Supplementary Table 3. List of Clinical Questions

Internal Medicine

1. Could 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 HCC surveillance test reduce mortality in high-risk group?
   P: Group with high risk of liver cancer
   I: Group that underwent liver cancer surveillance test
   C: Group that did not undergo liver cancer surveillance test
   O: Mortality related to HCC
3. What should be done for 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 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

Supplementary Table 3. List of Clinical Questions (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 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 (RFA, TACE, sorafenib) treatment group
    O: Survival rate
11. What is definition of TACE refractoriness and 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 molecular targeted agents and immunotherapy agents that can be primarily used on progressive HCC patients aside from sorafenib, and what are 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 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 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

Supplementary Table 3. List of Clinical Questions (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 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 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 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 standard method of imaging diagnosis for patients suspected of having HCC?
   P: Patients suspected of having HCC
   I: Opinions about washout 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
4. Is standard method of imaging diagnosis same in 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 image diagnosis standard different from initial diagnosis
   O: Accuracy of diagnosis

Supplementary Table 3. List of Clinical Questions (Continued)

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 RFA 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 RFA superior to ethanol injection?
   P: HCC patients
   I: RFA
   C: Ethanol
   O: OS, PFS, TTP, complications
8. Is combined treatment of RFA 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 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 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

Supplementary Table 3. List of Clinical Questions (Continued)

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 EBRT (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: EBRT including particle radiotherapy, hypofractionated radiotherapy, or stereotactic body radiotherapy)
   C: TACE
   O: Treatment result (OS, local control, progression free survival, toxicity)
2. In what case can EBRT be performed safely? What are indications?
   P: HCC patients
   I: EBRT
   C: Dose-volumetric parameters
   O: Radiation induced liver toxicity
3. Is combined treatment with EBRT effective for HCC in which TACE is expected to show inadequate effect?
   P: Locally advanced HCC patients
   I: Combined treatment with TACE and EBRT
   C: TACE alone
   O: OS
4. Can EBRT be performed for HCC with macrovascular invasion?
   P: HCC patients with macrovascular invasion
   I: EBRT
   C: Targeted agent (sorafenib)
   O: OS
5. Can EBRT 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: EBRT
   C: Supportive care or systemic treatment
   O: Symptom palliation/local control
6. Can EBRT perform role of down staging for surgical treatment in progressive HCC?
   P: Locally advanced HCC patients
   I: EBRT
   C: Targeted agent (sorafenib)
   O: Safety survival/OS
7. Can EBRT be performed for HCC that has relapsed (refractory) after hepatic resection, RFA, ethanol injection, or TACE?
   P: Recurrent or refractory HCC after locoregional treatment
   I: EBRT
   C: Repeated resection, RFA, ethanol injection, or TACE
   O: Treatment result (OS, local control, progression free survival, toxicity)

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