APPENDIX 3,
LIST OF CLINICAL QUESTIONS

Internal Medicine

1. Could the incidence of HCC be reduced by primary, secondary, or tertiary prevention?
P: General public subject to preventive measures (primary prevention), group with risk of HCC (secondary prevention), and group with risk of HCC recurrence (tertiary prevention)
I: Group that underwent preventive measures
C: Group that did not undergo preventive measures
O: HCC incidence rate (primary and secondary prevention), recurrence rate (tertiary prevention), survival rate

1-1. Does DAA reduce HCC incidence in chronic hepatitis C?
P: Group of patients with chronic hepatitis C
I: DAA treatment group
C: Non-DAA treatment group
O: HCC incidence rate

2. Can an HCC surveillance test reduce mortality in the high-risk group?
P: Group with high risk of liver cancer
I: Group that underwent a liver cancer surveillance test
C: Group that did not undergo a liver cancer surveillance test
O: Mortality related to HCC

3. What should be done for an indeterminate nodule not definitively diagnosed by imaging?
P: Patients with indeterminate nodules that cannot be diagnosed definitively as HCC
I: Pathologic diagnosis through biopsy
C: Repeated imaging and follow-up of tumor markers
O: Accuracy of diagnosis

4. What tests should be performed to investigate extrahepatic spread after HCC diagnosis?
P: Patients diagnosed with HCC
I: Additional imaging performed
C: Additional imaging not performed
O: Evaluation of extrahepatic spread and accurate staging

5. Which HCC staging system is suitable for South Korea?
P: HCC staging system
I: mUICC staging
C: Non-mUICC staging
O: Accuracy in prediction of prognosis and treatment plan

6. Which criteria can be used to assess the response to HCC treatment?
P: HCC patients
I: Assessment of tumor response (WHO criteria, RECIST, mRECIST, RECIST 1.1, iRECIST, CHO criteria)
C: Survival rate
O: Correlation

7. Is additional anticancer adjuvant therapy or immunotherapy necessary after radical hepatic resection or locoregional therapy?
P: Patients who underwent radical hepatic resection or locoregional therapy
I: Additional adjuvant therapy, such as anticancer treatment or immunotherapy
C: Monitoring without additional adjuvant therapy
O: Decrease in recurrence rate, increase in survival rate

8. Does systemic therapy improve the overall survival of HCC patients with preserved liver function, vascular invasion, and/or extrahepatic metastasis compared to the best supportive care?
P: HCC patients with vascular invasion and/or extrahepatic metastasis
I: Systemic therapy
C: Best supportive care
O: Overall survival (OS)

9. Does systemic therapy improve the overall survival of HCC patients with preserved liver function and vascular invasion compared to locoregional therapy?
10. What is the definition of TACE refractoriness, and what is the effective treatment for these patients?
   P: HCC patients with TACE refractoriness
   I: Systemic therapy, HAIC
   C: TACE or best supportive care
   O: OS, PFS, safety

11. What is the first-line systemic therapy for patients with advanced HCC?
   P: Treatment naïve HCC patients
   I: Immune checkpoint inhibitor-based systemic therapy
   C: Tyrosine kinase inhibitor
   O: OS, safety

12. Does second-line systemic therapy show improvement in the overall survival for patients with sorafenib failure compared to the best supportive care?
   P: HCC patients with sorafenib failure
   I: Systemic therapy
   C: Best supportive care
   O: OS

13. What is an effective second-line treatment for HCC patients who have failed first-line therapy other than sorafenib?
   P: HCC patients with first-line failure other than sorafenib
   I: Systemic therapy
   C: Best supportive care
   O: OS

14. Does the combination of systemic therapy and locoregional therapy show improvement in the overall survival compared to systemic treatment alone for patients with preserved liver function and vascular invasion?
   P: HCC patients with vascular invasion
   I: Systemic therapy and/or TACE/TARE and/or radiotherapy, HAIC combination therapy
   C: Systemic therapy alone
   O: OS

