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The General Rules for the Study of Primary Liver Cancer

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The General Rules for the Study of Primary Liver Cancer was published in June 2001 as the first edition. Since then, the 5th edition of the General Rules for the Study of Primary Liver Cancer was published by the 17th Committee of the Korean Liver Cancer Association based on the most recent data. The 5th edition of the General Rules for the Study of Primary Liver Cancer ranged over numerous topics such as anatomy, medical assessment of the patients, staging of hepatocellular carcinoma, description of the image findings, summary of hepatic resection, description of the surgical specimens, liver transplantation, reporting the pathological findings, pathological examinations of liver specimen, non-surgical treatment, radiotherapy, and assessment of tumor response after non-surgical treatment of hepatocellular carcinoma. The 5th General Rules for the Study of Primary Liver Cancer will not only become the basis of academic development for liver cancer studies in Korea, but also serve as the primary form of national liver cancer data accumulation based on standardized rules. (**J Liver Cancer 2017;17:19-44**)

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ANATOMY

1. Anatomy of the liver

In 2000, the International Hepato-Pancreato-Biliary Association (IHPBA) established a unified terminology of anatomy in Brisbane in order to prevent confusion in terminology related to liver anatomy. To maintain consistency in academic communication, this edi-

Figure 1. The anatomical division of liver segments.

tion of The General Rules for the Study of Primary Liver Cancer will use the Brisbane 2000 terminology.^{1,2}

The first division of the liver (based on the side that crosses the gallbladder and the inferior vena cava) is into 2 hemilivers: the right hemiliver (or the right liver) and the left hemiliver (or the left liver). “Section” is used for the second division. “Segment” is used for the third division, and Arabic numerals—instead of Roman numerals—are used for the division numbers. Each section of the liver and the definitions of the segments are presented in Table 1, Table 2, and Fig.1.

2. Lymph node (Fig. 2)³3. Bile duct (Fig. 3)³

The right hepatic duct and the left hepatic duct of the liver are defined as the first-order branches of the common hepatic duct. The intrahepatic duct comprises the section from the second-order branches of the bile duct to the peripheral branches of the intrahepatic duct. The common bile duct (CBD) is divided into the common hepatic duct, which is proximal to the cystic duct, and the distal CBD. The distal CBD is further divided into the middle CBD and distal CBD along the upper border of the pancreas.

MEDICAL ASSESSMENT OF PATIENTS WITH HEPATOCELLULAR CARCINOMA

1. Risk factors of hepatocellular carcinoma

The exact pathogenesis of hepatocellular carcinoma (HCC) has not yet been identified, but in Korea, the main risk factors of HCC are chronic hepatitis or liver cirrhosis caused by hepatitis B virus,

Table 1. The second-order division of the anatomy of the liver

Terminology	Abbreviation	Couinaud segments
Right anterior section	A	The section between the right hepatic vein and the middle hepatic vein (S5, S8)
Right posterior section	P	The posterolateral section of the right hepatic vein (S6, S7)
Left lateral section	L	The lateral section of the falciform ligament (S2, S3)
Left medial section	M	The section between the falciform ligament and the middle hepatic vein (S4)
Caudate lobe	C	The section between the posterolateral side of the porta hepatis and the anterior side of the inferior vena cava (S1)

Table 2. The third-order division of the anatomy of the liver

Terminology	Abbreviation	Couinaud segments
Caudate lobe	S1	The part between the posterolateral side of the porta hepatis and the anterolateral side of the inferior vena cava
Left lateral superior segment	S2	The posterior part of the left hepatic vein in the left lateral section
Left lateral inferior segment	S3	The anterior part of the left hepatic vein in the left lateral section
Left medial segment	S4	The part between the falciform ligament and the middle hepatic vein
Right anterior inferior segment	S5	The inferior part of the main Glissonean pedicle in the right anterior section
Right posterior inferior segment	S6	The inferior part of the main Glissonean pedicle in the right posterior section
Right posterior superior segment	S7	The superior part of the main Glissonean pedicle in the right posterior section
Right anterior superior segment	S8	The superior part of the main Glissonean pedicle in the right anterior section

Figure 2. Groups of lymph nodes surrounding the liver and biliary tract. 1. Lymph nodes in the right cardinal region; 2. Lymph nodes in the left cardinal region; 3. Lymph nodes along the lesser curvature of the stomach; 4. Lymph nodes along the greater curvature of the stomach; 5. Lymph nodes in the suprapyloric region; 6. Lymph nodes in the infrapyloric region; 7. Lymph nodes along the left gastric artery; 8. Lymph nodes along the common hepatic artery; 9. Lymph nodes along the celiac artery; 10. Lymph nodes at the splenic hilum; 11. Lymph nodes along the splenic artery; 12. Lymph nodes in the hepatoduodenal ligament; 13. Lymph nodes on the posterior surface of the pancreatic head; 14. Lymph nodes at the root of the mesentery; 15. Lymph nodes along the middle colic vessels; 16. Lymph nodes along the abdominal aorta; 17. Lymph nodes on the anterior surface of the pancreatic head; 18. Lymph nodes along the inferior margin of the body and tail of the pancreas; 19. Infradiaphragmatic lymph nodes; 20. Lymph nodes in the esophageal hiatus of the diaphragm; 110. Paraesophageal lymph nodes in the lower thorax; 111. Supradiaphragmatic lymph nodes.

Figure 3. Bile duct anatomy.

hepatitis C virus, and alcohol. In addition, nonalcoholic steatohepatitis, aflatoxin B1 intake, and liver cirrhosis from any cause are additional risk factors of HCC. When examining these at-risk populations, the risk factors of HCC should be reported.

2. Assessment of liver function

In addition to the tumor stages of HCC, liver function is another important factor that affects the treatment and prognosis of patients with HCC. The Child-Pugh classification comprising of laboratory and clinical elements (Table 3)^{4,5} and serum creatinine should be recorded. In addition, the Model for End-Stage Liver Disease (MELD) score,⁶ a different standard of assessing liver function, can be recorded (Table 4). The result of indocyanine green test (ICGR15) may also be recorded to assess the remaining liver function before surgery.

Table 3. Child-Pugh classification

Clinical and laboratory findings	Score		
	1	2	3
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
Serum bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Prothrombin time (seconds)	1-4	4-6	>6
Ascites	Absent	Slight	Moderate
Encephalopathy	None	Grade 1-2	Grade 3-4

Grade A: ≤ 6, Grade B: 7-9, Grade C: ≥ 10.

Table 4. MELD score

$$\text{MELD score} = 9.57 \times \log_e (\text{serum creatinine}) + 3.78 \times \log_e (\text{serum bilirubin}) + 11.2 \times \log_e (\text{INR}) + 6.43$$

- A score is computed after inputting the exam values at <http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/meld-model>

- The maximum value is 40. Serum creatinine is calculated as 4.0 for patients who have received more than 2 blood dialyses in the last 7 days. A measured value of less than 1.0 is entered as 1.0.

MELD, Model for End-Stage Liver Disease.

Table 5. Criteria for assessing the physical vigor of patients

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

Table 6. Criteria for recording the endoscopic findings of esophageal and gastric varices

Factors	Symbol	Subdivision
Location	L	Ls: locus superior Lm: locus medialis Li: locus inferior Lg-c: adjacent to the cardiac orifice Lg-cf: extension from the cardiac orifice to the fornix Lg-f: isolated in the fornix Lg-b: located in the gastric body Lg-a: located in the gastric antrum
Form	F	F0: no varicose appearance F1: straight, small-caliber varices F2: moderately enlarged, beady varices F3: markedly enlarged, nodular or tumor-shaped varices
Color	C	Cw: white varices Cb: blue varices Cw-Th: thrombosed white varices Cb-Th: thrombosed blue varices
Red color sign	RC	The red color sign refers to red wale marking (RWM), cherry red spots (CRS), and hemocystic spots (HCS). If there is a red color sign, record it even if a score of F0 is given. RC(-): no red color sign RC(+): red color sign present

3. Assessment of overall functional status

The assessment of a patient's overall functional status is necessary for decisions regarding the treatment method, adjustment of drug doses, and decision for palliative treatment. Of the several assessment methods, the Eastern Cooperative Oncology Group (ECOG) scale⁷ should be used in patients with HCC (Table 5).

4. Assessment of portal hypertension

1) Endoscopic findings of esophageal/gastric varices

As esophageal and gastric variceal bleeding can affect the prognosis of patients with HCC, the presence of varices and the corresponding bleeding risk must be taken into account. The risk of variceal bleeding shows a close relation to endoscopic findings. According to the Japanese Research Society for Portal Hypertension criteria,⁸ the location (L), form (F), and red color sign (RC) should be recorded (Table 6).

2) Splenomegaly

If splenomegaly (>12.0 cm) is present on imaging tests, it should be recorded.

3) Thrombocytopenia

The platelet count at the time of diagnosis should be recorded.

4) Hepatic venous pressure gradient (HVPG)

The hepatic venous pressure gradient (mm Hg) could optionally be recorded.

Table 7. Modified UICC staging classification

Stage	Tumor	Node	Metastasis
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IV-A	T4	N0	M0
	T1-4	N1	M0
IV-B	T1-4	N0-N1	M1

T-stage	T1 (All criteria are fulfilled)	T2 (Two criteria are fulfilled)	T3 (Only one criterion is fulfilled)	T4 (No Criteria are met)
① Single
② Maximum size <2 cm
③ Portal or hepatic vein or bile duct invasion (-)

UICC, Union for International Cancer Control.

