Advancing HCC Management: Updated Guidelines and VHA's Innovative Screening Trial

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Hepatocellular carcinoma (HCC) accounts for ~90% of liver cancers worldwide.[1] Population-based data indicate that in many regions 60% or more of HCC cases are diagnosed at intermediate or advanced stages, reflecting a high proportion with local extension or distant metastases at presentation—limiting curative options.[2] Posttreatment recurrence reaches 70% within 5 years after resection (higher after ablation) but ~10% after liver transplantation.[1] Veterans in VHA care face 4 to 5 times higher HCC incidence than the general United States population due to elevated cirrhosis prevalence; however, the VHA's integrated system and population health focus enables higher screening rates.[3,4]

The VHA 2023 PREMIUM trial is comparing abbreviated MRI (aMRI) with standard ultrasound screening, aiming to detect HCC earlier, increase curative treatments, and reduce mortality in high-risk veterans. If the study is successful, aMRI could become the new VA screening standard.[5] These advancements reflect ongoing efforts to improve HCC outcomes through refined guidelines and innovative screening tailored to high-risk veterans.

The American Association for the Study of Liver Disease (AASLD) updated HCC Practice Guidance (2025) advises against systemic adjuvant therapies outside clinical trials, prioritizing surveillance and salvage transplantation or liver-directed therapies for recurrence.[6] This change in guidance is based on updated findings from the IMbrave050 trial, but many more regimens are being studied that could further impact treatment recommendations in this setting.

VA PREMIUM Study: aMRI and Ultrasound for Early HCC Detection[5]

Rationale

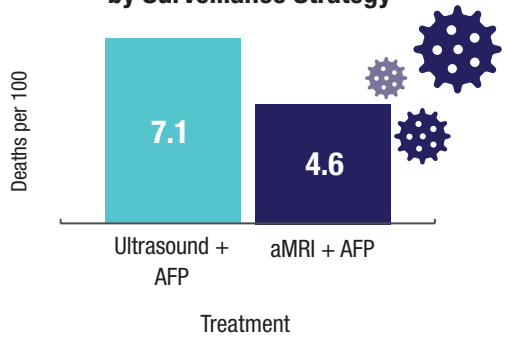
- Early detection boosts curative treatment, reducing mortality
- aMRI protocols are brief, cost-effective, and available at VA sites

This 8-year, 2-arm study compares aMRI + alpha-fetoprotein (AFP) screening versus ultrasound + AFP in patients with cirrhosis at high risk for HCC.

A total of 2350 participants per group will undergo screening every 6 months, HCC-related mortality is the primary endpoint.

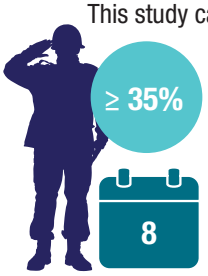
Proven mortality benefits could position aMRI as the new screening standard.

Projected 8-Year HCC Mortality by Surveillance Strategy



Hypothesized Power Calculation

This study can detect a



reduction in HCC-related mortality at 8 years

AASLD HCC Guidance Update: Adjuvant Therapy and Recurrence Management[6]

AASLD advises against adjuvant and neoadjuvant systemic therapies for patients with HCC undergoing resection/local ablation (level 1, strong recommendation)

Management post-resection/ablation with complete response by clinical scenario

- Recurrence within Milan criteria
  - Salvage liver transplantation
- Liver-localized recurrence within downstaging criteria
  - Liver-directed therapy, consider transplantation if downstaged or systemic therapy if disease progresses
- Recurrence with vascular invasion, extrahepatic spread, or unsuitable or locoregional therapy
  - First-line systemic therapy

Current Standard

Surveillance post-resection/ablation, even for high-risk patients

Ongoing Trials

Adjuvant (Phase III)
- ✓ Pembrolizumab (KEYNOTE-937)
- ✓ Nivolumab (CheckMate-9DX)
- ✓ Durvalumab + bevacizumab (EMERALD-2)
- ✓ Camrelizumab + apatinib

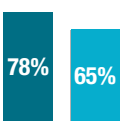
Neoadjuvant (Phase II)
- ✓ Atezolizumab + bevacizumab
- ✓ Nivolumab + ipilimumab
- ✓ Lenvatinib + pembrolizumab

Although the initial analysis of IMbrave050 showed promise, atezolizumab plus bevacizumab lacked sustained recurrence-free survival (RFS) benefit for HCC, with immature overall survival (OS) data in a second interim analysis. No FDA-approved adjuvant or neoadjuvant HCC therapies exist; surveillance remains standard post-treatment. Early interim analyses may overestimate benefits due to nonproportional hazards, underscoring the need for robust trial designs. Ongoing trials may identify effective therapies, but current practice relies on surveillance and established recurrence management.

Initial Analysis
Median follow-up: 17.4 months

RFS
HR 0.72

12-month RFS
78% vs 65%
(Treatment vs placebo)



Treatment duration
11 months

Adverse events
34.9%
grade 3-4

Second Interim Analysis
Median follow-up: 35.1 months

RFS
HR 0.90

OS
HR 1.26; >80% alive in both arms

Subgroups
No difference

Safety
No new concerns

HR, hazard ratio