Surgery

1. In what case is hepatic resection suitable for primary treatment of HCC?
   P: HCC patients
   I: Liver resection
   C: Other treatment modalities
   O: OS

2. Is hepatic resection suitable for HCC accompanied by portal hypertension or hyperbilirubinemia?
   P: HCC patients with portal hypertension or hyperbilirubinemia
   I: Liver resection
   C: Other treatment modalities
   O: OS, quality of life

3. Is hepatic resection useful for progressed HCC patients?
   P: Advanced stage HCC patients
   I: Liver resection
   C: TACE, RT, sorafenib
   O: DFS, OS

4. In what case can laparoscopic hepatic resection be performed?
   P: HCC patients
   I: Laparoscopic liver resection
   C: Conventional open liver resection
   O: DFS, OS, complications, quality of life

5. In what case is liver transplantation suitable for primary treatment of HCC?
   P: HCC patients
   I: Liver transplantation
   C: TACE, RT, sorafenib
   O: OS
6. When is the right time to perform bridging therapy for HCC prior to liver transplantation?
   P: HCC patients within Milan criteria
   I: Local ablation treatment or TACE
   C: Conservative treatment
   O: DFS, OS

7. Is liver transplantation useful after downstaging for progressive HCC patients?
   P: Advanced stage HCC patients
   I: Liver transplantation after downstaging
   C: TACE, RT, sorafenib
   O: DFS, OS

8. Is liver transplantation useful for HCC patients beyond the Milan criteria without vascular invasion or extra-hepatic metastasis?
   P: HCC patients above Milan criteria without vascular invasion or extra-hepatic metastasis
   I: Liver transplantation
   C: TACE, RT, sorafenib
   O: DFS, OS

9. Is salvage liver transplantation useful for HCC patients whose disease recurred after hepatic resection?
   P: Recurred HCC patients after liver resection
   I: Salvage liver transplantation
   C: Liver resection, ablation therapy, TACE
   O: DFS, OS

Radiology

1. What is the definition of high-risk group that allows non-invasive diagnosis with typical imaging features of HCC?
   P: Patients suspected of having HCC
   I: High-risk group
   C: Low-risk group
   O: HCC prevalence, sensitivity, specificity

2. Can contrast-enhanced ultrasound using Kupffer cell-specific contrast agent (Sonazoid) be a non-invasive diagnostic test for HCC?
   P: Newly detected liver nodule (≥1 cm) in high-risk patients
   I: Sonazoid-enhanced CEUS
   C: SonoVue-enhanced CEUS, CT, MRI
   O: Sensitivity, specificity

3. Can different imaging modalities be comprehensively interpreted to evaluate typical imaging features?
   P: Newly detected liver nodule (≥1 cm) in high-risk patients
   I: Two or more imaging modalities
   C: Single imaging modality
   O: Sensitivity, specificity

4. Can arterial subtraction imaging be used to detect arterial phase hyperenhancement on MRI?
   P: Liver nodule (≥1 cm) on MRI
   I: Arterial subtraction imaging is used
   C: Arterial subtraction imaging is not used
   O: Sensitivity, specificity

5. Which imaging criteria can be used to diagnose “probable” HCC?
   P: Liver nodule (≥1 cm) without typical imaging features
   I: Combination of radiological hallmarks and ancillary imaging features
   C: Combination of ancillary imaging features
   O: Sensitivity, specificity

6. Can “definite” or “probable” HCC be non-invasively diagnosed for nodules smaller than 1 cm?
   P: Liver nodule smaller than 1 cm
   I: Non-invasive diagnosis using typical imaging findings (+ancillary imaging features) is allowed
   C: Non-invasive diagnosis is not allowed
   O: Sensitivity, specificity

7. Which imaging criteria can be used to diagnose intrahepatic recurrent HCC for newly detected nodule in the follow-
up study after treatment of HCC?
P: Newly detected nodule in the post-treatment follow-up study
I: Combination of radiological hallmarks and ancillary imaging features
C: Same to the nodule detected in treatment-naïve patients
O: Sensitivity, specificity

