Prevention of Hepatocellular Carcinoma

Presented by

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The need to prevent hepatocellular carcinoma.

- There are two reasons that are especially relevant in considering the need to prevent this tumor.
- The first is the high incidence of HCC, and the second its grave prognosis.
- HCC is now the fifth most common global cancer (fifth in males and eighth in females) if colon and rectal cancers and mouth and pharyngeal cancers are grouped together .
- Moreover, it is either the most common tumor or among the three most common tumors in many of the most populous regions of the world .
- HCC accounted for 4.8% of all new human cancers (6.4% among men and 3.0% among women) .
- Approximately 650 000 people die from hepatocellular carcinoma (HCC) each year.

The need to prevent hepatocellular carcinoma.

- Despite these scientific advances and the implementation of measures for the early detection of HCC in patients at risk, patient survival has not improved during the last three decades. This is due to the advanced stage of the disease at the time of clinical presentation and limited therapeutic options.

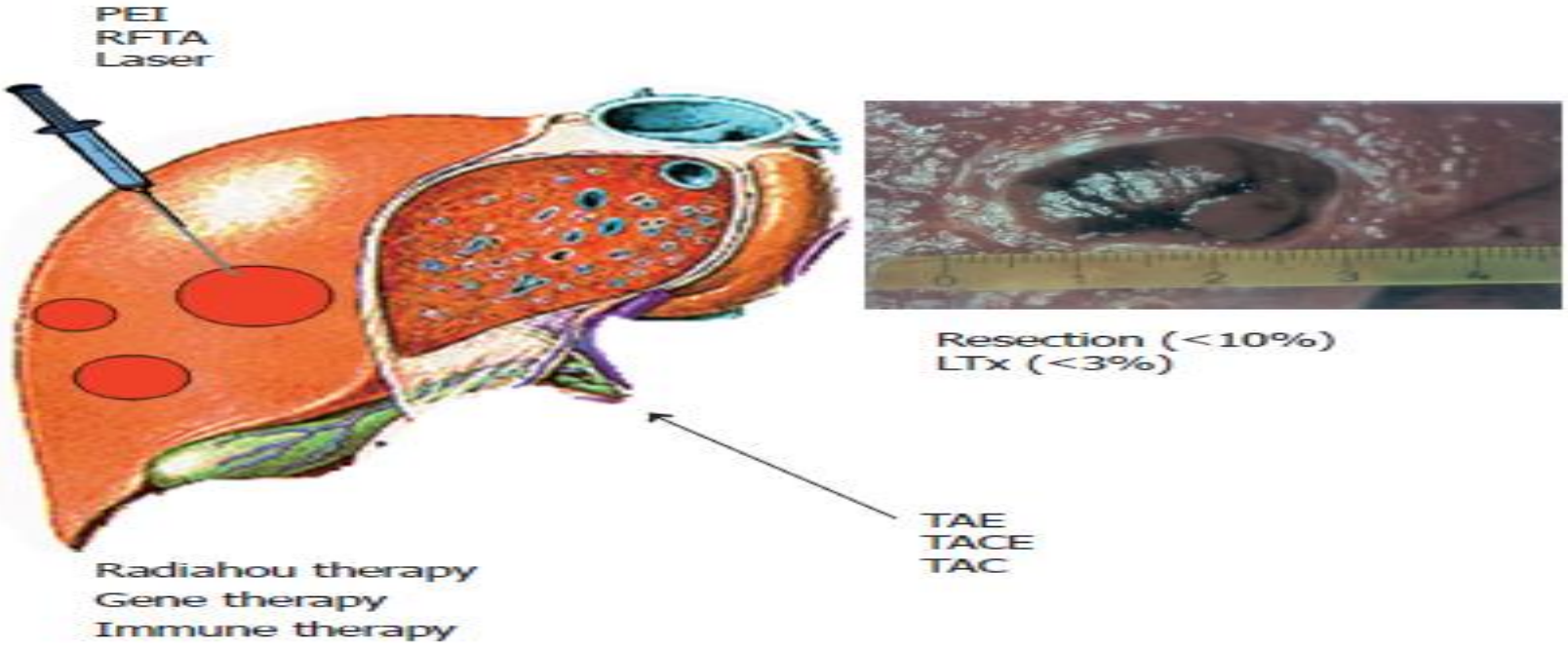


Figure 2 HCC treatment

Though surgery, percutaneous and transarterial interventions are effective in patients with limited disease (1-3 lesions, <5 cm in diameter) and compensated underlying liver disease (cirrhosis Child A), at the time of diagnosis more than 80% patients present with multicentric HCC and advanced liver disease or comorbidities that restrict the therapeutic measures to best supportive care.

In order to reduce the morbidity and mortality of HCC:

Early diagnosis.

The development of novel systemic therapies for advanced disease, including drugs, gene and immune therapies .

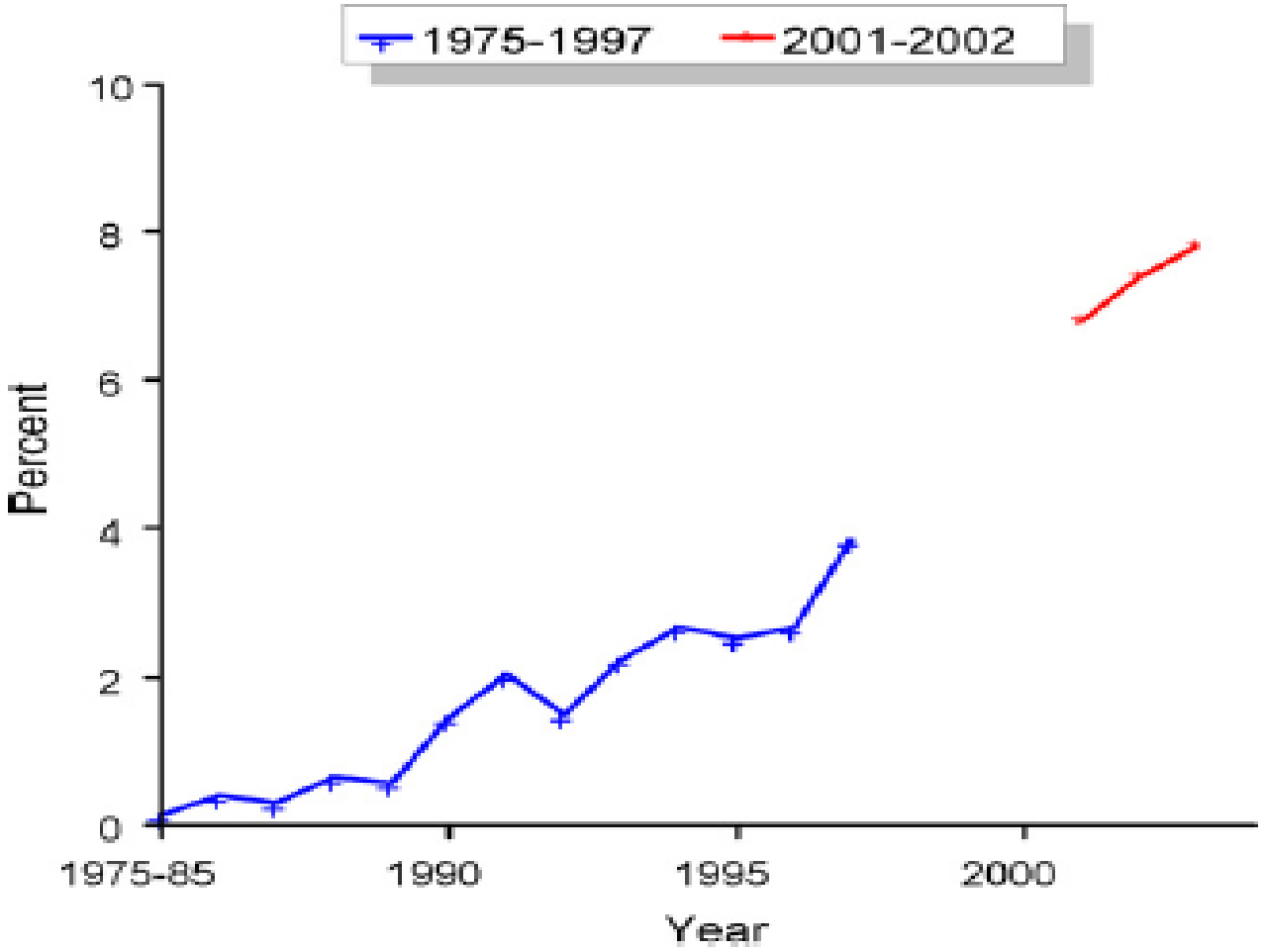
Primary HCC prevention .

