

Clinical Practice Guidelines for Hepatocellular Carcinoma, List of Clinical Questions/Recommendations

Chapter	Section	CQ No.	Clinical Question	Recommendation	Grade
Chapter 1 Prevention	1	Interferon Therapy			
		1	Does interferon therapy chronic hepatitis C infection effectively prevent HCC?	Antiviral therapy, mainly with interferon, is recommended to prevent carcinogenesis in patients with chronic hepatitis C or compensated hepatitis C-related cirrhosis.	B
	2	Liver Support Therapy			
		2	Does liver support therapy effectively prevent HCC?	Intravenous administration of glycyrrhizin is recommended to prevent cancer in patients with chronic hepatitis C. In some patients, phlebotomy and an iron-limited diet can effectively prevent cancer in patients with active chronic hepatitis C and advanced fibrosis who are difficult to treat with antiviral therapy or are contraindicated for the same.	B C1
		3	Does antiviral therapy against chronic hepatitis B infection effectively prevent HCC?	Nucleoside analogs are recommended to prevent cancer in patients with HBV-DNA-positive, compensated HBV cirrhosis.	A
				Interferon therapy is recommended in some patients with chronic hepatitis B.	C1
		1	Surveillance		
		4	Who are eligible candidates for surveillance?	The risk factors for HCC include liver cirrhosis, chronic hepatitis C, chronic hepatitis B, male gender, older age, alcohol consumption, smoking, obesity, and diabetes mellitus. Of these risk factors, it is recommended that patients with chronic hepatitis C, chronic hepatitis B, or nonviral cirrhosis be screened at regular intervals for HCC.	B
		5	Does surveillance improve prognosis?	Regular screening for HCC can lead to early detection and curative treatment and may improve prognosis.	B
		6	What methods are used in surveillance?	HCC screening should primarily include ultrasound examination with tumor marker testing, and dynamic CT or dynamic MRI can be concurrently used for extremely high-risk patients such as those with cirrhosis.	B
				Regular screening every 3–6 months, primarily using ultrasound examination and tumor marker testing in combination with dynamic CT or dynamic MRI, increases HCC detectability at the solitary, small nodular stage .	B
		7	What size (cm) of atypical liver nodules using dynamic CT or dynamic MRI should be further examined?	It is recommended that the lesions visualized as high-attenuation areas in the arterial phase and measuring ≥ 1 cm be examined carefully.	B
2		Tumor Markers			

	8	Is it useful to measure two or more tumor markers for diagnosing HCC?	It is recommended to measure two or more tumor markers when diagnosing HCC.	A
	9	Is tumor marker measurement an effective post-treatment indicator for HCC?	Measurement of post-treatment tumor marker levels in patients with elevated tumor marker levels before treatment is an effective indicator of treatment outcome.	B
3 Diagnostic Imaging				
	10	What are the best tests for diagnosing early-stage HCC in patients with cirrhosis?	Gd-EOB-DTPA-enhanced MRI is a very accurate diagnostic tool for the detection of early-stage HCC in patients with cirrhosis.	B
	11	What are the best tests for diagnosing typical HCC in high-risk patients?	Dynamic CT, dynamic MRI, or contrast-enhanced ultrasound is recommended to diagnose typical HCC .	A
	12	Is angiography necessary before hepatocellular carcinoma treatment?	Angiography is not recommended for HCC diagnosis.	D
	13	Is CTAP/CTHA necessary before HCC treatment?	Lesions are more easily detected with CT during arterial portography (CTAP)/CT during hepatic arteriography (CTHA) than with noninvasive imaging tests such as dynamic CT and dynamic MRI. These methods should be considered when more accurate staging is desired.	B
	14	What test methods are useful for diagnosing liver tumors in patients with decreased kidney and liver functions?	Noncontrast MRI with diffusion-weighted imaging and ultrasound using Sonazoid® are useful techniques that can be safely performed in patients with impaired kidney or liver function and are therefore recommended.	B
			When conducting dynamic CT and dynamic MRI in patients with renal impairment, if the eGFR is 30–60 mL/min/1.73 m ² , Gd-EOB-DTPA-enhanced MRI can be performed. For an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m ² , MRI with SPIO can be considered, and dialysis patients may undergo MRI with SPIO or dynamic CT	C1
	15	How should contrast media be used for the diagnostic imaging of HCC?	There is an insufficient amount of research on the selection of appropriate test methods and contrast agents for contrast-enhanced CT/MRI in patients with liver impairment equivalent to Child–Pugh class C.	—
			When evaluating hypervascular HCC, rapid injection of the contrast agent and optimal timing of image acquisition are recommended.	A
	16	Are brain MRI, chest CT, bone scintigraphy, and FDG-PET necessary for determining the stage of HCC?	When evaluating hypovascular nodules, it is recommended that images be obtained during the hepatobiliary phase using a hepatocyte-specific contrast agent.	A
			Chest CT, bone scintigraphy, and FDG-PET scans can be recommended for HCC patients with risk factors for extrahepatic metastases.	B
			It is worth considering a brain CT/MRI to search for brain metastasis in HCC patients with neurological findings and lung metastasis.	C1

