



Diagnostic Imaging Pathways - Hepatocellular Cancer (Surveillance)

Population Covered By The Guidance

This pathway provides guidance on which adult patients with risk factors for hepatocellular carcinoma should undergo surveillance and which method(s) to use.

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Quick User Guide

Move the mouse cursor over the **PINK** text boxes inside the flow chart to bring up a pop up box with salient points.

Clicking on the **PINK** text box will bring up the full text.

The relative radiation level (RRL) of each imaging investigation is displayed in the pop up box.

SYMBOL	RRL	EFFECTIVE DOSE RANGE
	None	0
	Minimal	< 1 millisieverts
	Low	1-5 mSv
	Medium	5-10 mSv
	High	>10 mSv

Pathway Diagram

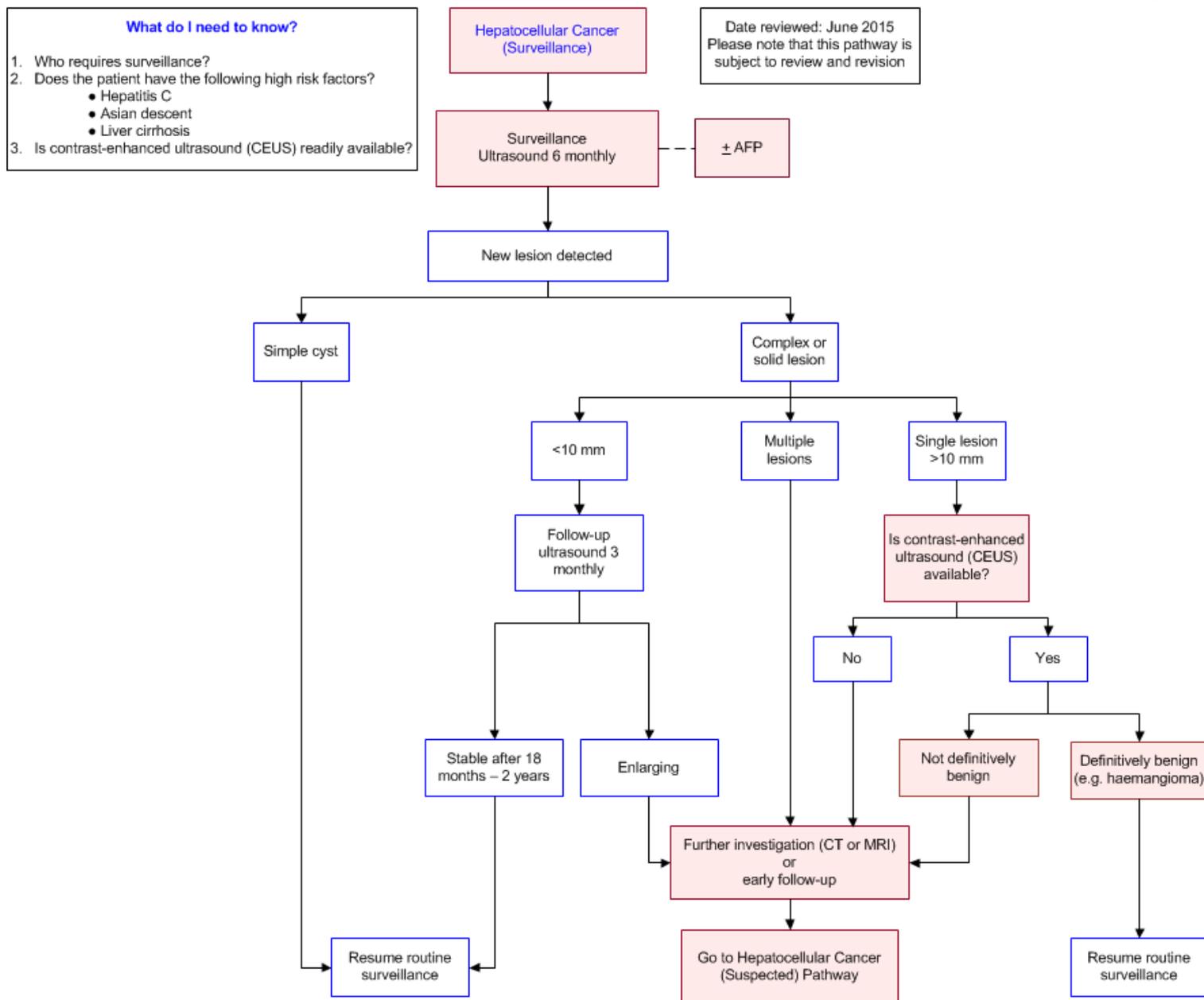
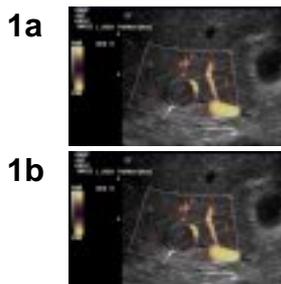