8. Are similar results expected from RFA for surgical resection for HCC in terms of survival rate?
P: HCC patients
I: RFA
C: Hepatic resection
O: OS, PFS, TTP, complications

9. Is RFA superior to ethanol injection for HCC patients?
P: HCC patients
I: RFA
C: Ethanol
O: OS, PFS, TTP, complications

10. Is the combined treatment of RFA and TACE superior to RFA alone for HCC patients?
P: HCC patients
I: RFA + TACE
C: RFA alone
O: OS, PFS, TTP, complications

11. Are cryoablation and microwave ablation useful local ablation therapies compared to RFA for HCC?
P: HCC patients
I: Cryoablation, microwave ablation
C: RFA, ethanol ablation
O: OS, PFS, TTP, complications

12. In what cases is TACE appropriate as an initial treatment for HCC?
P: HCC patients
I: TACE
C: Other treatment modalities
O: OS

13. Is superselective TACE useful in TACE for HCC?
P: HCC patients
I: Selective TACE
C: Non-selective TACE
O: Tumor response, OS

14. Is it appropriate to perform TACE for advanced-stage HCC?
P: Advanced stage HCC patients
I: TACE
C: Conservative treatment, systemic chemotherapy
O: OS, quality of life

15. Is the combined treatment of TACE and systemic therapy superior to TACE alone for HCC?
P: HCC patients
I: TACE + systemic therapy
C: TACE alone
O: Tumor response, TTP, OS

16. Can DEB-TACE be considered as a standard therapy alternative to cTACE?
P: HCC patients
I: DEB-TACE
C: Conventional TACE
O: OS, PFS, TTP, complications, cost

17. Can TARE be considered as an alternative standard therapy to cTACE?
P: HCC patients
I: TARE
C: TACE
O: OS, PFS, TTP, complications, cost

**Radiation Oncology**

1. Can external-beam radiation therapy (radiotherapy including hypofractionated radiotherapy, stereotactic body radiotherapy, and particle radiotherapy) be performed for HCC in which hepatic resection or locoregional therapy is impossible?
P: HCC in which hepatic resection or locoregional therapy is impossible
I: External-beam radiation therapy (including particle radiotherapy, hypofractionated radiotherapy, or stereotactic body radiotherapy)
C: TACE (transarterial chemoembolization)
O: Treatment result (overall survival, local control, progression-free survival, toxicity)

2. In what case can external-beam radiation therapy be performed safely? What are the indications?
P: HCC patients
I: External-beam radiation therapy
C: Dose-volumetric parameters
O: Radiation-induced liver toxicity

3. Is the combined treatment with external-beam radiation therapy effective for HCC in which TACE is expected to show an inadequate effect?
P: Locally advanced HCC patients
I: Combined treatment with transarterial chemoembolization and external-beam radiation therapy
C: Transarterial chemoembolization alone
O: Overall survival

4. Can external-beam radiation therapy be performed for HCC with macrovascular invasion?
P: HCC patients with macrovascular invasion
I: External-beam radiation therapy
C: Targeted agent (sorafenib)
O: Overall survival

5. Can external-beam radiation therapy be performed to alleviate pain caused by distant metastases of HCC or symptoms of metastatic cancer?
P: Patients with symptomatic HCC or metastatic disease
I: External-beam radiation therapy
C: Supportive care or systemic treatment
O: Symptom palliation/local control

6. Can external-beam radiation therapy perform the role of down-staging for surgical treatment in progressive HCC?
P: Locally advanced HCC patients
I: External-beam radiation therapy
C: Targeted agent (sorafenib)
O: Safety/overall survival

7. Can external-beam radiation therapy be performed for HCC that has relapsed (refractory) after hepatic resection, radiofrequency ablation, ethanol injection, or TACE?
P: Recurrent or refractory HCC after locoregional treatment
I: External-beam radiation therapy
C: Repeated resection, radiofrequency ablation, ethanol injection, or transarterial chemoembolization
O: Treatment result (overall survival, local control, progression-free survival, toxicity)