Table 8. Barcelona Clinic Liver Cancer (BCLC) staging classification. All criteria should be fulfilled for stage 0, A and B; At least one criteria of PS 1-2 or vascular invasion/extrahepatic spread should be fulfilled for stage C; At least one criteria of PS 3-4 or Child-Pugh C should be fulfilled for stage D

Stage	Performance status (PS)	Tumor status	Liver functional status (Child-Pugh)
Stage 0: Very early HCC	0	Single <2 cm	A
Stage A: Early HCC	0	Single ≥2 cm or ≤3 tumors and ≤3 cm	A-B
Stage B: Intermediate HCC	0	Multinodular	A-B
Stage C: Advanced HCC	1-2	Vascular invasion or extrahepatic	A-B
Stage D: Terminal HCC	3-4	Any	C

HCC, hepatocellular carcinoma.

Table 9. AJCC TNM classification of primary liver cancer, 8th Edition (2017)

T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	Solitary tumor >2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none > 5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
N1	Regional lymph node metastasis
M1	Distant metastasis

Stage	Tumor	Node	Metastasis
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

Adapted from Amin et al¹¹, pp287-293.

AJCC, the American Joint Committee on Cancer; TNM, the tumor, node, and metastasis.

5) Tumor markers

It is necessary to record levels of alpha-fetoprotein (AFP), the most well-known and best-proven tumor marker for HCC, and it is optional to include levels of des-gamma-carboxy prothrombin (DCP), also known as protein induced by vitamin K absence-II (PIVKA-II).

STAGING OF PRIMARY LIVER CANCER

1. Staging of hepatocellular carcinoma

The most commonly used staging classification for hepatocellular carcinoma (HCC) is the Barcelona Clinic Liver Cancer (BCLC) classification.⁹ However, the Practice Guidelines for the Management of HCC of the Korean Liver Cancer Group and National Cancer Center¹⁰ have adopted the modified Union for International Cancer Control (UICC) TNM classification published by the Liver Cancer Study Group of Japan (fourth edition, 2000) instead of the BCLC

Table 10. AJCC Classification of intrahepatic cholangiocarcinoma, 8th Edition (2017)

Tis	Carcinoma <i>in situ</i> (intraductal tumor)
T1	Solitary tumor without vascular invasion, ≤5 cm or >5 cm
T1a	Solitary tumor ≤5 cm without vascular invasion
T1b	Solitary tumor >5 cm without vascular invasion
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving local extrahepatic structures by direct invasion
N1	Regional lymph node metastasis present
M1	Distant metastasis present

Stage	Tumor	Node	Metastasis
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIB	Any T	N1	M0
IV	Any T	Any N	M1

Adapted from Amin et al¹¹, pp295-302.

AJCC, the American Joint Committee on Cancer.

classification. Since international staging classifications such as the BCLC and the American Joint Committee on Cancer (AJCC)/UICC TNM classification¹¹ systems must also be taken into account, the staging of HCC should be principally recorded with the modified UICC classification, with additional inclusion of the BCLC and AJCC/UICC classifications (Table 7-9).⁹⁻¹²

2. Staging of intrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinomas are classified according to the seventh AJCC/UICC TNM classification and the modified UICC TNM classification published by the Liver Cancer Study Group of Japan (fourth report, 2000) (Table 10, 11).^{11,12}

DESCRIBING IMAGE FINDINGS OF HEPATOCELLULAR CARCINOMA

Both general imaging findings and the imaging features of indi-

Table 11. Modified UICC staging classification¹

Stage	Tumor	Node	Metastasis
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IVA	T4	N0	M0
	T1-3	N1	M0
IVB	T4	N1	M0
	T1-4	N0-1	M1
T-stage	① Single ② Maximum size <2 cm ③ Vascular [*] or bile duct invasion(-)		
T1	All criteria are fulfilled		
T2	Two criteria are fulfilled		
T3	Only one criterion is fulfilled		
T4	No criteria are met		

*portal vein or hepatic artery.

vidual hepatocellular carcinoma (HCC) should be recorded according to the following guidelines.

1. Reporting general image findings

The total number of HCC should be recorded, as well as their size and imaging features.

1) Number

HCC is recorded as single or multiple depending on the number of nodules (≥ 1 cm), and the number of nodules is only recorded in cases of multiple tumors. HCC with 6 or more nodules should be recorded as having numerous nodules.

2) Size

The tumor size is measured by its largest diameter in centimeters. For multiple tumors, only the diameters of the 5 largest tumors are recorded, ranging from the largest to the smallest.

3) Tiny nodules

Due to advances in imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI), subcentimeter (<1cm) hepatic lesions suspected to be malignant are frequently detected. However, non-invasive diagnostic criteria are currently not available for subcentimeter hepatic lesions, and percutaneous biopsy of these lesions is also not recommended. Nevertheless, the subtype of tiny nodules should be recorded in order to remark the potentially malignant hepatic lesions smaller than 1 cm. If tiny nodules are suspected to be malignant, the number of suspicious nodules should be recorded separately, and if 6 or more suspicious tiny nodules are present, they should be recorded as numerous tiny nodules.

4) Portal vein invasion (Vp)

The presence or absence of portal vein invasion and its extent should be evaluated and recorded. Portal vein invasion should be described as sectional if it is limited to the portal vein branches in a

single hepatic section; as right or left if it has extended into either the right or left main portal vein, respectively; and as main if it has extended to the main portal vein.

5) Bile duct invasion (B)

The presence or absence of bile duct invasion and its extent should be evaluated and recorded. The extent of bile duct invasion is considered sectional if it is limited to only intrahepatic bile ducts in a single hepatic section; as right or left invasion if it has extended into the right or left bile duct, respectively; and as main if it has extended into the common hepatic duct or the common bile duct.

6) Hepatic vein invasion (Vv)

The presence or absence of tumor invasion of the hepatic vein and the affected hepatic vein (right, middle, or left) should be recorded.

7) Metastasis

Metastases of HCC should be classified as peritoneal dissemination, lymph node metastases, and distant metastases, and the presence or absence of metastasis should be recorded accordingly. A lymph node is considered metastatic if it is 1.5 cm or larger in its shortest diameter or if it has internal necrosis. The organ in which distant metastasis is found should be recorded specifically within parentheses.

2. Reporting imaging findings of representative lesions¹³⁻¹⁷

Imaging findings should be recorded for individual HCC. If multiple nodules show similar radiologic features, the radiologic features of the largest nodule should be recorded. If nodules show different radiologic features, then a maximum of 5 nodules can be described in a separate table.

1) Lesion number

The lesions whose radiological features are being characterized should be numbered. For any other lesions showing characteristics similar to those that are described, the corresponding lesion numbers should be noted in parentheses.

2) Location

The location of nodules should be recorded using the abbreviations S1-8 following the anatomical segment classification. If a tumor is located across more than two hepatic segments, the primary segment should be recorded first, and the secondary segment should be recorded next with an inequality sign. When the locations of the nodules are not clear, all possible segments should be recorded (Table 12).

3) Size

The diameter of the largest tumor should be recorded as described in 2) size. If the measurements of tumor size differ depending on the measurement techniques or the imaging planes used, the largest diameter measured should be used, and the specific measurement technique, imaging plane, and acquisition time should be recorded (Table 13).

4) Enhancement pattern^{15,16}

① Arterial hypervascularity

Table 12. Describing image findings of tumor location

(Example 1)	If a tumor is located predominantly in segment 8 extending into segment 5, it should be recorded as S8 > 5.
(Example 2)	If a small tumor lies in the posterior section of the right liver, but it is not clear whether it lies in segment 6 or segment 7, it should be recorded as S6/7.

Table 13. Describing image findings of tumor size

(Example)	A nodule that is measured as 5 cm in the transverse plane in the arterial phase of a CT scan should be recorded as 5 cm, CT/arterial phase/transverse plane.
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CT, computed tomography.

Table 14. Describing image findings of enhancement pattern: arterial hypervascularity

(Example 1)	If on MRI, a nodule shows low signal intensity in pre-contrast T1-weighted images and similar signal intensity in arterial phase images relative to the surrounding liver parenchyma, the arterial hypervascularity of the nodule should be graded as "yes".
(Example 2)	If on MRI, a nodule shows high signal intensity in both pre-contrast T1-weighted images and arterial phase images relative to the surrounding liver parenchyma, the nodule should be graded as "?" because it is not possible to determine the presence of arterial hypervascularity.
(Example 3)	If on MRI, a nodule with high signal intensity in pre-contrast T1-weighted images shows high signal intensity in subtraction images, the tumor should be graded as "yes" due to the clear presence of arterial hypervascularity.

MRI, magnetic resonance imaging.

The contrast enhancement of a tumor and the surrounding liver parenchyma should be evaluated by comparing the arterial phase images and pre-contrast images, and the presence or absence of arterial hypervascularity should be indicated with a yes, no, or question mark (Table 14).

② Washout pattern

According to the criteria above, the presence or absence of washout should be indicated only for hypervascular liver lesions. Washout is only considered present when tumors show low attenuation or signal intensity relative to the surrounding liver parenchyma. Even when hepatobiliary contrast agents are used in MRI, nodules showing low signal intensity relative to the surrounding liver parenchyma in the portal venous or transitional phase should be regarded as presence of washout. However, low signal intensity in the hepatobiliary phase should not be considered as washout pattern (Table 15).

5) Capsular appearance

Capsular appearance should be recorded. The appearance of a capsule should be evaluated subjectively as "complete," "partial," or "none," and the phase of appearance should be recorded with "portal venous phase," "delayed phase," or "both."

Table 15. Describing image findings of enhancement pattern: washout pattern

(Example 1)	When nodules are not detected in the pre-contrast images or in the arterial phase but are present in the portal venous or delayed phase with low attenuation or signal intensity, they are excluded from evaluation.
(Example 2)	When hypervascular liver tumors show isoattenuation or isointensity with the surrounding liver parenchyma in the portal venous or delayed phase, no washout is considered to be present, and they therefore should be graded as "no."