Secondary HCC prevention after successful therapeutic interventions needs to be improved in order to make an impact on the survival of patients with HCC.

Pattern of HCC and its risk factors in Egypt

- In Egypt, several attempts were made to establish cancer registries. Among these attempts in 1998, the Egyptian Ministry of Health and Population in collaboration with several partners established a population-based Cancer Registry (NCR) in Gharbiah Governorate, in addition to a multi-institutional cancer statistics collected in collaboration with the National Cancer Institute of Cairo University ***(Elattar, 2003).*** This was intended to estimate the size of the problem nationally. The NCR data confirmed the high incidence of HCC in Egypt and the change in the trends.

Trends in freqnency of liver cancer, in Egypt according to the National Cancer Institutes records, NCI 1975-2003 *(Elattar, 2003)*



The National Cancer Institute Pathology Registry indicated that liver cancer formed 11.75% of the malignancies of all digestive organs and 1.68% of total malignancies. Liver tumors were mostly HCC (70.48%), while hepatoblastoma constituted 10.24%, non-Hodgkin's lymphoma 4.21% of hepatic malignancies and adenocarcinoma unspecified 9.03% ***(Nadia et al., 2007).***

El- Zayadi et al (2005) concluded that the annual proportion of HCC showed a significant rising trend from 4.0% in 1993 to 7.2% in 2002.

The rising incidence of HCC in Egypt may be explained by the increasing prevalence of risk factors such as the emergence of hepatitis C virus (HCV) over the same period of time ***(Mostafa, 2004),*** the contribution of HBV infection, and improvements in screening programmes and diagnostic tools ***,*** as well as the increased survival rate among patients with cirrhosis allowing time for some of them to develop HCC ***(Anwar et al., 2008).***

Ezzat et al (2005) reported even higher estimate of the attributable fraction (around 90%) of current HCC due to chronic HCV infection ***(Ezzat, et al., 2005).*** This likely represents the current status of HCV as the predominant and increasing cause underlying the epidemic of HCC in Egypt ***(Anwar et al., 2008).*** The changes in prevalence of HCV is very well correlated in time and geographical regions to the mass treatment injection campaigns for Schistosomiasis during the years 1950–1980 ***(Frank et al., 2000, Ghaffar et al., 1991 and Mostafa, 2004).*** Schistosomiasis also induces immune suppression , which could result in increased persistence viraemia, following acute infection of either hepatitis B or C ***(Ezzat et al., 2005).*** The combination of Schistosomiasis and HCV infection was found to have more severe effects on liver pathology and progression into worsening complications than HCV infection alone. Fortunately, recent epidemiologic surveys have reported a declining prevalence of Schistosoma infection ***(El Khoby, 2000).***

Aetiologies of HCC

- Most (80%) are attributable to cirrhotic liver disease resulting from chronic HBV or HCV infection, alone or exacerbated by comorbid factors such as combined infections, chronic excessive alcohol intake (lifetime exposure), obesity and type 2 diabetes (T2D), and cigarette smoking.
- Alcoholic liver disease, non-alcoholic steatohepatitis (NASH), hemochromatosis and other causes of cirrhosis may also underlie cirrhotic liver disease predisposing to HCC . Other environmental contaminants may play a role, particularly fungal contaminants of crops (aflatoxin , fumonisin), selenium deficiency and algal contamination of water supplies .Water contaminated by blue-green algae that produce tumour-promoting microcystins in parts of China and membraneous obstruction of IVC inNepal,South africa,Japan,China and Korea is a risk factor.

