Appendix H. Evidence Table: Patient Outcomes for Staging

(Randomized Controlled Trials)

**Table H1. Characteristics of randomized controlled trials of patient outcomes for staging**

| **Author,**  **Year** | **Imaging Tests Used for Screening** | **Details of Imaging Tests** | **Definition of a Positive Test on Imaging and Followup** | **Population Characteristics** | **Eligibility Criteria** | **Country, Setting** | **Number Approached, Eligible, Enrolled, Analyzed** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Trinchet JC, 2011[277](#_ENREF_277) | Ultrasound  Note: AFP was assesed but after analyses, high rates of AFP observed in 2 groups precluded interpretation based on AFP randomization and analysis was restricted to ultrasound randomization | Technical details of ultrasound not reported | In cases of focal liver lesions, diagnostic procedure using contrast-enhanced imaging, serum AFP, and/or guided biopsy was performed according to EASL guidelines; HCC diagnosis based on histology, if lesion >2 cm in diameter then early arterial hypervascularization on 2 contrast-enhanced methods, or when there was an association between serum AFP >400 ng/mL plus early arterial hypervascularization on one contrast-enhanced method; in case of increased AFP with no focal liver lesion on ultrasound, CT scan was performed | Age (mean): 55 years  Male: 69%  Race: NR  Alcoholic cirrhosis: 39%  HCV-related cirrhosis: 44%  HBV-related cirrhosis: 13%  Hemochromatosis-related cirrhosis: 1.6%  Cirrhosis due to other etiology: 2.5%  Note: other etiology = nonalcoholic steatohepatitis, primary biliary cirrhosis, autoimmune hepatitis, cryptogenic cirrhosis | Patients >18 years with histologically proven cirrhosis due to either excessive alcohol consumption, chronic HCV or HBV, or hereditary hemochromatosis, with no complications from cirrhosis, patients with Child-Pugh class A or B and no focal liver lesion. Excluded patients with Child-Pugh class C, severe uncontrolled extrahepatic disease resulting in estimated life expectancy <1 year, co-infection with HIV | France and Belgium; Selected from clinical centers in a cooperative group that included specialized liver disease centers | Overall (3-month surveillance vs. 6-month surveillance)  Number approached: NR  Number eligible: 1340  Number enrolled: 1340 (668 vs. 672)  Number analyzed: 1278 (640 vs. 638) |
| Wang JH, 2013[278](#_ENREF_278) | Ultrasound | Technical details of ultrasound not reported | Newly detected hepatic nodule on ultrasound >1cm in diameter suspicious for HCC; referrred to medical centers for further diagnositic procedures; followup by public health nurses; final diagnosis based on histology, EASL imaging criteria, or AASLD imaging criteria | Age (mean): 65.2 years  Male: 50%  Race: NR  HBV: 28%  HCV: 65%  HBV and HCV: 7%  Liver cirrhosis: 32% | Patients >40 years with either positive HBsAg or anti-HCV and a platelet count <150 (x109)/l. Excluded those with history of hepatic malignancy. | Taiwan; Selected from health data for 10 townships | Overall (4-month surveillance vs. 12-month surveillance)  Number approached: 28,722  Number eligible: 1581 (785 vs. 796)  Number enrolled: 744 (387 vs. 357)  Number analyzed: 744 (387 vs. 357) |
| Zhang BH, 2004[279](#_ENREF_279) | Ultrasound (in conjunction with AFP) | Technical details of ultrasound not reported | Solid liver lesion on ultrasound or AFP >20 mcg/l; individuals with an initial positive test underwent retesting; individuals with a positive retest underwent additional diagnostic evaluation (history, physical exam, serum AFP, ultrasound by senior doctor, CT or MRI as required); final diagnosis based on histology or long-term followup | Age (mean): 41.5a years  Male: 63%  Race: NR  HBsAg positive: 64%  Hepatitis: 27%  HBsAg positive and hepatitis: 9% | People aged 35 to 59 years with serum evidence of HBV infection or a history of chronic hepatitis without HBV infection (abnormal biochemistry ≥6 months). Excluded those with history of HCC, or other malignant diseases, or serious illness. | China; Selected from medical records of primary care centers | Overall (screening vs. control)  Number approached: NR  Number eligible: 19,200 (9757 vs. 9373)  Number enrolled:18,816 (9373 vs. 9443)  Number analyzed:18,816 (9373 vs. 9443) |