6) Major and ancillary features on CT and MRI^{15,16}

The major features on CT or MRI include arterial hypervascularity and portal venous or delayed washout appearance. When the following features are found on CT or MRI, they should be treated as ancillary imaging findings suspicious of liver cancer and should be marked with "yes":

- MRI findings: hypointensity in the hepatobiliary phase, moderate hyperintensity on T2-weighted images, hyperintensity in diffusion-weighted images.
- CT or MRI findings: mosaic appearance, nodule-in-nodule appearance, intralesional fatty changes, intralesional bleeding and necrosis, and increased tumor size during follow-up.
- Hypointensity in the hepatobiliary phase: When a hepatobiliary contrast agent (e.g., gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid [Gd-EOB-DTPA] or gadobenate dimeglumine [Gd-BOPTA]) is used, it is necessary to record whether nodules show reduced uptake of the contrast agent relative to the surrounding liver parenchyma in the hepatobiliary phase^{15,17}. The general level of intensity (hypointensity/isointensity/hyperintensity) of the nodules relative to the surrounding liver parenchyma in the hepatobiliary phase should be indicated.
- Moderate T2 hyperintensity: If a nodule shows moderate hyperintensity relative to the surrounding liver parenchyma on T2-weighted images, an assessment of "yes" should be given.
- Hyperintensity on diffusion-weighted images: If a nodule shows hyperintensity relative to the surrounding liver parenchyma on diffusion-weighted images, an assessment of "yes" should be given.
- Mosaic appearance: If the signal intensity within the nodule is heterogeneous, showing a mosaic pattern, it should be given an assessment of "yes."
- Nodule-in-nodule appearance: When tiny nodules with varying signal intensities are found within a tumor, or when contrast-enhanced tiny nodular enhancing regions are found within the tumor, it should be given an assessment of "yes."
- Intralesional fat: The presence or absence of fatty changes within the tumor should be recorded, and if fatty changes are found, the extent of fatty changes should be described as "total" or "partial."
- Intralesional bleeding or necrosis: The presence or absence of regions suspected of necrosis or hemorrhage, which are not affected by contrast enhancement, should be recorded. If necrosis or hemorrhage is present, it is necessary to indicate the propor-

Figure 4. Vaguely nodular type. Vaguely nodular lesions are small lesions whose boundaries are not distinct from the surrounding liver parenchyma.

Figure 5. Expanding nodular type. Expanding nodular lesions have a clear boundary without infiltrative tumor growth.

tion of the regions relative to the size of the whole nodule as one of the following proportions: $<1/4$, $1/4-3/4$, or $>3/4$.

- Increased tumor size: If the nodule increases in size in the follow-up tests, it should be given an assessment of “yes” for this parameter.

7) Classification by gross morphology¹³

The classification of liver cancer lesions is based on gross morphology, irrespective of nodule size (Fig. 4-11). The pre-existing Eggel classification system is not applied. The following types are present:

- Vaguely nodular type
- Expanding nodular type

Figure 6. Multinodular confluent type. Multinodular confluent tumors involve a cluster of multiple small nodules with extranodular growth.

- Multinodular confluent type
- Nodular with perinodular extension type
- Infiltrative type
- Pedunculated type
- Cirrhotomimetic type

8) Margin definition

Based on the degree of clarity of the boundary, 3 main types of boundaries of nodules can be distinguished: well-defined (when more than three-fourths of the boundary is distinct), poorly defined (when more than three-fourths of the boundary is indistinct), or mixed-irregular (when both distinct and indistinct boundaries are present).

9) 18F-fluorodeoxyglucose or 11C acetate uptake

It is necessary to evaluate and describe whether the nodule shows a greater uptake in radiotracers relative to surrounding liver tissue on positron emission tomography-computed tomography (PET-CT). The type of radiologic isotope tracer used should be indicated (either 18F-fluorodeoxyglucose [FDG] or 11C-acetate). If a nodule shows increased uptake, it should be marked with a plus sign (“+”) and the standardized uptake value (SUV) should be recorded.

SUMMARY OF HEPATIC RESECTION

1. Terminology

The terminology used for hepatectomy in this rule follows the Brisbane 2000 Terminology suggestions.^{2,3} Hepatectomies are classi-

Figure 7. Perinodular extension type. In such lesions, less than 50% of the region within the tumor that is undergoing expansive growth infiltrates into the surrounding tissues (arrow).

Figure 8. Infiltrative type. Infiltrative cancer occurs when more than 50% of the tumor border shows irregular infiltration into the surrounding tissue.

Figure 9. Pedunculated type. Pedunculated cancers have portions that protrude from the liver.

fied as anatomical or non-anatomical. Findings should be recorded according to the following guidelines.

Figure 10. Cirrhotomimetic type. Cirrhotomimetic cancers contain numerous nodules that are impossible to distinguish from liver cirrhosis by gross morphology alone.

Figure 11. Magnetic resonance imaging (MRI) findings of a typical hepatocellular carcinoma (HCC). HCC typically shows hyperintensity in the arterial phase of dynamic contrast-enhanced MRI, washout in the portal venous phase, hypointensity in the hepatobiliary phase, and hyperintensity on T2-weighted and diffusion-weighted images.

1) Anatomical hepatectomy

The liver is primarily divided into the right liver and left liver by a plane that crosses the gallbladder fossa and the fossa of the inferior vena cava (IVC). Primary surgical divisions of the liver are categorized as right hemihepatectomy (or right hepatectomy) and left hemihepatectomy (or left hepatectomy).

The boundary of the second division is the intersectional plane, according to which resections are referred to as right anterior sectionectomy, right posterior sectionectomy, left medial sectionectomy, and left lateral sectionectomy. Central bisectionectomy is a surgical procedure in which the right anterior section and left medial section are simultaneously resected.

The boundary of the third division is the intersegmental plane, which can be used to divide the liver into 8 segments, which can be resected in a procedure known as segmentectomy (Sg). The resection of 2 consecutive segments is called bisegmentectomy. Resecting segments 4, 5, 6, 7, and 8 is referred to as right trisectionectomy, while resecting segments 2, 3, 4, 5, and 8 segments is referred to as left trisectionectomy.

Since all anatomical hepatectomies can be described in terms of the third division, resections should be recorded using the Korean terminology and the abbreviation “Sg (Arabic numeral of the resected segment)” (Table 16).

Table 16. Anatomical hepatectomy terminology and abbreviations

Resection boundary	Resection terminology	Abbreviations
Primary division	Right hemihepatectomy	Sg (5678)
	Left hemihepatectomy	Sg (234)
Second division	Right anterior sectionectomy	Sg (58)
	Right posterior sectionectomy	Sg (67)
	Left medial sectionectomy*	Sg (4)
	Left lateral sectionectomy	Sg (23)
Third division	Segmentectomy of segment 6	Sg (6)
	Caudate lobectomy	Sg (1)
Other	Right trisectionectomy	Sg (45678)
	Left trisectionectomy	Sg (23458)
	56 bisegmentectomy	Sg (56)

*Left medial sectionectomies and the segmentectomy of segment 4 have the same resection boundary.

Table 17. Description of hepatic resection: nonanatomical hepatectomy

(Example)	For the wedge resection of S5, the abbreviation Wg (5) should be used.
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Table 18. Description of hepatic resection: the boundary of the wedge resection

(Example)	For the wedge resection of S58, the abbreviation Wg (58) should be used.
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Table 19. Description of hepatic resection: hepatectomy of multiple sections

Example
Right hemihepatectomy and wedge resection of S2: Sg (5678) + Wg (2)
Left medial sectionectomy (segmentectomy of S4) and segmentectomy of S6: Sg (4) + Sg (6)
Left hemihepatectomy and caudate lobe resection: Sg (234) + Sg (1)
Left lateral sectionectomy and 56 bisegmentectomy: Sg (23) + Sg (56)

2) Non-anatomical hepatectomy

Wedge resection (Wg) is non-anatomical hepatectomy in which the segments defined by the third division are not all resected. The resected segmental area is placed in front of the surgical procedure name, and “Wg (Arabic numeral of the resected segment)” should be used as the abbreviation (Table 17).

In cases where the boundary of the wedge resection stretches over 2 segments, all resected segments should be marked (Table 18).

3) Hepatectomy of multiple sections

The technique used for each section should be recorded. For cases of non-anatomical hepatectomy involving the combination of a segment that is completely resected and a segment that is incompletely resected, the following abbreviations should be used: “Sg (Arabic numeral of the completely resected segment) + Wg (Arabic numeral of the incompletely resected segment).” (Table 19).

2. Lymphadenectomy (dissection)

If metastasis to a lymph node is suspected during hepatocellular carcinoma surgery, a combined organ resection can be performed of

the lymph node as well as of the primary focus. Lymph node resection should be indicated and the specific location of the resected lymph node should be marked using the numerical lymph node group notation system according to the anatomical location.

No: Cases in which lymph node resection is not performed.

Yes: Cases in which lymph node resection is performed.

3. Residual tumor and curative resection

If residues of a tumor that was intended to be resected are identifiable with the naked eye, it should be marked as R2. Cases where cancer cells are exposed on the resection margin in a microscopic biopsy should be defined as R1. Curative resection should be defined as R0 if no invasion of cancer cells is seen on the resection margin in microscopic and macroscopic findings.

R0: The tumor has been completely removed, as indicated through microscopic and macroscopic findings.

R1: Invasion of cancer cells on the resection margin is observed in microscopic findings.

R2: A tumor that cannot be completely resected is seen macroscopically.

4. Surgical procedures

Surgical procedures should be differentiated (traditional open method, laparoscopy, or robotic) and recorded. If an unusual method was used, it should be marked as “other” and a separate description should be written.

SURGICAL FINDINGS AND DESCRIBING RE-SECTED SPECIMEN

1. Guidelines for recording tumor size, number, and location

1) Size and number of the tumor

The maximum diameter of each tumor should be recorded in centimeters to indicate tumor size. Arabic numerals should be used to indicate the number of tumors.

2) Location of the tumor (based on the description for image findings)

Following the anatomical classification method, the location of the tumor should be marked with the abbreviations S1-8. If a tumor is located in 2 or more segments, the section that it is mostly occupies should be marked first, and then an inequality sign should be used to mark the next section that it occupies (Table 20).