	17	Does contrast-enhanced ultrasound improve the ability to diagnose HCC?	Contrast-enhanced ultrasound is useful for the differential diagnosis of liver tumors and the differential and locational diagnoses of HCC.	B
	18	Is contrast-enhanced ultrasound useful for determining the outcomes of percutaneous ablation therapy and TACE?	Contrast-enhanced ultrasound is useful for visualizing areas with residual tumors.	B
	1 Indications for Surgery/Surgical Procedures			
	19	What assessment modalities are appropriate for evaluating liver function prior to liver resection? What are the indications for surgery from the perspective of liver function?	Preoperative assessment of liver function should include measurement of the indocyanine green retention rate at 15 min (ICG-15) as well as general liver function tests. Surgery is indicated depending on the balance between these values and the planned extent of liver resection.	B
	20	What is the standard surgical procedure for liver resection?	Anatomical liver resection over a small area or partial resection as limited resection (particularly in patients with poor liver function) is chosen for the treatment of a small HCC lesion (maximum diameter ≤ 5 cm). Extended resection (including right or left lobectomy) of two or more segments is chosen for large HCC lesions.	C1
	21	What are the indications for liver resection in terms of tumor condition?	Liver resection is indicated for HCC if there are three or fewer tumors and all are limited to the liver. There is no restriction on tumor size. It is suggested that patients with tumor invasion to the portal vein be indicated for surgery if the tumor has not progressed beyond the first-order branches.	B
	2 Prognostic Factors			
	22	What are the prognostic factors after liver resection?	Major prognostic factors after liver resection are stage classification, vascular invasion, liver function, and tumor number.	B
	23	Does the size of the resection margin affect prognosis?	A minimum surgical margin is sufficient for liver resection.	B
	24	Does anatomical liver resection affect prognosis?	Anatomical resection is recommended for liver resection.	B
	3 Perioperative Management			
Chapter 3 Surgery	25	Is proactive, perioperative administration of blood products recommended?	Homologous red blood cell transfusion should be avoided if possible.	B
			Administration of fresh frozen plasma is not always necessary.	B
	26	Does hepatic pedicle clamping and decreased central venous pressure decrease bleeding during liver resection?	Hepatic pedicle clamping is effective for decreasing the amount of blood loss during liver resection.	A
			Decreasing central venous pressure (CVP) is also an effective means for decreasing the amount of blood loss during liver resection.	C1
27	Is abdominal drain placement necessary for liver resection?	Intra-abdominal drainage is not always necessary for elective liver resection.	B	
	4 Adjuvant Therapy			