Image Gallery

Note: These images open in a new page



Hepatocellular Carcinoma

Image 1a and 1b (Ultrasound): Within segment 6 of the liver, there is an approximately 2cm subcapsular hypoechoic lesion (arrow) which does not demonstrate any increased vascularity.



Image 1c, 1d, 1e and 1f (Triphasic Computed Tomography): CT of the same patient shows a cirrhotic liver with patent hepatic and portal veins as well as ascites. Within segment 6, there is a

nodular area which demonstrates slight enhancement corresponding to the lesion identified on ultrasound (arrow). This lesion could represent either a dysplastic cirrhotic nodule or an early hepatocellular carcinoma.

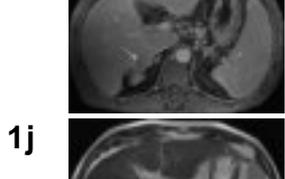
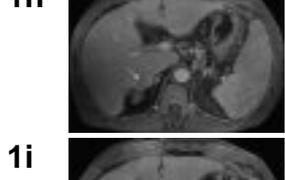
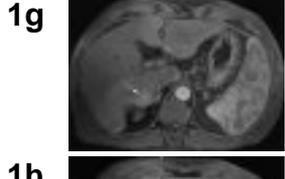
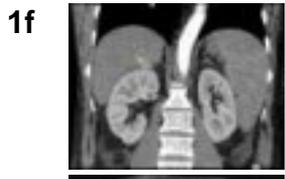
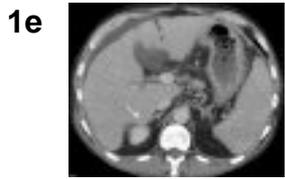
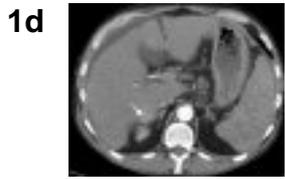


Image 1g, 1h, 1i and 1j (Magnetic Resonance Imaging): MRI of the same patient demonstrates a lesion measuring approximately 2.5 cm in diameter on the inferomedial aspect of segment 5 in a subcapsular location. This is bulging the capsule of the liver at the level of the upper pole of the right kidney. The lesion is essentially isointense to the rest of the liver on T1 weighted imaging (out of phase) but is slightly hyperintense on in-phase imaging suggesting that the rest of the liver has some fatty infiltration. The lesion is slightly hyperintense on first echo T2 but is not clearly visible on more heavily weighted T2 imaging. The lesion shows arterial enhancement but washes out in the portal venous phase, with the rim of the lesion remaining enhanced. The appearances are consistent with a hepatocellular carcinoma.



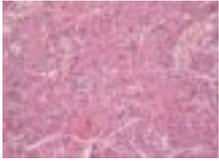
Hepatocellular Carcinoma

Image 2a and 2b : Hepatectomy specimens showing a multifocal hepatocellular carcinoma with areas of necrosis and haemorrhage arising in a cirrhotic liver.



Image 2c (H&E, x2.5) and 2d (H&E, x10): Histological sections of a hepatocellular carcinoma arising on a background of cirrhosis. The usual lobular architecture is replaced by irregular and thickened trabeculae of malignant hepatocytes. There is mild nuclear pleomorphism.