If the location of the tumor is not clear, all possible segments should be recorded (Table 21).

2. How to report surgical findings and resected specimens

Below is a list of 7 items (and their abbreviations) to enter for macroscopic observational findings regarding hepatocellular carcinoma and liver cirrhosis that are identifiable in resected specimens. The

pathological classification standard should be followed for the macroscopic classification of tumor forms. Each item should be separately recorded.

- Growth type: Expansive growth (Eg) vs. infiltrative growth (Ig)
- Serosal invasion (S)
- Vascular invasion (V), portal vein invasion (Vp), hepatic vein invasion (Vv)
- Bile duct invasion (B)
- Peritoneal dissemination (P)
- Surgical margin (SM)
- Liver cirrhosis (LC)

[Note]

Tumor thrombus: The phenomenon in which cancer cells have invaded the blood vessels and bile duct; tumor that has filled the lumen.

1) Growth type of the tumor

Expansive growth (Eg): Cases where expansive proliferation is observed.

Infiltrative growth (Ig): Cases where infiltrative proliferation is observed.

2) Serosal invasion

Tumors that protrude over the surface should be classified according to the status and condition of serosal invasion observed with the naked eye.

No: Cases where serosal invasion is not present.

Yes: Cases where invasion is present in the serous membrane and beyond.

3) Vascular invasion

Vascular invasion is divided into portal vein invasion (Vp) and hepatic vein invasion (Vv). Vascular invasion should be marked and the region of tumor invasion should be recorded according to the following categories.

- Portal vein invasion (Vp): Main, right (Rt), left (Lt), or below section
- Hepatic vein invasion (Vv): Rt, middle, Lt, or IVC

Table 20. Example of recording tumor location

(Example) If a tumor is primarily spread over segment 8 and has also invaded segment 5: S8 >5

Table 21. Example of recording tumor location

(Example) If a small tumor is located in the right posterior section, but it is difficult to distinguish whether it is in segment 6 or segment 7: S6/7

Table 22. Example of recording the surgical margin

(Example) SM (0.5): The distance between the tumor and the surgical margin is 0.5 cm.
SM (0): The tumor is observed on the surgical margin.

4) Bile duct invasion

Any bile duct invasion (B) should be marked and the regions of invasion should be recorded according to the following categories:

Main, Rt, Lt, or below section

5) Peritoneal dissemination

In surgical findings, any peritoneal dissemination should be recorded.

No: Cases with no macroscopic observations of peritoneal dissemination.

Yes: Cases where dissemination is present in the visceral and parietal peritoneum.

6) Shortest distance between the tumor and the surgical margin

The shortest distance between the surgical margin and the tumor should be measured and recorded. Centimeters should be used as the units (Table 22).

7) Liver cirrhosis

Macroscopic observations of liver cirrhosis should be recorded.

No: No macroscopic observation of liver cirrhosis.

Yes: Macroscopic observation of liver cirrhosis.

SUMMARY OF LIVER TRANSPLANTATION^{3,18}

1. Classification of donor type

The following information should be entered regarding donor type.

1) Deceased donor liver transplantation

For deceased donor liver transplantations, the condition of the donor should be recorded, either as donor after brain death (DBD) or donor after cardiac death (DCD).

While whole liver transplantations are usually carried out in most deceased donor liver transplantation cases, split liver transplantations or reduced liver transplantations can also be performed depending on the situation. It should be recorded if a split liver transplantation or reduced liver transplantation was conducted.

2) Living donor liver transplantation

Living donor liver transplantation refers to surgically removing part of the liver from a living donor and transplanting it into the recipient.

2. Classification of transplantation type

1) Whole liver transplantation

For whole liver transplantations, the following anastomosis methods of the hepatic veins should be separately recorded.

- (a) Conventional technique: A technique in which the entire retrohepatic vena cava of the recipient is resected along with the liver, and the upper and lower part of the graft inferior vena cava (IVC) is anastomosed with the recipient IVC in an end-to-end manner.

- (b) Piggyback technique: A technique in which only the liver is removed, with preservation of the native retrohepatic vena cava during the recipient hepatectomy. The hepatic veins of the recipient are combined into one orifice, and end-to-end anastomosis is carried out on the upper part of the graft IVC while the lower side of the graft IVC is closed. Using a modified method, side-to-side anastomosis can also be performed on the anterior part of the recipient's lower IVC and the posterior part of the graft IVC.

2) Partial liver transplantation

This is a transplantation type that is mainly used for living donor liver transplantations. It can also be utilized as a reduced liver transplantation or a split liver transplantation in deceased donor liver transplantation cases. The type of graft should be recorded according to the following classifications.

- Right liver (RT): A right liver graft that does not include the middle hepatic vein.
- Modified right liver (MR): A right liver graft in which the middle hepatic vein is reconstructed during bench surgery for future anastomosis in order to prevent congestion in segments 5 and 8.
- Extended right liver (ER): A right liver graft that includes the middle hepatic vein.
- Left liver (LT): A left liver graft that does not include the middle hepatic vein.
- Extended left liver (EL): A left liver graft that includes the middle hepatic vein.
- Left lateral section (LL): A left lateral section graft that is mainly used in pediatric transplantations.
- Dual graft: A transplantation type in which 2 grafts are performed in a single patient. For dual graft cases, each graft type should be recorded.
- Other grafts: While such cases are rare, right posterior grafts, segment 3 grafts, segment 1 grafts, and other grafts can be utilized depending on the situation. If a transplantation is carried out using a rarely performed graft, the graft type should be separately recorded.

3. Primary factors that influence the results of liver transplantation

1) Donor-recipient ABO match

In the past, transplantation was only possible in cases where transfusion could be carried out between the blood types of the donor and the recipient. Recently, due to the advances in technology and accumulation in experiences for treating patients before and after transplantation, successful transplantations have been achieved between donors and recipients even if blood transfusion is impossible. "Compatible" should be recorded if the ABO of the donor and recipient match, and "incompatible" if they do not.

2) Graft-to-recipient weight ratio (GRWR)

The GRWR should be recorded as an index to identify whether or

not the size of the graft was appropriate for the recipient. The weight of the graft is divided by the weight of the recipient, multiplied by 100, and the resulting percentage (%) is recorded (Table 23).

3) Ischemic time

- Cold ischemic time refers to the amount of time that the graft is cooled and preserved, and is defined as the amount of time beginning with the instillation of cold preservation solution through the graft until the time that anastomosis of the blood vessels begins in the recipient's body. This time should be recorded in minutes.
- Warm ischemic time refers to the amount of time in which the blood circulation of the graft is halted, but the graft is not cooled. It should be divided into the following times and recorded in minutes.
 - The first warm ischemic time is the amount of time beginning with the halting of the blood circulation to the graft until the instillation of the cold preservation solution. This can be accomplished within 1 minute in unremarkable brain-death donor liver transplantations or living donor liver transplantations, and it is not necessary to record this time in such cases.
 - The second warm ischemic time is the amount of time beginning with the anastomosis of the blood vessels in the patient's body until the reperfusion of blood flow after portal vein anastomosis.
- Total ischemic time is the sum of the cold ischemic time and the warm ischemic time.

4) Steatosis

It is known that a higher probability of primary nonfunction occurs after liver transplantation in cases of severe steatosis of the graft liver. Therefore, based on a histological examination of the graft, the following items should be recorded as percentages (%).

- Macrovesicular steatosis: Large droplets in the form of fat vesicles push the nuclei aside. This can be classified as mild, moderate, or severe, using 30% and 60% as cut-offs.
- Microvesicular steatosis: The vesicles are smaller than the cell nuclei.

Table 23. Graft-to-recipient weight ratio (GRWR)

GRWR = weight of the graft/weight of the recipient × 100 (%)

Table 24. The Milan criteria

• Milan criteria

- If there is one tumor, its maximum diameter must be equal to or less than 5 cm.
- If there are multiple tumors, there must not be more than 3, and the maximum diameter of the largest one must be equal to or less than 3 cm.
- There must be no major vessel invasion or distant metastasis.

4. The Milan criteria

It should be recorded whether liver transplantation in a patient with hepatocellular carcinoma (HCC) is carried out within or beyond the Milan criteria (Table 24).

5. Other entries

1) Auxiliary partial orthotopic liver transplantation (APOLT)

APOLT is a method in which only a part of the patient's liver is removed and a partial liver is transplanted in its place. It is mainly performed in patients with acute liver failure or metabolic liver disease. If an APOLT is carried out, it should be recorded.

2) Extracorporeal circulation

To prepare for cases in which the blood flow of the portal vein and the IVC is temporarily cut off during liver transplantation, extracorporeal circulation is a technique in which the blood flow of the portal vein and the pelvic limb is bypassed using a separate cannula and the extracorporeal circulatory system to make it circulate into the axillary vein or the jugular vein. If extracorporeal circulation is carried out during liver transplantation, it should be recorded.

REPORTING THE PATHOLOGICAL FINDINGS OF PRIMARY LIVER CANCER

The macroscopic and microscopic findings of hepatocellular carcinoma (HCC) in hepatic resection specimens should be recorded as follows. They are complementary to the information recorded by surgeons after the operation.

I. Hepatocellular Carcinoma

1. Macroscopic findings of hepatocellular carcinoma

1) Tumor size

The tumor size should be documented in centimeters as length × width × height.

2) Tumor numbers

For multiple tumors, the number should be recorded. "Multiple" refers to the presence of 2 or more tumors of similar size, regardless of the microscopic findings.

3) Satellite nodules

The presence of any satellite nodules should be recorded. A satellite nodule is a small nodule close to the main tumor, which includes intrahepatic metastasis and multicentric occurrence.

4) Macroscopic classification

The macroscopic classification of HCC is as follows (Fig. 12-20).

