppress recurrence and improve survival after hepatectomy or percutaneous ablation.	Weak	252
After liver transplantation, management with mTOR inhibitors may suppress the recurrence of HCC.	Weak	257
The treatment algorithm used for primary HCC is also used for the treatment of recurrent HCC after hepatectomy or percutaneous ablation.	Strong	261

Recurrent HCC after transplantation may be resected if resectable or treated with molecular-targeted drugs if unresectable.	Weak	266