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

6. What criteria can we use to assess the response to HCC treatment?
   P: HCC patients
   I: Assessment of tumor response (WHO criteria, RECIST, mRECIST, RECIST 1.1, iRECIST, Choi criteria)
   C: Survival rate
   O: Correlation

7. At what intervals and how should we follow up recurrence after radical treatment, such as locoregional therapies, hepatic resection, liver transplantation, etc.?
   P: HCC patients with radical treatment
   I: Dynamic contrast-enhanced imaging
   C: Alternate interval (3 months/6 months/9 months/12 months) test
   O: HCC incidence rate, survival rate

8. 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
Appendix 3. Continued

9. After full recovery of HCC, does DAA increase recurrence of HCC?
   P: Group showing full recovery after HCC treatment
   I: DAA treatment group
   C: Non-DAA treatment group
   O: HCC recurrence rate

10. What is the suitable secondary treatment for HCC that has recurred after radical treatment, such as locoregional therapies, hepatic resection, liver transplantation, etc.?
    P: HCC relapsed after radical treatment
    I: Surgical (hepatic resection, liver transplantation) treatment group
    C: Non-surgical (radiofrequency ablation, TACE, sorafenib) treatment group
    O: Survival rate

11. What is the definition of TACE refractoriness and the secondary treatment for these patients?
    P: Patients who received TACE for HCC where hepatic resection/transplantation is impossible
    I: Sorafenib, HAIC, TACE+sorafenib
    C: Continue TACE or best supportive care
    O: Survival rate

12. What are the molecular targeted agents and immunotherapy agents that can be primarily used on progressive HCC patients aside from sorafenib, and what are the effects?
    P: Progressive HCC patients
    I: Molecular targeted agents and immunotherapy agents
    C: Placebo or standard treatment (sorafenib)
    O: Total survival period

13. What is the effective secondary targeted agent for patients who failed treatment with sorafenib?
    P: Patients who received sorafenib treatment for HCC but failed treatment
    I: Regorafenib, nivolumab, cabozantinib
    C: Conservative treatment
    O: Survival rate

14. What are the effects and safety of combined treatment of sorafenib and locoregional therapy for progressive HCC?
    P: Progressive HCC patients
    I: Combined treatment of sorafenib and locoregional therapy
    C: Sorafenib alone
    O: Survival rate and safety

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
Appendix 3. Continued

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 suitable diagnostic test for patients suspected of having HCC?
   P: Patients suspected of having HCC
   I: Dynamic contrast-enhanced CT
   C: Dynamic contrast-enhanced MRI, hepatocyte-specific contrast-enhanced MRI, contrast-enhanced sonography
   O: Sensitivity, singularity

2. What is the standard method of imaging diagnosis for patients suspected of having HCC?
   P: Patients suspected of having HCC
   I: Opinions about wash out in arterial phase contrast enhancement/portal phase or delayed phase
   C: Auxiliary image opinions
   O: Sensitivity, singularity

3. Can HCC be diagnosed for nodules smaller than 1 cm on patients suspected of having HCC?
   P: Patients suspected of having HCC
   I: HCC smaller than 1 cm
   C: HCC that is 1 cm or bigger
   O: Sensitivity, singularity
Appendix 3. Continued

4. Is the standard method of imaging diagnosis the same in the initial diagnosis as in already diagnosed HCC patients?
   P: HCC patients already diagnosed
   I: Application of the same image diagnosis standard as initial diagnosis
   C: Application of an image diagnosis standard different from initial diagnosis
   O: Accuracy of diagnosis

5. Should radiation dose be considered when performing CT for HCC patients?
   P: HCC patients
   I: CT performed
   C: CT not performed
   O: Risk-benefit analysis

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

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

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

9. Is cryoablation, microwave ablation a useful locoregional therapy for HCC compared with RFA?
   P: HCC patients
   I: Cryoablation, microwave ablation
   C: RFA, ethanol ablation
   O: OS, PFS, TTP, complications

10. In what case is TACE suitable for adjuvant treatment of HCC?
    P: HCC patients
    I: TACE
    C: Other treatment modalities
    O: OS

11. Is performing TACE in advanced stage appropriate?
    P: Advanced stage HCC patients
    I: TACE
    C: Conservative treatment, systemic chemotherapy
    O: OS, quality of life

12. Is superselective TACE useful in TACE for HCC?
    P: HCC patients
    I: Selective TACE
    C: Nonselective TACE
    O: Tumor response, OS
13. In what case is DEB-TACE adaptable? What benefits does it have compared with conventional TACE, and can it be recommended as a standard therapy?
P: HCC patients
I: DEB-TACE
C: Conventional TACE
O: OS, PFS, TTP, complications, cost

14. Can TARE be considered as a standard therapy (that replaces TACE)?
P: HCC patients
I: TARE
C: TACE
O: OS, PFS, TTP, complications, cost

15. Is TACE useful for treatment of HCC that has relapsed after hepatic resection?
P: Recurred HCC following hepatectomy
I: TACE
C: RFA, Surgery
O: OS, PFS, TTP, complications

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
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 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)

HCC, hepatocellular carcinoma; DAA, direct-acting antiviral; mUICC, modified Union for International Cancer Control; WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST; iRECIST, immunotherapy RECIST; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; OS, overall survival; RT, radiation therapy; DFS, disease-free survival; CT, computed tomography; MRI, magnetic resonance imaging; RFA, radiofrequency ablation; TTP, time-to-progression; DEB, drug-eluting bead.