- Vaguely nodular type
- Expanding nodular type
- Multinodular confluent type
- Nodular with perinodular extension type
- Infiltrative type
- Specific types
 - Pedunculated
 - Cirrhotomimetic

5) Note for gross classification

- ① The vaguely nodular type refers to a small-sized nodule with an indistinct margin and poor demarcation from the surrounding liver tissue.

Figure 12. Gross classification of hepatocellular carcinoma.

Figure 13. Hepatocellular carcinoma, vaguely nodular type. This tumor (indicated by arrowheads) is a vaguely nodular tumor with indistinct margins.

Figure 14. Hepatocellular carcinoma, expanding nodular type.

Figure 15. Hepatocellular carcinoma, expanding nodular type.

Figure 16. Hepatocellular carcinoma, multinodular confluent type.

Figure 17. Hepatocellular carcinoma, nodular with perinodular extension type.

Figure 18. Hepatocellular carcinoma, infiltrative type.

Figure 19. Hepatocellular carcinoma, cirrhotomic type.

Figure 20. Hepatocellular carcinoma, nodular with perinodular extension type.

Figure 21. Hepatocellular carcinoma, Edmondson-Steiner grade I (above the dotted line). The tumor cells are arranged in thin trabeculae and demonstrate a replacing growth pattern (hematoxylin and eosin stain, $\times 200$).

Figure 22. Hepatocellular carcinoma, Edmondson-Steiner grade I. Stromal invasion by the tumor cells is seen (arrowheads) (hematoxylin and eosin stain, $\times 200$).

Figure 23. Hepatocellular carcinoma, Edmondson-Steiner grade II (hematoxylin and eosin stain, $\times 200$).

Figure 24. Hepatocellular carcinoma, Edmondson-Steiner grade III. Giant cells are seen. (hematoxylin and eosin stain, $\times 200$).

- ② The expanding nodular type HCC has distinct smooth margins without infiltrative growth.
- ③ The multinodular confluent type HCC is characterized by a cluster of contiguous nodules, resulting in a multilobulated appearance. HCCs are classified as multinodular confluent even if there is a minor expanding nodular or infiltrative component in part of the nodule.
- ④ The nodular with perinodular extension type HCC is an otherwise expanding nodular type HCC with an infiltrative

growth pattern in less than 50% of the tumor circumference.

- ⑤ The infiltrative type refers to cases in which more than 50% of the tumor margin demonstrates an infiltrative growth.
- ⑥ The terminologies “small HCCs” and “massive HCCs” are based on tumor size, and therefore are excluded from the gross classification, as tumor size is separately documented.

6) Tumor necrosis

The presence of necrosis within the tumor should be documented as a percentage (%).

Figure 25. Hepatocellular carcinoma, trabecular type (hematoxylin and eosin stain, ×200).

Figure 26. Hepatocellular carcinoma, pseudo-glandular type. Bile formation is seen (hematoxylin and eosin stain, ×200).

Figure 27. Hepatocellular carcinoma, compact type (hematoxylin and eosin stain, ×200).

7) Hemorrhage and peliosis

Any hemorrhage within the mass should be noted, as well as the presence of peliosis. The extent should be recorded as a percentage (%).

8) Major vascular invasion

The presence of grossly identifiable invasion of the portal vein, hepatic vein or hepatic artery should be documented.

9) Bile duct invasion

The presence of grossly identifiable bile duct invasion should be documented.

10) Serosal invasion

The presence of Glisson's capsule invasion should be documented.

11) Surgical resection margin

If the surgical resection margin is grossly involved by the tumor, it should be recorded. The shortest distance between the tumor and the surgical resection margin (safety margin) should also be recorded.

2. Microscopic findings of hepatocellular carcinoma

1) Histologic differentiation

The degree of differentiation of HCC is categorized as grade I, II, III, and IV according to the Edmondson-Steiner system (Fig. 21-24). The worst grade should be recorded first, followed by the major grade (i.e., the grade that occupies the largest portion of the tumor).

① Differentiation of HCC

- Edmondson-Steiner Grade I: Well-differentiated tumor cells that are almost indistinguishable from the adjacent non-neoplastic hepatocytes. The cell density is approximately 2-fold of the surrounding liver parenchyma due to the high nuclear/cytoplasmic ratio. The tumor cells form thin trabeculae that are composed of 1-2 cell layers and frequently show pseudoglandular structures. Fatty change is often observed.
- Edmondson-Steiner Grade II: The tumor cells show larger hyperchromatic nuclei compared to grade I tumors, more abundant eosinophilic cytoplasm, and distinct nucleoli. In most cases, the tumor cells are arranged in trabeculae of moderate thickness (3 or more layers). Pseudoglandular structures are also frequently seen, and sometimes they contain bile inside.

- Edmondson-Steiner Grade III: The tumor cells show increased nuclear/cytoplasmic ratio and nuclear atypia compared to grade II tumors, and giant cells are commonly seen. The tumor cells are arranged in moderately or markedly thickened trabeculae or show compact growth.

- Edmondson-Steiner Grade IV: Compared to grade III, there is a decrease in the amount of cytoplasm resulting in a very high nuclear/cytoplasmic ratio. Spindle-shaped or round tumor cells exhibit compact or trabecular growth patterns. Due to the poor differentiation of tumor cells, immunohistochemical stains are often needed to confirm the diagnosis of HCC.

② Early HCC

Early HCC is defined as a well-differentiated HCC (Edmondson-Steiner grade I) that is vaguely nodular. Most early HCCs are 2 cm or smaller, and demonstrate a replacing growth pattern without fibrous capsule formation.^{19,20}

2) Histological type

The histological types of HCC are categorized as follows (Fig. 25-28).

- Trabecular
- Pseudoglandular
- Compact
- Scirrhus
- Fibrolamellar
- Sarcomatoid
- Lymphoepithelioma-like carcinoma
- Undifferentiated carcinoma
- Other

3) Cell type

The cell types of HCC are categorized as follows (Fig. 29-31).

- Hepatic (classical)
- Clear cell
- Pleomorphic
- Spindle cell

4) Fatty change in HCC

The presence of fatty change within the tumor should be recorded, in addition to its extent, as a percentage (%) (Fig. 32).

Figure 28. Hepatocellular carcinoma, scirrhous type (hematoxylin and eosin stain, $\times 100$).

Figure 29. Hepatocellular carcinoma, hepatic type (hematoxylin and eosin stain, $\times 400$).

Figure 30. Hepatocellular carcinoma, clear cell type (hematoxylin and eosin stain, $\times 400$).

Figure 31. Hepatocellular carcinoma, spindle cell type (hematoxylin and eosin stain, $\times 200$).

Figure 32. Fatty change in hepatocellular carcinoma (hematoxylin and eosin stain, $\times 400$).

Figure 33. The gross classification of intrahepatic cholangiocarcinoma.

5) Fibrous capsule formation

The presence of a fibrous capsule should be documented as follows.

No capsule: No capsule formation observed.

Partial capsule: Partial capsule formation observed.

Complete capsule: Formation of a fibrous capsule in more than 90% of the tumor circumference.

6) Capsular infiltration by the tumor

If the tumor has formed a fibrous capsule, the presence of capsular infiltration by the tumor should be documented.

7) Septum formation

The presence of fibrous septum formation within the tumor should be recorded.

8) Serosal invasion

No invasion: No invasion of the Glisson's capsule.

Glisson's capsule invasion: Invasion of the Glisson's capsule without extrahepatic invasion.

Peritoneal invasion: Invasion through the Glisson's capsule into the peritoneal cavity.

Adjacent organ invasion: Invasion through the Glisson's capsule into adjacent organs.

9) Portal vein invasion

Any portal vein invasion near the tumor should be documented.

10) Hepatic vein invasion

Any hepatic vein invasion near the tumor should be documented.

11) Hepatic artery invasion

Any hepatic artery invasion near the tumor should be documented.

12) Microvessel invasion

Any microscopic vascular invasion near the tumor should be documented.

13) Bile duct invasion

Any bile duct invasion near the tumor should be documented.

14) Intrahepatic metastasis and multicentric occurrence

While it is often difficult to distinguish intrahepatic metastasis from multicentric occurrence based on morphological findings alone, the presence of intrahepatic metastasis or multicentric occurrence should be documented where possible.

① The following findings favor intrahepatic metastasis

(a) A tumor arising from a neoplastic portal vein thrombus.

(b) Several satellite nodules observed near the main mass without evidence of a well-differentiated component (Edmondson-Steiner grade 1) in the nodules.

(c) An isolated nodule near the main tumor, with similar histological findings to the main mass. Differentiation is worse than moderate (Edmondson-Steiner grade II), and similar to or worse than the histologic grade of the main mass.

Figure 34. Intrahepatic cholangiocarcinoma, mass-forming type.

Figure 35. Intrahepatic cholangiocarcinoma, periductal infiltrating type.

Figure 36. Intrahepatic cholangiocarcinoma, intraductal growth type. The tumor (arrow) fills the bile duct lumen.

Figure 37. Cholangiocarcinoma, well differentiated (hematoxylin and eosin stain, x200).

Figure 38. Cholangiocarcinoma, poorly differentiated (hematoxylin and eosin stain, x200).

Figure 39. Combined hepatocellular cholangiocarcinoma. A mixture of hepatocellular carcinoma (white arrows) and cholangiocarcinoma (black arrows) is seen.

- ② The following findings favor multicentric occurrence
 - (a) When more than 2 tumors are present, at least one of them has a well-differentiated (Edmondson-Steiner grade I) HCC or dysplastic nodule component in at least part of the tumor.
 - (b) Two or more tumors of similar size are observed in different segments, with histologic evidence of multistep hepatocarcinogenesis.

15) Pathological tumor stage (pTNM)

The pathological T-stage and N-stage should be documented.