Table 1 Major etiologies of HCC

Chronic viral hepatitis B, C, D
Toxins (e.g., alcohol, aflatoxins)
Hereditary metabolic liver diseases (e.g., hereditary hemochromatosis, α-1-antitrypsin deficiency)
Autoimmune hepatitis
Overweight, especially in males, and diabetes mellitus; nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD)

HCC prevention

- HCC prevention falls into two categories:

- Primary prevention that is aimed at the prevention of HCC development in patients with chronic liver diseases of different etiologies.
- Secondary prevention that is aimed at preventing the recurrence and/or the development of new HCC lesions after successful surgical or non-surgical HCC treatment.

Primary HCC prevention

- Primary prevention is aimed at the interference with HCC development at four stages.

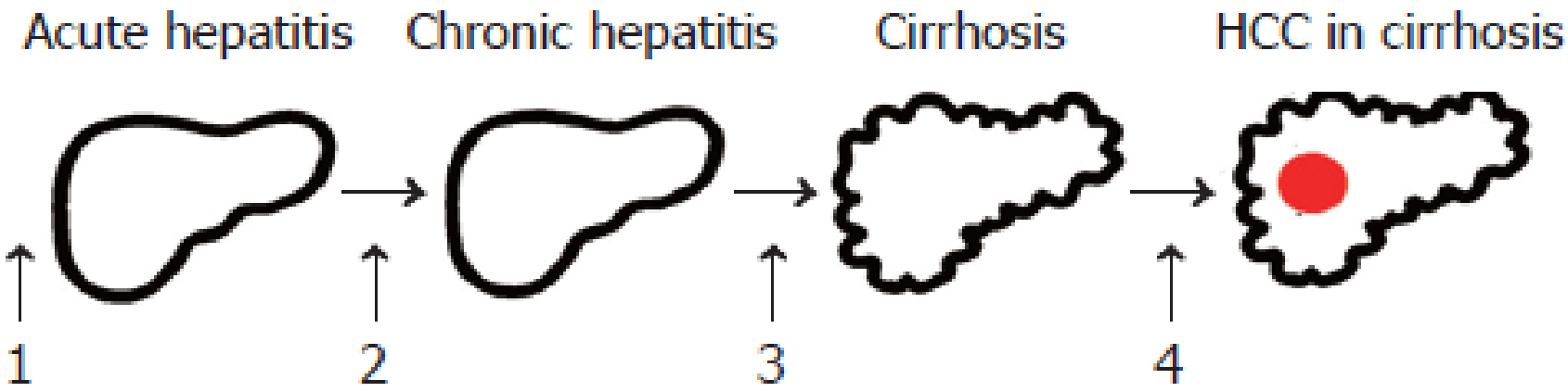


Figure 5 Primary HCC Prevention.

Stage 1:

Interventions at this step are aimed at the prevention of acquired liver diseases.

Apart from avoiding liver toxins, including alcohol and certain drugs, or infections with HBV or HCV by hygienic measures, avoiding parenteral exposure to blood, blood products or contaminated needles etc., a prime example is vaccination against HBV infection using commercially available active and passive vaccines.

Universal vaccination in Taiwan has indeed already resulted in a decline of the incidence of HCCs.

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For the **prevention of HCV infection**, however no effective vaccine is available till date. While several HCV vaccination concepts are being evaluated, including HCV proteins , HCV-like particles as well as intravenous, intrahepatic, intraepidermal, intramuscular or oral cDNA immunization , it is not expected that a vaccine against HCV infection will become commercially available within the next few years.