	28	Does neoadjuvant therapy improve prognosis after liver resection?	There is no recommended neoadjuvant chemotherapy aimed at improving prognosis after liver resection for HCC.	C2
	29	Does adjuvant therapy improve prognosis after liver resection?	There is no recommended adjuvant chemotherapy for improving prognosis after liver resection for HCC.	C2
	5 Liver Transplantation			
	30	Does pretransplantation tumor downstaging improve the prognosis of liver transplantation?	There is insufficient scientific evidence to support that tumor downstaging prior to liver transplantation improves HCC prognosis.	C1
	31	What are the indications of liver transplantation for HCC?	Liver transplantation can be considered for HCC patients with decompensated cirrhosis if disease control is not possible using other treatment methods. Tumor diameter, tumor number, tumor marker levels, extent of vascular invasion, and degree of tumor differentiation are strong predictors of recurrence. Factors that can be evaluated before surgery include tumor diameter, tumor number, and tumor marker levels. Although it has been widely proposed that the Milan criteria be extended, these criteria are currently valid.	B
Chapter 4 Percutaneous Ablation Therapy	32	Who are eligible candidates for percutaneous ablation therapy?	Percutaneous ablation is indicated for patients with Child–Pugh class A or B liver function, 3 or fewer tumors, and tumor diameters of 3 cm or less.	B
	33	How should a type of percutaneous ablation therapy be selected?	RFA is recommended for percutaneous ablation therapy.	A
			If gastrointestinal perforation is suspected, other methods (e.g., RFA with artificial ascites and PEI) are effective .	B
	34	Does a combination of TACE and percutaneous ablation therapy improve prognosis?	TACE before RFA extends the range of necrosis.	A
			A favorable prognosis can be expected if local control is achieved. However, there is inadequate evidence demonstrating that pretreatment with TACE will improve RFA outcomes.	C1
	35	Are contrast-enhanced ultrasound and fusion imaging useful guides for percutaneous ablation therapy?	Contrast-enhanced ultrasound (US) and fusion imaging are useful guides for treating HCC lesions that are difficult to visualize on B-mode US.	B
36	What type of diagnostic imaging is useful for assessing treatment response of percutaneous ablation therapy?	Dynamic CT/MRI is the fundamental method for determining the outcomes of percutaneous ablation therapy. Contrast-enhanced ultrasound may be substituted in patients with allergies to contrast media or renal impairment .	A	

Chapter 5 Transcatheter Arterial Chemoembolization (TACE)	37	Which patients are indicated for TACE/TAE?	TACE/TAE is a recommended treatment procedure for hypervascular hepatocellular carcinoma with level A or B liver damage (or Child-Pugh class A and B) that is inoperable and ineligible for percutaneous ablation therapy. Selective TACE/TAE is recommended, which takes into consideration the ratio of the volume of noncancerous liver to be chemoembolized to the total volume of noncancerous liver and the residual liver reserve.	A
			Although it has been reported that TACE/TAE is useful for patients with intravascular tumor emboli and no extrahepatic metastasis (particularly portal vein tumor emboli), there is insufficient evidence.	C1
	38	What type of embolic material or anticancer agent should be used for TACE/TAE?	It is recommended that Lipiodol® be used for TACE/TAE or the lipiodol TACE (Lip-TACE) procedure be performed. Responsiveness to anticancer agents varies among cases, and any specific effective drug that can be used in an emulsion mixed with Lipiodol R has not been found. In Japan, porous gelatin spherical beads (Gelpart®; particle diameter of 1 or 2 mm) can be used as an embolic material.	C1
	39	When should repeat TACE/TAE be scheduled?	Repeat TACE/TAE should be performed if a tumor develops with ample blood flow, if tumor marker levels are elevated, or if tumor diameter has increased.	B
	40	What types of diagnostic imaging are useful for determining the treatment effects of TACE?	Dynamic CT or dynamic MRI is recommended.	B
Chapter 6 Chemotherapy	41	Which cases are indicated for systemic chemotherapy?	Systemic chemotherapy is indicated for patients in whom surgical resection, liver transplantation, local therapy, and TACE are contraindicated. In particular, sorafenib is indicated for the treatment of Child-Pugh class A patients with a good PS.	A
	42	Does hepatic arterial infusion chemotherapy improve prognosis?	Hepatic arterial injection chemotherapy may improve prognosis, but there is insufficient evidence to support the effectiveness.	C1
	43	What chemotherapy regimens (drug regimens) are effective?	Sorafenib is recommended for systemic chemotherapy for Child-Pugh class A unresectable hepatocellular carcinoma.	A
	44	Is hormone therapy effective?	Hormone therapy is not recommended because it is ineffective against advanced hepatocellular carcinoma.	D
	45	What are the predictive and prognostic factors for the treatment effects of chemotherapy (drug therapy)?	There are no scientific evidence-based predictive or prognostic factors for the treatment effects of chemotherapy (drug therapy).	C1
	46	How should the treatment effects of chemotherapy be determined?	In determining the effects of hepatocellular carcinoma treatment, modified RECIST, RECICL, and EASL criteria are useful for correctly evaluating areas with necrosis and surviving tumor tissue, which are taken into consideration by the criteria.	C1