II. Intrahepatic Cholangiocarcinoma

3. Macroscopic classification of intrahepatic cholangiocarcinoma

The macroscopic classification of intrahepatic cholangiocarcinoma is as follows (Fig. 33-36).²⁰

- Mass-forming type
- Periductal infiltrating type
- Intraductal growth type
- Mixed type

1) Note for the macroscopic classification of intrahepatic cholangiocarcinoma

- ① The mass-forming type is a well-demarcated mass that is distinguishable from the surrounding liver.
- ② The periductal infiltrating type demonstrates an infiltrative growth along the bile duct, and often invades the blood vessels and hepatic parenchyma.
- ③ The intraductal growth type demonstrates a papillary growth of the tumor into the bile duct lumen, and it is often associated with an intraductal papillary neoplasm of the bile duct.
- ④ Mixed type cholangiocarcinomas demonstrate a mixture of 2 or more growth types, and should be recorded as the predominant type + secondary type.

4. Microscopic findings of intrahepatic cholangiocarcinoma

1) Differentiation of cholangiocarcinoma

Cholangiocarcinoma is classified according to degree of differentiation as well differentiated, moderately differentiated, poorly differentiated, or undifferentiated (Fig. 37, 38).

Figure 40. Combined hepatocellular and cholangiocarcinoma (hematoxylin and eosin stain, $\times 200$).

2) Histological type of cholangiocarcinoma

The histological types of cholangiocarcinoma are as follows:

- Adenocarcinoma
- Variants: Mucinous carcinoma, signet ring cell carcinoma, adenosquamous carcinoma, squamous cell carcinoma, mucoepidermoid carcinoma, and sarcomatous cholangiocarcinoma.

3) Note for the TNM of intrahepatic cholangiocarcinoma

For the pathological TNM staging of intrahepatic cholangiocarcinoma, the latest (seventh) edition of the American Joint Committee on Cancer (AJCC) staging of intrahepatic cholangiocarcinoma should be followed.¹¹

III. Combined Hepatocellular Cholangiocarcinoma

Combined hepatocellular cholangiocarcinoma refers to a tumor in which HCC and cholangiocarcinoma coexist within a single mass. Morphologically, it can be divided into the classical type and the combined hepatocellular cholangiocarcinoma with stem cell features type (Fig. 39, 40).²⁰ The classical type demonstrates a mixture of the typical findings of HCC and cholangiocarcinoma in the same tumor. The stem cell features type show a prominent component of tumor cells resembling hepatic stem/progenitor cells. For the pTNM staging of combined hepatocellular cholangiocarcinoma, the latest (seventh) edition of the AJCC staging of intrahepatic cholangiocarcinoma should be followed.

IV. Pathology of the Adjacent (non-tumorous) Liver

5. Pathology of the adjacent (non-tumorous) liver

1) Chronic hepatitis

The etiology, activity grade, and fibrosis stage of chronic hepatitis should be documented.

① Etiology

Etiologies such as hepatitis B virus, hepatitis C virus, alcohol, or others should be documented. If there are 2 or more etiologies, all etiologies should be recorded.

② Grading and staging of chronic hepatitis

Lobular activity and porto-periportal activity should be docu-

Figure 41. Intraductal papillary neoplasm of the bile duct (hematoxylin and eosin stain, $\times 12.5$).

mented as grades 0 to 4. The degree of hepatic fibrosis stage is also documented as stage 0 to 4. Chronic hepatitis should be graded and staged according to the rules established by the Gastrointestinal Pathology Study Group of the Korean Society of Pathologists.²¹

③ Liver cirrhosis (chronic hepatitis stage 4)

If cirrhosis is present, the type should be recorded as macronodular, micronodular, or mixed.

2) Dysplastic nodules

Dysplastic nodules are classified as low-grade and high-grade. If HCC is seen within a dysplastic nodule, it should be documented separately.

- Low-grade dysplastic nodule
- High-grade dysplastic nodule
- HCC in a dysplastic nodule

3) Hepatocellular adenoma

If a hepatocellular adenoma is seen in the adjacent hepatic parenchyma, or if HCC is seen within a hepatocellular adenoma, they should be recorded separately.

4) Biliary epithelial dysplasia

If biliary intraepithelial neoplasia (BilIN) or an intraductal papillary neoplasm of the bile duct (Fig. 41) is seen in the biliary epithelium, it should be recorded separately, along with the degree of dysplasia.

5) Other liver diseases

Any other liver diseases should be documented.

PATHOLOGICAL EXAMINATION OF LIVER SPECIMENS

- 1) The size and weight of the liver should be measured
- 2) A general inspection of external shape of the liver, the shape and the characteristics of the capsule, and the presence of Glisson's capsular invasion by the tumor is performed.
- 3) In the case of a partially resected liver, the specimen should be sectioned at 1-cm intervals perpendicularly from the largest dimension of the tumor demonstrating the distance between the tumor and the resection margin (Fig. 42A). If the entire liver is

Figure 42. Gross sampling of a resected liver specimen. (A) For partially resected livers, the specimens are sliced at 1-cm intervals perpendicularly to the surgical resection margin so that the relationship between the tumor and the resection margin is visible on the same plane. (B) After examining the cut surface of the tumor, sections are obtained for further microscopic examination. Sections should include (1) the relationship between the tumor and the Glisson's capsule; (2) the relationship between the tumor, the fibrous capsule and the adjacent liver parenchyma; (3) any areas of the tumor that grossly appear different, and necrosis, if present; (4) vascular invasion, if present; and (5) the relationship between the tumor and the surgical resection margin. To examine the non-neoplastic liver parenchyma, a section (6) should be obtained from the area furthest from the mass as possible. (C) For tumors with nodule-in-nodule patterns, sections that demonstrate the relationships between the inner nodule, outer nodule, and the surrounding parenchyma should be obtained.

removed for autopsy or liver transplantation, the liver should be sectioned at 1-cm intervals containing the largest cross-section of the liver and the porta hepatis.

- 4) Gross examination of the tumor, including the presence of vascular or bile duct invasion, is performed.
- 5) The cut section of the liver is fixed on a flat surface in a large container filled with 10% formalin solution with a volume 10 times that of the tissue.
- 6) After adequate fixation, sections from the tumor and the adjacent tissues should be obtained for microscopic examination as follows.
 - ① Sections should be taken from tumor parts showing different tumor characteristics, including the tumor and the adjacent parenchyma. Additional sections should be obtained if there is gross evidence of vascular or bile duct invasion, or satellite nodules (Fig. 42B).
 - ② If a nodule-in-nodule pattern is seen, sections including the inner nodule, outer nodule and the surrounding parenchyma on a same slide should be obtained (Fig. 42C).
 - ③ To assess surgical margin and Glisson's capsule involvement status, the surgical resection margin and the Glisson's capsule are inked, and sectioned at the points closest to the tumor. If the tumor is near the surgical resection margin or

the Glisson's capsule, sections including the tumor should be obtained.

- 7) To examine the non-neoplastic liver, additional sections are obtained from the liver parenchyma as far from the tumor as possible.
- 8) Note for pathologic examination of liver specimens
 - ① If necessary, the specimen can be sliced at planes that correlate with radiologic findings. The rest of the gross examination is performed as described above.
 - ② If necessary, gross photographs of the specimen are taken before and after fixation.
 - ③ In cases of multiple tumors, sections should be obtained from each nodule.

NON-SURGICAL TREATMENT OF HEPATOCELLULAR CARCINOMA

1. Types of non-surgical treatment

The non-surgical treatment of hepatocellular carcinoma (HCC) can be broadly divided into transarterial embolization (TAE), loco-regional therapy, and systemic chemotherapy. TAE is further divided into transarterial chemoembolization (TACE) and transarterial radioembolization (TARE). TACE is further divided into conventional TACE (cTACE), which uses lipiodol and gelfoam, and drug-eluting bead TACE (debTACE), which uses drug-eluting beads. Some loco-regional therapies currently in use are radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), cryoablation, and microwave ablation. Moreover, systemic chemotherapy can be divided into targeted therapy and cytotoxic chemotherapy.

2. Transarterial embolization²²

TAE should be recorded according to the following guidelines.

1) Number, size, and location

The number, size, and location should be recorded for the HCC that underwent treatment.

2) Portal vein thrombosis

The presence or absence of portal vein thrombosis should be recorded based on a computed tomography (CT) scan taken before the procedure or indirectly based on angiography conducted during the procedure.

No: Absence of portal vein thrombosis.

Yes: Presence of portal vein thrombosis.

3) Extrahepatic collateral arteries supplying the tumor(s)

No: Absence of extrahepatic collaterals.

Yes: Presence of extrahepatic collaterals.

4) Type of procedure

① Transarterial chemoinfusion

② Transarterial embolization

(a) Conventional TAE

(b) Transarterial radioembolization

③ Transarterial chemoembolization

- (a) Conventional TACE (cTACE)
- (b) Drug-eluting bead TACE (debTACE)

5) Extent of embolization

No: No embolization.

Yes: Extent of embolization (1 = only the tumor; 2 = segment including the tumor; 3 = lobe including the tumor; 4 = the entire liver).

3. Radiofrequency ablation²³⁻²⁷

Radiofrequency ablation for HCC should be recorded according to the following guidelines.

1) Number, size, and location

The number, size, and location should be recorded for HCC that underwent treatment.

2) Treatment pathway

The treatment pathway should be recorded as percutaneous, laparoscopic, or laparotomic.

3) Type of electrode

The type of electrode used for the procedure should be recorded, along with the length of the active tip.

4) Guiding modality

The guiding modality used for electrode implantation should be recorded as ultrasonography (US), CT, or fluoroscopy. If a different modality was used, the modality should be recorded in the "other" column.

5) Use of artificial ascites/artificial pleural effusion

The use of artificial ascites or artificial pleural effusion during the procedure should be recorded. If used, the dosage should be recorded as well.

6) Total procedure time and ablation time

The total procedure time and the ablation time should be recorded, respectively.