Prevention of Aflatoxin B1 exposure:

-Foodstuffs that might be affected are screened for their aflatoxin content by governmental agencies and do not enter the market if unacceptably high levels are found.

-Replacing crops that are highly susceptible to fungal contamination with others, such as rice, at lower risk.

-Spraying with fungicides and increasing the resistance of the plants to fungal infection by ensuring adequate irrigation .

-Introduction of non-aflatoxigenic strains of Aspergillus to compete with the aflatoxin-producing strains.

- Genetically engineering foodstuffs that are resistant to infection by Aspergillus species.

-Sun-drying of the crops before storage and drying on cloth rather than directly on the earth.

Well ventilated, rain-proof storage facilities.

Storage in jute rather than plastic sacks and in wooden containers rather than on the earth.

Removal of visibly moldy plants by hand sorting; and the use of insecticides to control insect damage and fungicides to prevent spread of fungal spores.

Blue-green algae and microcystins

Since 1973 the Chinese government has been urging the rural population to drink water from deep wells .

In addition, in some regions the drinking water is treated by granular activated carbon filtration.

It is too soon to assess the effect of these interventions on the occurrence of HCC.

Stage 2:

Interventions at this step are aimed at the early treatment of acute liver diseases, thereby blocking their transition into chronic hepatitis that carries the risk of developing liver cirrhosis and its sequelae, including HCC development.

While the principles mentioned above regarding liver toxins can also be applied here, the early diagnosis and treatment of inherited liver diseases, such as Wilson’s disease and hemochromatosis , are of paramount importance. Furthermore, recent studies suggest that early treatment of acute HCV infection prevents its progression to chronic hepatitis C.

Stage 3:

Interventions at this step are aimed at the prevention of the progression of chronic hepatitis to liver cirrhosis that carries a high risk of HCC development.

Apart from avoiding liver toxins and long-term use of high dose androgens or other anabolic steroids, the treatment of chronic hepatitis is of paramount importance.

This includes :

the treatment of inherited, cholestatic or autoimmune liver diseases as well as the treatment of chronic viral hepatitis B or C.

Reduction of iron overload by phlebotomy, for example, has been shown to stop the progression of hemochromatosis to liver cirrhosis and HCC.

Treatment of chronic hepatitis B with interferon alpha or nucleoside analogs and chronic hepatitis C with interferon alpha and now the combination of PEG interferon alpha and ribavirin has demonstrated biochemical, virological , and histopathological improvements and a lower incidence of HCC development

Use of IFN-a in preventing HCV-related HCC

The beneficial effect of IFN was confined to patients in whom a sustained viral clearance was achieved, whereas in others it also accompanied a sustained biochemical response (normalization of serum transaminase levels) .

The mechanism or mechanisms by which IFN reduces the risk for HCC are uncertain.

Clearance of the virus and reduction in hepatic inflammation are obvious factors, but another mechanism may be upregulating the function of tumor suppressor genes .

The combination of pegylated IFN and ribavirin has improved the sustained virological clearance rates in patients with chronic HCV infection. However, the use of this combination in the prevention of HCC development has not yet been reported

Stage 4:

Interventions at this step are aimed at interfering with the molecular events leading to HCC development, usually in a cirrhotic liver.

These strategies include all treatment modalities detailed above (stage 3) as far as they can be implemented in patients with compensated or decompensated liver cirrhosis.

In addition, some of the measures to prevent HCC recurrence after successful HCC treatment (secondary prevention) should in principle be useful for HCC prevention at this stage of the disease.

Furthermore, some concepts of molecular therapy of HCCs should be applicable also in the prevention of HCCs. Without experimental pre-clinical data on these issues, it would be premature to discuss their potential clinical impact.

Secondary HCC prevention

- The prevention of a local recurrence and/or the development of new HCC lesions in patients after successful surgical or non-surgical HCC treatment is of paramount importance and can significantly improve disease-free and overall patient survival.