| **Author,**  **Year** | **Duration of Followup** | **Attrition** | **Interventions** | **Outcomes** | **Adverse Events/Harms** | **Sponsor** | **Risk of Bias** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Trinchet JC, 2011[277](#_ENREF_277) | Mean followup 47.1 months in 3-month surveillance group vs. 46.8 months in 6-month surveillance group | 0.9% (12/1340) patients lost to followup; 11.9% (143/1278) of patients not compliant with protocol, 14.6% (86/638) in 6-month surveillance group, 9.4% (57/640) in 3-month surveillance group  Note: the raw numbers do not exactly equal the reported proportions for compliance | A: Ultrasound every 3 months  B: Ultrasound every 6 months | A vs. B  Cases of HCC/ new focal liver lesion  53/183 (30%) vs. 70/155 (45%)  2 and 5-year cumulative incidence of HCC  4.0%, 10.0% vs. 2.7%, 12.3%  Prevalence and cumulative incidence of HCC <30 mm  79%, 7.8% vs. 70%, 9.1%  Survival rates for all patients  At 2 years: 95.8% vs. 93.5%  At 5 years: 84.9% vs. 85.8%  Cases of HCC-related mortality  17/72 (23.6%) vs. 12/82 (14.6%)  Note: all associations were NS | NR | French Ministry of Health; French Ligue de Recherche contre le Cancer | Moderate |
| Wang JH, 2013[278](#_ENREF_278) | 4 years; individuals in 4-month surveillance scanned mean 7.13+/-2.0 times and individuals in 12-month surveillance scanned mean 2.53+/-0.5 times | NR: 27.4% of 4-month surveillance group and 45.7% of 12-month surveillance group attended all exams (67.6% in 4-month surveillance group attended >6 exams, 73.1% in 12-month surveillance group attended >2 exams) | A: Ultrasound every 4 months  B: Ultrasound every 12 months | A vs. B  Cases of HCC/ new hepatic nodule  24/46 (52%) vs.15/28 (54%), including 5 patients diagnosed outside of surveillance schedule in B  3-year cumulative incidence of HCC  11.7% vs. 9.7%  1-,2-, and 4- year cumulative survival rates for patients with HCC  95.8%, 78.8%, 57.4% vs. 80%, 64%, 56% | NR | National Scientific Council of Taiwan | Moderate |
| Zhang BH, 2004[279](#_ENREF_279) | 5 years; all individuals offered screening 5 to 10 times | NR; Screened group completed 58% of offered screening (median: 5 screens) | A: Serum AFP test and ultrasound every 6 months  B: No screening, usual care | A vs. B  Cases (incidence per 100,000) of HCC  86 (223.7) vs. 67 (163.1); rate ratio, 1.37 (95% CI 0.41 to 0.98);  Cases (incidence per 100,000) of HCC-associated death  32 (83.2) vs. 54 (131.5); rate ratio, 0.63 (95% CI 0.41 to 0.98) | NR | NR | High |

AASLD = American Association for the Study of Liver Disease; AFP = alphafetoprotein; CT = computed tomography; EASL = European Association for the Study of the Liver; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HBsAb = antibody to hepatitis B surface antigen; HBcAb = antibody to hepatitis B core antigen; HBeAg = hepatitis B e antigen; HBeAb = antibody to hepatitis B e antigen; HCC = hepatocellular cancer; NR = not reported; NS = not significant

a Calculated