7) Safety of the electrode insertion route

The safety of the electrode insertion route used for the treatment of HCC should be assessed. The assessment should be marked with a 1 if the expected insertion route is more than 5 mm away from a blood vessel, and if no other organs (e.g., ribs, lower lungs, or gastrointestinal tract) are located within the route. The assessment should be marked with a 2 if the expected insertion route is 3-4 mm away from a blood vessel, and marked with a 3 if the expected route is 1-2 mm away from a blood vessel. The assessment should be marked with a 4 if blood vessels or other organs (e.g., ribs, lower lungs, gastrointestinal tract) are located within the expected insertion route.

8) Topology of the adjacent organs

The topology of HCC and the adjacent organs, such as the diaphragm, bile duct and the gall bladder, lower lungs, stomach, and the large intestine, should be assessed. The assessment should be marked

with a 1 if the HCC is more than 5 mm away from an adjacent organ. The assessment should be marked with a 2 if the HCC is 3-4 mm away from an adjacent organ, and marked with a 3 if the carcinoma is 0-2 mm apart from an adjacent organ. If the HCC is tangent to the adjacent organ at an angle greater than 90°, the assessment should be marked with a 4. In such cases, the topology with the adjacent organs can be reassessed after injection of artificial ascites or artificial effusion.

9) Topology of the surrounding blood vessels

The topology of the HCC and its surrounding blood vessels should be assessed. The assessment should be marked with a 1 if the HCC is 5 mm away from a blood vessel that is larger than 3 mm. The assessment should be marked with a 2 if the HCC is 3-4 mm away from such a blood vessel, and marked with a 3 if the HCC is 0-2 mm away from such a blood vessel. If the HCC is tangent to a blood vessel larger than 3 mm at an angle greater than 90°, the assessment should be marked with a 4.

10) Conspicuity of the HCC on ultrasonography

The conspicuity of the treated HCC should be assessed using US. The assessment should be marked with a 1 if the HCC is clearly visible, regardless of the respiration cycle. The assessment should be marked with a 2 if the HCC is clearly visible during certain respiration cycles, and marked with a 3 if only parts of the HCC are visible during certain respiration cycles involving deep breathing. If the HCC is not visible, the assessment should be marked with a 4. To accurately identify HCC, techniques such as contrast-enhanced US, or fusion imaging combining US with CT or magnetic resonance is needed.

4. Targeted therapy

Currently, sorafenib is the only drug of targeted therapy for the treatment of HCC. Targeted therapy should be recorded according to the following guidelines.

1) Type and quantity of the targeted therapy drug

The type and quantity of the targeted therapy drug should be recorded. If the dosage is reduced, it should be recorded along with the amount of the reduction.

No: No reduction.

Yes: Reduction of dosage. The amount and the reason of reduction should be recorded.

2) Adverse event to the targeted therapy drug

Any adverse event that occurs following the treatment should be recorded. The severity of the adverse event is generally divided into 5 grades (with grades 1-5 corresponding to mild, moderate, severe, life-threatening, and fatal, respectively). The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) should be used as a reference when recording the entries.

3) Treatment duration

The treatment duration (days) of the targeted therapy should be

recorded.

4) Treatment response

The most favorable tumor response observed out of all the treatment modalities should be assessed and recorded. Refer to Chapter 12 (Assessment of Tumor Response after Nonoperative Treatment of Hepatocellular Carcinoma) for defining the tumor response.

5) Reason for termination/discontinuation

The reason for termination or discontinuation should be described.

SUMMARY OF RADIOTHERAPY FOR HEPATOCELLULAR CARCINOMA²⁸

1. Basic information, risk factors, and liver function assessment of patients before radiotherapy

Before performing radiotherapy for hepatocellular carcinoma (HCC), the baseline information and the liver function of the patient should be recorded according to the method used for entering medical findings.

2. Summary of the previous treatments before radiotherapy

Treatments other than radiotherapy should be summarized according to the guidelines below.

1) Summary of HCC treatment before radiotherapy

Treatments carried out 4 weeks or more before the start of radiotherapy are not considered to be concurrent, and should therefore be summarized as part of the previous treatment history.

- Surgery: Whether it was carried out, date of operation, type of surgery, and number of operations.
- Radiofrequency ablation: Whether it was carried out, date of operation, and number of operations.
- Transarterial chemoembolization: Whether it was carried out, date of operation, and number of operations.
- Transarterial chemoinfusion: Whether it was carried out, date of operation, and number of operations.
- Percutaneous ethanol injection: Whether it was carried out, date of operation, and number of operations.
- Hepatic arterial infusion chemotherapy: Whether it was carried out, date of operation (duration), number of operations, and chemotherapy drugs.
- Systemic chemotherapy: Whether it was carried out, date of operation (duration), number of operations, and chemotherapy drugs.
- Other treatment: Treatment name, whether it was carried out, date of operation (duration), and number of operations.

2) Summary of combined therapy during radiotherapy

- ① If treatments other than radiotherapy (e.g., transarterial chemoembolization or hepatic arterial infusion chemotherapy)

are carried out as combined therapies, they should be indicated as such.

- ② Because not all combined therapies are carried out simultaneously, only treatments performed within 4 weeks before or after radiotherapy should be considered combined therapies.
- ③ Treatment details should be summarized according to the contents of item ①.

3. Staging and radiological findings of hepatocellular carcinoma before radiotherapy

The staging system and the methods of reporting radiological findings described in the rulebook should be used as a reference when recording the staging and radiological findings of HCC before radiotherapy.

4. Summary of radiotherapy for hepatocellular carcinoma

Radiotherapy should be summarized and recorded as follows.

1) Overall summary

- ① Duration of radiotherapy: The start date and the end date should be recorded.
- ② Total dose
- ③ Daily dose (fraction size)
- ④ Radiotherapy machines: Linear accelerator, tomotherapy, cyberknife radiosurgery system, proton therapy, or other

2) Summary of techniques of radiotherapy

- ① Techniques of radiotherapy
 - (a) Two-dimensional radiotherapy
 - (b) Three-dimensional conformal radiotherapy
 - (c) Intensity-modulated radiotherapy
 - (d) Stereotactic body radiotherapy
- ② Whether a 4-dimensional computerized tomography scan was conducted.
- ③ Whether respiratory control was carried out during treatment, with options including free breathing, respiratory control, and abdominal pressure.
- ④ Whether respiration-gated radiotherapy was conducted. The method, such as gating, tracking, and breath-holding, should be recorded.
- ⑤ Whether image-guided radiation therapy was conducted and its cycle.

3) Notation for tumor volume, normal organs, and treatment sites

- ① For proper radiotherapy, the tumor site and the adjacent normal organs should be recorded, as well as the following:
 - Gross tumor volume
 - Planned target volume
 - Total liver volume
 - Normal liver volume: The total liver volume minus the gross tumor volume (optional entry)
- ② The radiotherapy site should be recorded based on the items

Table 25. Description of radiotherapy for HCC

(Example)	Hepatocellular carcinoma and lymph node metastasis, hepatocellular carcinoma and portal vein invasion - Hepatocellular carcinoma - Portal vein/hepatic vein/inferior vena cava invasion - Bile duct invasion - Metastatic lesion: Describe whether it is lymph node metastasis, distant organ metastasis, or peritoneal seeding, and additionally record the organ or site.
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HCC, hepatocellular carcinoma.

below. The items can be aggregated and used according to the treatment plan (Table 25).

5. Assessment of tumor response after radiotherapy

The assessment of tumor response after radiotherapy should be recorded according to the standards in the rulebook for the assessment of tumor response after nonoperative treatment. However, because the response after radiotherapy can appear as early as 1 to 2 months and as late as 3 to 6 months, the assessment time for treatment response should be determined using clinical judgment.

ASSESSMENT OF TUMOR RESPONSE AFTER NON-SURGICAL TREATMENT OF HEPATOCELLULAR CARCINOMA

1. Patients who should be assessed

The tumor response assessment targets patients who have undergone treatment other than curative hepatic resection or liver transplantation for hepatocellular carcinoma (HCC) based on a histological diagnosis or the clinical diagnostic criteria of the Korean Liver Cancer Association Guidelines.

2. Checklist for tumor response assessment²⁹

When assessing the tumor response, the following parameters should be reported.

- Method of HCC diagnosis
- Initial treatment or treatment for a recurrent tumor
- Type and method of treatment
- Start date, end date, and duration of the treatment
- Any side effects of the treatment
- Any recurrence after the assessment of treatment response, as well as time of recurrence
- Any extrahepatic metastasis

3. Principles of tumor response assessment

The tumor response should be assessed based on the revised Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) or the modified RECIST for HCC (mRECIST for HCC).^{30,31}

The principles underlying these criteria are as follows.

1) Measurement of the tumor lesion

The size of the tumor lesion should be measured using a same

method during the assessment period. It is advisable to conduct imaging tests using a same protocol. Usually, the slice thickness for dynamic contrast-enhanced computed tomography (CT) should not exceed 5 mm. Comparisons of imaging test results should be made using the same anatomical cross-section. The metric system should be used for all measurements. It is recommended that the assessment of all data during the baseline study be carried out within 4 weeks before treatment.

A viable tumor is defined by mRECIST as a site where contrast enhancement appears inside the tumor in the arterial phase of contrast-enhanced CT or magnetic resonance imaging (MRI). The maximum diameter of continuous arterial enhancement inside the tumor should be measured and must not extend into the necrosis site. The maximum diameter of the viable tumor does not have to be measured on the same image plane before and after treatment.

Tumor markers cannot be used to assess tumor response. However, in principle, tumor markers must be normalized if a tumor exhibits complete response (CR).

2) Tumor lesion at baseline

① Measurable and non-measurable lesions

The tumor lesions found in the baseline study are categorised into measurable lesion and non-measurable lesion. For special circumstances, additional considerations should be applied.³⁰

(a) Measurable lesions

- A tumor lesion ≥ 10 mm observed in dynamic contrast-enhanced CT.
- For lymph nodes, the short axis observed in CT imaging should be ≥ 15 mm.

