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

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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

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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)

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