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?

P: HCC patients with vascular invasion
I: Systemic therapy
C: TACE/TARE or EBRT, HAIC
O: OS

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)