(b) Non-measurable lesions

- A tumor lesion < 10 mm observed in dynamic contrast-enhanced CT.
- An abnormal lymph node ≥ 10 mm and < 15 mm.
- Cases involving ascites and pleural effusion, pericardial effusion, lymphatic vessels, or lymphangitic involvement of the lungs, which is not actually measurable by imaging tests.
- Under mRECIST, malignant portal vein thrombosis is classified as a non-measurable lesion.

(c) Special considerations

- Decisions regarding special circumstances, such as bone metastasis, cystic lesion, and preexisting lesions treated with radiation therapy or loco-regional therapy, should be made by a clinician according to the following criteria.

* In the case of bone metastasis, if the soft tissue component of an osteolytic metastatic lesion meets the above criteria, it can be classified as a measurable lesion, while osteoblastic metastatic lesions should be classified as non-measurable lesions.

* While simple cysts are not included as a subject of assessment, in the case of tumor lesions with cystic changes, the lesion should be classified as measurable or non-measurable according to the above criteria.

* Lesions treated with radiation therapy or loco-regional therapy

Table 26. Definitions of target lesion response according to RECIST version 1.1 and mRECIST

Criterion		RECIST version 1.1	mRECIST
Measurable lesion		A tumor ≥ 10 mm, lymph node with a short axis ≥ 15 mm	A non-interrupted arterially enhancing portion of the hepatic lesion ≥ 10 mm
Measurement method		Sum of the largest diameters of the measurable lesions (short axis for lymph nodes)	Sum of the largest diameters of the measurable lesions
Response criteria	Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in the short axis to < 10 mm	Disappearance of any intratumoral arterial enhancement in all target lesions
	Partial response (PR)	A decrease of at least 30% from baseline in the sum of the diameters of the target lesions	A decrease of at least 30% from baseline in the sum of diameters of viable (enhancement in the arterial phase) target lesions
	Stable disease (SD)	Any cases that do not qualify for CR, PR, or PD	Same as RECIST version 1.1
	Progressive disease (PD)	An increase of at least 20% in the sum of the diameters of the target lesions, taking as reference the smallest sum that was studied (including the baseline sum if that is the smallest). The sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of the viable (enhancing) target lesions

CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Table 27. Definitions of non-target lesion responses according to RECIST version 1.1 and mRECIST

Criterion		RECIST version 1.1	mRECIST
Complete response (CR)		Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (< 10 mm short axis)	Disappearance of any intratumoral arterial enhancement in all non-target lesions
Incomplete response/non-progressive disease (non-CR/non-PD)*		Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker levels above the normal limits	Persistence of intratumoral arterial enhancement in 1 or more non-target lesions
Progressive disease (PD)		Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression)†	Same as RECIST version 1.1‡

*mRECIST uses the terms "incomplete response" and "stable disease."

†Determining a non-target lesion to be an instance of progressive disease (PD) should only be limited to cases where a significant difference is exhibited before and after treatment. Minor changes in certain lesions should not be determined as indicative of PD.

‡mRECIST only defines cases as progressive disease when effusion (in which the cytological diagnosis has been advanced) newly arises or when the amount increases. This is because regardless of the state of HCC, ascites and pleural effusion could occur as a result of the underlying liver disease, and because the peritoneal and pleural metastasis of HCC is relatively rare.

CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors; SD, stable disease.

are classified as non-measurable unless distinct signs of progression are present, but if necessary, a determination of whether such lesions are measurable should be made beforehand.

② Target lesions and non-target lesions

A target lesion is defined as a lesion that is subject to measurement. More than 1 measurable lesion must be present during the baseline study. Up to 2 target lesions can be selected per involved organ. If more than 5 target lesions are present in the involved organs, only 5 of the lesions should be selected, in order of size. According to

mRECIST, the target lesion must be an intrahepatic lesion that includes an arterially enhancing portion larger than 10 mm, and the reproducibility of the targeted lesion measurement must be excellent. It is advisable to define atypical hypovascular or diffuse infiltrative HCC as non-target lesions. The following should also be considered non-target lesions: perihilar lymph nodes with a short axis larger than 20 mm, malignant portal vein thrombosis, and malignant effusion that is confirmed cytologically. The sum of the longest (short axis for lymph node) diameters of all target lesions at baseline becomes a

Table 28. Criteria for overall tumor response according to RECIST version 1.1

Target lesion	Non-target lesion	New lesion	Overall tumor response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Non-target lesions should be regarded as non-CR/non-PD, unless they are CR (disappearance of all non-target lesions and normalization of tumor marker levels, with all lymph nodes non-pathological in size [<10 mm short axis]) or PD (unequivocal progression of existing non-target lesions, or the appearance of 1 or more new lesions).

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Table 29. Criteria for overall tumor response according to mRECIST

Target lesion	Non-target lesion	New lesion	Overall tumor response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR, complete response; IR, incomplete response; PD, progressive disease; PR, partial response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; SD, stable disease.

comparator for subsequent assessments. All measurable and non-measurable lesions other than target lesions should be classified as non-target lesions and should be identified during the baseline study.

3) Post-treatment tumor response

In RECIST version 1.1 and mRECIST, the overall tumor response is determined by considering the criteria for the target lesions, non-target lesions, and new lesions.

① Target lesions

The response criteria for target lesions are as follows (Table 26).

② Non-target lesions

The response criteria for non-target lesions are as follows (Table 27).

③ New lesions

If a new lesion is definitely confirmed, progressive disease should be declared regardless of favorable responses of the target or non-target lesion. Therefore, decisions on detection of a new lesion must be made carefully, and only lesions that imaging studies definitively confirm should be included. A fluorodeoxyglucose-positron emission tomography (FDG-PET) scan can be used to determine the presence or absence of new lesions. If a FDG-PET scan was not obtained before treatment, the new lesions discovered by FDG-PET must be also confirmed as new lesions on a CT or MRI scan.

Based on the American Association for the Study of Liver Diseases (AASLD) practice guidelines, a new intrahepatic lesion is defined by mRECIST as a lesion larger than 10 mm that shows both arterial hyperenhancement and portal venous/delayed washout. If an arterially enhancing lesion <10 mm is discovered and not determined to be a new lesion (or progressive disease), but later determined to be a new lesion due to the increase in tumor size, the time of disease progression should be inferred retrospectively, and should be recorded as the time when the lesion <10 mm was first discovered. If the lesion is ≥ 10 mm but does not exhibit the typical enhancement pattern, it can be diagnosed as HCC if an additional increase in size occurs in later follow-up imaging.

4) Overall tumor response

The assessment of the overall tumor response should take into account the target lesions, non-target lesions, and new lesions (Table 28, 29).

4. Assessment of response according to treatment methods

When the tumor is treated using a cyclic anticancer therapy, assessment of the tumor response can be usually repeated over 6-week

to 8-week intervals (usually double the treatment intervals). However, because the tumor response for HCC differs depending on the treatment, the time point for the assessment should be determined based on clinical judgment. In particular, the response after radiation therapy could appear as early as 1-2 months and as late as 3-6 months.

Dynamic contrast-enhanced CT is generally used for assessment after transarterial chemoembolization (TACE) and other local treatment. In many cases, the change in tumor size is small despite extensive necrosis of the tumor, so mRECIST that reflects the degree of necrosis could be considered.^{31,32} Lipiodol in the tumor may decrease the accuracy of contrast-enhanced CT, dynamic contrast-enhanced MRI can be an alternative. The criteria for the imaging assessment of treatment effects after TACE and local treatment are presented below.

1) Transarterial chemoembolization (TACE) and drug-eluting bead transarterial chemoembolization (debTACE)

- ① The site where lipiodol is deposited within the HCC should be regarded as necrosis. Because debTACE does not use lipiodol, the size of the viable tumor should be determined as in other cases of local treatment.
- ② For HCC that was contrast-enhanced during the arterial phase of pre-treatment CT, the intratumoral portion without lipiodol uptake is considered a viable tumor if it is contrast-enhanced.
- ③ When determining contrast enhancement using Hounsfield units (HU), an increase of more than 20 HU after contrast enhancement in intratumoral portions without lipiodol uptake is considered to be contrast enhancement.
- ④ If HU cannot be measured, contrast enhancement should be determined by a radiologist.

2) Percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA)

- ① For HCC that was contrast-enhanced during the arterial phase of pre-treatment CT, low-density sites without contrast enhancement should be regarded as necrosis.
- ② If focal contrast enhancement is present within the tumor, it should be considered a viable tumor.
- ③ If focal contrast enhancement is present around the necrosis site, a decision should be made by a radiologist by evaluating the following imaging features in the portal venous or delayed phase.
 - Viable tumor: if washout appears in the focal enhancing area.
 - Arterioportal shunt: if the focal enhancing area appears to become isodense to the liver.
 - Blood vessel or reactive hyperemia: if the focal enhancing area appears to become hyperdense to the liver.
- ④ Hypovascular HCC should be determined as having no viable tumor immediately after treatment if a low-density area from treatment covers the entire tumor.

3) Systemic anti-cancer therapy (targeted therapy and cytotoxic chemotherapy)

The treatment response should be assessed using the criteria defined by RECIST version 1.1 or mRECIST.

4) Radiation therapy and 90 Y transarterial radioembolization

- ① The treatment response should be assessed using the criteria defined by RECIST version 1.1 or mRECIST. Non-target lesion assessment is important because it is often used to assess treatment response in infiltrative HCC and malignant portal vein thrombosis.
- ② If focal contrast enhancement is present around the tumor, a decision should be made by a radiologist by evaluating the following imaging features in the portal venous or delayed phase.
 - Viable tumor: if washout appears in the focal enhancing area.
 - Arterioportal shunt: if the focal enhancing area appears isodense to the liver.
 - Blood vessel or reactive hyperemia: If the focal enhancing area appears hyperdense to the liver.
- ③ Hypovascular HCC should be determined as having no viable tumor immediately after treatment if a low-density area from treatment covers the entire tumor.

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Supplementary material

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