Teaching Points

- In patients with cirrhosis, the risk of developing hepatocellular carcinoma (HCC) is highest with HCV, in Asians and in more advanced stages of cirrhosis [1](#)
- Ultrasonography (US) 6 monthly is recommended as the primary surveillance modality [2-5](#)
- Survival was significantly better in patients who underwent surveillance [18](#)
- The earliest identifiable HCCs often show atypical radiological features [19](#) and these are the very lesions that need to be diagnosed to enable a higher likelihood of cure
- Sensitivity for detecting hepatocellular carcinoma on US varies with the size of the lesion
- Utilizing contrast enhanced ultrasonography (CEUS) allows for dynamic real-time ultrasound angiogram with greater temporal resolution than contrast-enhanced CT or MRI, in addition to quantitative assessments
- The use of serum alpha-fetoprotein (AFP) alone as a surveillance tool is not recommended
- The use of AFP to complement US surveillance is controversial [31,32](#)

Hepatocellular Carcinoma (Surveillance)

- Hepatocellular carcinoma (HCC) is by far the commonest primary liver cancer. Major causes are Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV), alcoholic liver disease and (possibly) non-alcoholic fatty liver disease
- In patients with cirrhosis, the risk of developing HCC is highest with HCV, in Asians and in more advanced stages of cirrhosis [1](#)
- Surveillance for at-risk groups has been recommended by several major expert consensus groups [2-5](#). The American Association for the Study of Liver Diseases (AASLD) guidelines of 2005 [6](#) and the European Association for the Study of the Liver (EASL) guidelines of 2001 [7](#) have both been validated [8](#). Both sets of guidelines have been updated. [2,3](#)
- All sets of guidelines recommend US as the primary surveillance tool
- Despite these recommendations there is not a great deal of robust controlled evidence to support them. The real support for screening for liver cancer comes from the striking differences in response to therapy between screened populations in whom HCC is diagnosed and treated at early stages and patients with more advanced, incidentally detected tumors [9](#)
- In high-risk groups, regular screening with ultrasound and alpha-foetoprotein has been proven to reduce mortality from HCC in HBV patients in a large Chinese study. [10](#) However the overall strength of evidence of the effects of screening is low [11](#)
- There are no RCTs trialling surveillance for HCC in HCV patients or patients with cirrhosis. Several lesser quality studies have shown that patients under surveillance are diagnosed with HCC at an earlier stage and therefore are more likely to respond to therapy. [12-16](#) However, in these studies, lead- and length-time biases confound the effects on mortality [11,17](#)
- A recent European study showed that survival was significantly better in patients who underwent surveillance compared with those in whom surveillance was missed although indicated [18](#)
- Surveillance programs for the detection of HCC result in the detection of small lesions in the liver, some of which are HCCs, but others are regenerative or dysplastic nodules, or benign incidental findings. Unfortunately the earliest identifiable HCCs often show atypical radiological features. [19](#)

These are the very lesions that need to be diagnosed to enable a higher likelihood of cure

Who requires surveillance?

- Recommended for the following groups by the American Association for the Study of Liver Diseases (AASLD). Surveillance is deemed cost-effective if the expected HCC risk exceeds 1.5% per year in patients with hepatitis C and 0.2% per year in patients with hepatitis B [2](#)

Surveillance groups

- Cirrhotic patients (AASLD)
- Non-cirrhotic patients with active chronic hepatitis B infection
 - From Asian background
 - 40-50 years of age (AASLD)
- Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis [EASL [3](#) - lesser grade of recommendation]
- Cirrhotic patients due to hepatitis B or C [APASL, [4](#) JSH, [5](#)]
- Patients with active chronic hepatitis B or C [JSH, [5](#)]
- Patients with a family history of HCC
- Non-viral aetiology of liver cirrhosis [JSH, [5](#)]
 - e.g. alcoholic cirrhosis
 - Haemachromatosis
 - Primary biliary cirrhosis
 - Auto-immune hepatitis
 - Alpha-1 antitrypsin deficiency
 - Non-alcoholic steatohepatitis
- Evidence for surveillance in patients with the above conditions without cirrhosis is scanty [3](#)