		47	What are the adverse effects of chemotherapy and how should they be treated?	<p>Special attention should be paid to hematotoxicity because the patient is complicated with cirrhosis, and pancytopenia is often observed before treatment.</p> <p>The characteristic adverse effects frequently associated with sorafenib are hand-and-foot syndrome, rash, diarrhea, and hypertension. These effects often develop in the early stages of therapy initiation; therefore, the patient must be monitored carefully and treated accordingly.</p>	C1
Chapter 7 Radiation Therapy	48	Is 3D conformal radiation therapy useful for hepatocellular carcinoma?	<p>Radiotherapy using three-dimensional conformal radiation therapy can be considered for patients with portal vein tumor embolism, unresectable tumors, or contraindications for other standard treatment methods because of complications or other reasons.</p>	C1	
			<p>There is insufficient scientific evidence indicating that radiotherapy alone can extend survival; however, it can be expected that survival will be extended in patients with unresectable tumors if TACE is performed in combination with radiotherapy.</p>	C1	
			<p>There are no scientific evidence-based recommendations regarding fractionation regimens used in radiation therapy, total radiation dose, or treatment criteria based on liver function.</p>	—	
	49	Is stereotactic body radiation therapy useful against hepatocellular carcinoma?	<p>Stereotactic body radiation therapy can be considered for patients with hepatocellular carcinoma that are not indicated for other local therapies (no metastatic lesions, diameter \leq 5 cm). There is insufficient scientific evidence to show that stereotactic body radiation therapy extends survival.</p>	C1	
			<p>There are also no scientific evidence-based recommendations regarding fractionation regimens used in radiation therapy, total radiation dose, or treatment criteria based on liver function.</p>	—	
	50	Is particle radiation therapy [proton therapy, heavy particle (carbon ion) radiation therapy] useful against hepatocellular carcinoma?	<p>Particle radiation therapy [proton radiation therapy, heavy particle (carbon ion) radiation therapy] can be considered for hepatocellular carcinoma that is difficult to treat with other local therapies. Consideration may be given to therapeutically intractable tumors such as portal vein tumor embolism, tumor embolism in the inferior vena cava, and giant hepatocellular carcinoma.</p>	C1	
				<p>Radiotherapy is generally useful for the relief of pain resulting from bone metastases and is a recommended therapy.</p>	B

		51	Is radiation therapy indicated for distant metastases from hepatocellular carcinoma?	To extend survival in patients with brain metastases, either an appropriate combination of whole-brain irradiation and stereotactic surgery or treatment with either method is recommended.	B
Chapter 8 Post-Treatment Surveillance, Prevention, and Treatment of Recurrence		52	What type of follow-up care is given after hepatectomy and percutaneous ablation therapy?	After hepatectomy or percutaneous ablation therapy, strict follow-up with concurrent use of tumor marker analysis and imaging tests is recommended. The follow-up should be conducted according to surveillance used for extremely high-risk patients at the time of onset.	C1
		53	What methods are effective for preventing recurrence after hepatectomy and percutaneous ablation?	In patients with hepatitis-positive hepatocellular carcinoma, interferon therapy after hepatectomy and percutaneous ablation therapy may suppress recurrence and improve survival. Treatment may be conducted with careful monitoring for adverse events.	C1
				Other methods have been reported to be useful for preventing recurrence; however, there is not enough evidence to recommend them at this time.	C1
		54	What methods are effective for preventing recurrence after liver transplantation?	There are reports that immunosuppressive drug selection and dose adjustments contribute to the prevention of recurrence after liver transplantation.	C1
		55	What treatments are effective against recurrence after hepatectomy?	If recurrence occurs after liver transplantation, a treatment plan should be determined using the same criteria as those used at the time of initial onset. Repeat resection is recommended for patients with single recurrence and good liver function.	B
		56	What treatments are effective against recurrence after percutaneous ablation therapy?	If recurrence occurs after percutaneous ablation therapy, it is recommended that a treatment plan be determined after taking into consideration curability and hepatic functional reserve, as done for primary hepatocellular carcinoma.	B
		57	What treatments are effective against recurrence after liver transplantation?	If recurrence occurs after liver transplantation, resection of recurrent lesions may be considered.	C1