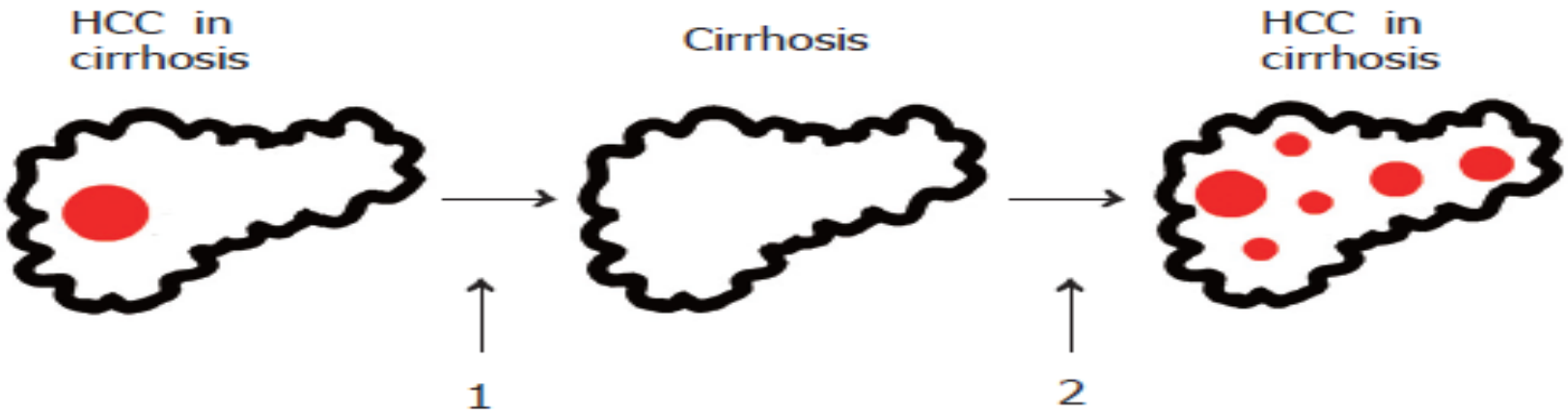


Figure 6 Secondary HCC Prevention.

After successful HCC resection or non-surgical ablation, HCC recurrence in the remaining cirrhotic liver is the major limitation of life expectancy of these patients. The probability of recurrence is about 50% within 3 years after successful treatment .

Apart from liver transplantation after successful resection , the strategies explored to date include administration of polyprenoic acid (an acyclic retinoid) interferon alpha and interferon beta .

Furthermore, adoptive immunotherapy and intra-arterial injection of 131iodine labeled lipiodol have been evaluated in clinical studies.

These findings have to be confirmed in larger randomized controlled studies.