Ultrasound

- All expert consensus guidelines recommend ultrasonography (US) 6 monthly as the primary surveillance modality. [2-5](#) According to a 2009 meta-analysis, pooled sensitivity for detecting hepatocellular carcinoma (HCC) at any stage was 94%. However, US was less effective for detecting early stage-potentially curable-HCC (63%). [20](#) After accounting for possible verification bias, this meta-analysis reported sensitivity to be as low as 33% and specificity as high as 90%
- A more recent systematic review and meta-analysis of the sensitivity of US in a surveillance setting, found few studies and concluded that the strength of evidence was low to insufficient, but quoted a sensitivity of 78% and specificity of 89% [21](#)
- Sensitivity for detecting hepatocellular carcinoma varies with the size of the lesion
- New techniques using sonographic contrast agents are described further down the pathway
- Advantages
 - Relatively cheap
 - Able to assess hepatic blood supply and presence of vascular invasion
- Limitations
 - Up to 30% of small lesions (<2cm) may be missed by US
 - Difficult to reliably distinguish hepatocellular carcinoma from other solid hepatic lesions
 - Variable appearance of larger masses
- A recent RCT comparing 6 monthly US with yearly CT showed the former to be marginally more

- sensitive and less costly in American patients with compensated cirrhosis [22](#)
- The addition of tumour markers, most commonly serum alpha-fetoprotein (AFP) is controversial

Contrast-Enhanced Ultrasound (CEUS)

- Ultrasound (US) contrast agents ('microbubbles') comprise an albumen or phospholipid shell containing a stable perfluorocarbon or sulfur hexafluoride gas. They are predominantly blood-pool agents, the encapsulated microbubbles being small enough to pass through pulmonary and systemic circulations after intravenous injection and durable enough to re-circulate for several minutes
- US contrast agents are mainly based on the dynamic assessment of macro- and microvasculature of organs and their pathologies. They are, in principle, comparable to the use of contrast agents for CT and MRI with the added advantage of the capability for imaging continuously during the passage of the contrast agent, thereby obtaining what is effectively a dynamic real-time ultrasound angiogram with greater temporal resolution than contrast-enhanced CT or MRI. In addition, quantitative assessment of contrast uptake can be measured by generating Time-Intensity Curves
- CEUS was endorsed by AASLD in its 2005 guidelines [6](#) but removed from the list of diagnostic techniques in 2011, [2](#) partly due to lack of availability of US contrast in the USA and partly due to false-positive diagnoses in patients with intrahepatic cholangiocarcinoma (ICC). ICC's may show peripheral ring enhancement, difficult to distinguish from small HCCs. In addition, washout of ICCs may mimic HCC washout; some small HCCs may fail to show washout. Nevertheless, controversy persists, since CEUS typical for hepatocellular carcinoma (HCC) has a positive predictive value (PPV) of >95% [23](#) and it is suggested that the CEUS pattern is enough to establish whether malignancy is present. [24-26](#) Only 1-3% of newly developed tumours in cirrhosis are ICCs [27](#)
- CEUS has been shown to be more cost-effective, using a Markov model, in HCC surveillance than US alone [28](#)
- CEUS improves diagnostic performance in differentiating HCCs from non-neoplastic nodules in cirrhotic patients compared with baseline ultrasound. [29](#) and can be recommended as the first diagnostic step when liver lesions are detected on US surveillance [30](#)

Serum Alpha-Fetoprotein (AFP)

- The use of serum alpha-fetoprotein (AFP) alone as a surveillance tool is not recommended. Hepatic injury and regeneration without hepatocellular carcinoma (HCC) development can elevate AFP levels reducing specificity. In addition, AFP levels are increased in a minority of patients with early HCC
- The use of AFP to complement ultrasound (US) surveillance is controversial [31,32](#). While US and AFP are imperfect tools, they appear to be complementary, although AASLD and EASL guidelines omit AFP
- However, in high-risk groups, regular screening with ultrasound and AFP has been proven to reduce mortality from HCC in HBV patients in a large Chinese study. [10](#) In one meta-analysis, the pooled sensitivity for early HCC increased from 63% for US alone to 70% for US plus AFP. [20](#) In a further study, a combination of US and AFP exhibited a sensitivity and specificity of 99.2% and 68.3% respectively, when a cut-off value for AFP of 20ng/ml was used [33](#)
- It is worthy of note that AFP levels are inexpensive and simple to perform [32](#)
- Other biomarkers for HCC are available and are under trial [34,35](#)

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Date of literature search: June 2015

The search methodology is available on request. [Email](#)

References are graded from Level I to V according to the Oxford Centre for Evidence-Based Medicine, Levels of Evidence. [Download the document](#)

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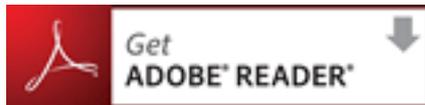
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