Recommendations for HCC surveillance

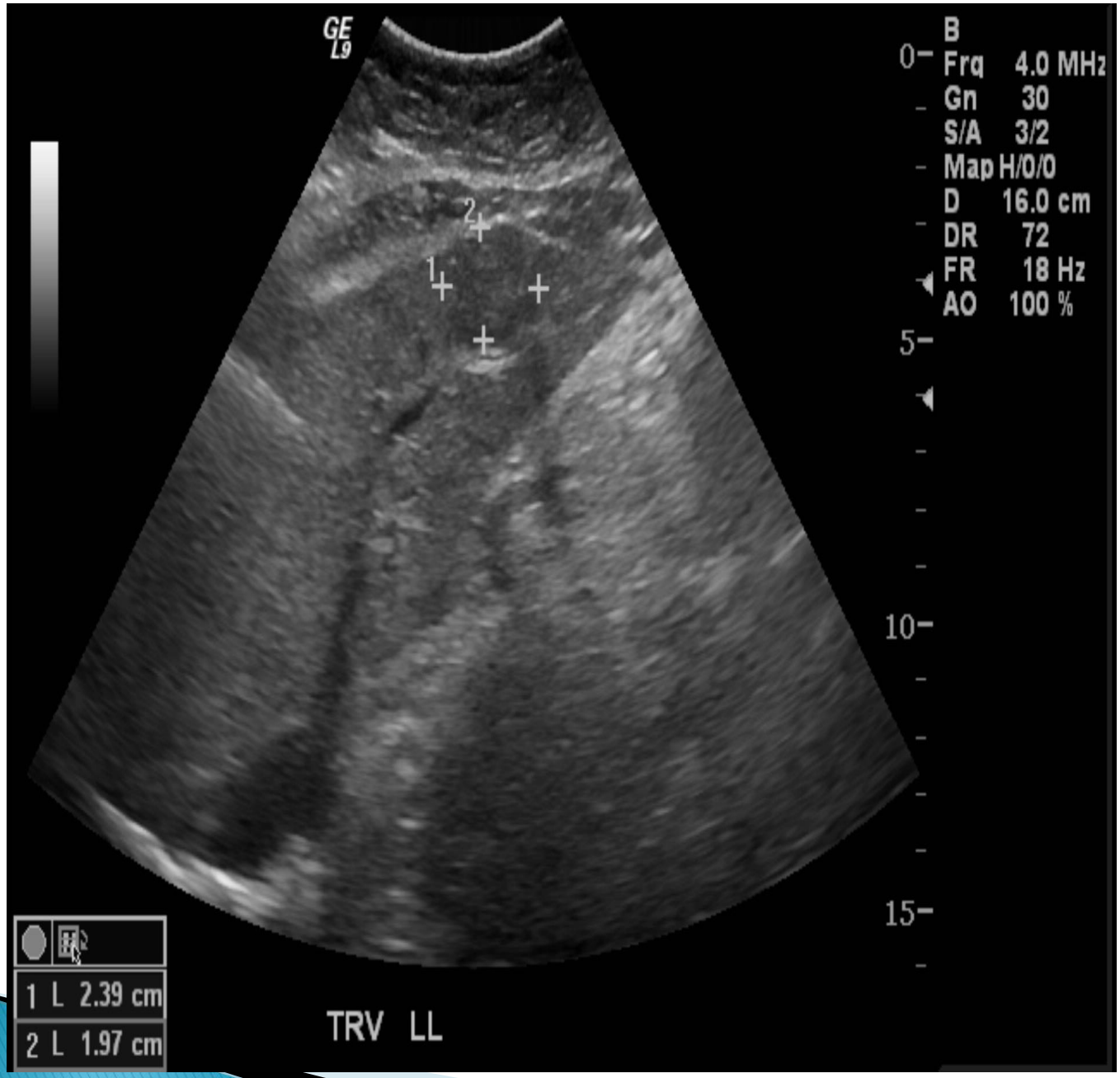
- Categories of adult patients in whom surveillance is recommended.
- 1. Cirrhotic patients, Child-Pugh stage A and B*
- 2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation**
- 3. Non-cirrhotic HBV carriers with active hepatitis , family history of HCC***or viral load more than 10000 IUlml
- 4. Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3****

Treated viral chronic hepatitis

Successful treatment, leading to sustained virological response in chronic hepatitis C, and HBeAg seroconversion or sustained HBV-DNA suppression in chronic hepatitis B, decreases, but does not eliminate the risk of HCC . Surveillance should be offered to treated patients with chronic hepatitis B who remain at risk of HCC development due to baseline factors, or to those with HCV-induced advanced fibrosis or cirrhosis, even after achieving sustained virological response.

Surveillance tests

- The most widely used for surveillance is ultrasonography (US).
- Nonetheless, US detection of HCC on a cirrhotic background is a challenging issue. the performance of US in early detection of HCC is highly dependent on the expertise of the operator and the quality of the equipment.
- There are no data to support the use of multidetector CT or dynamic MR imaging for surveillance except in the setting of :
- - the waiting list for liver transplantation .
- - when obesity, intestinal gas, and chest wall deformity prevent an adequate US assessment.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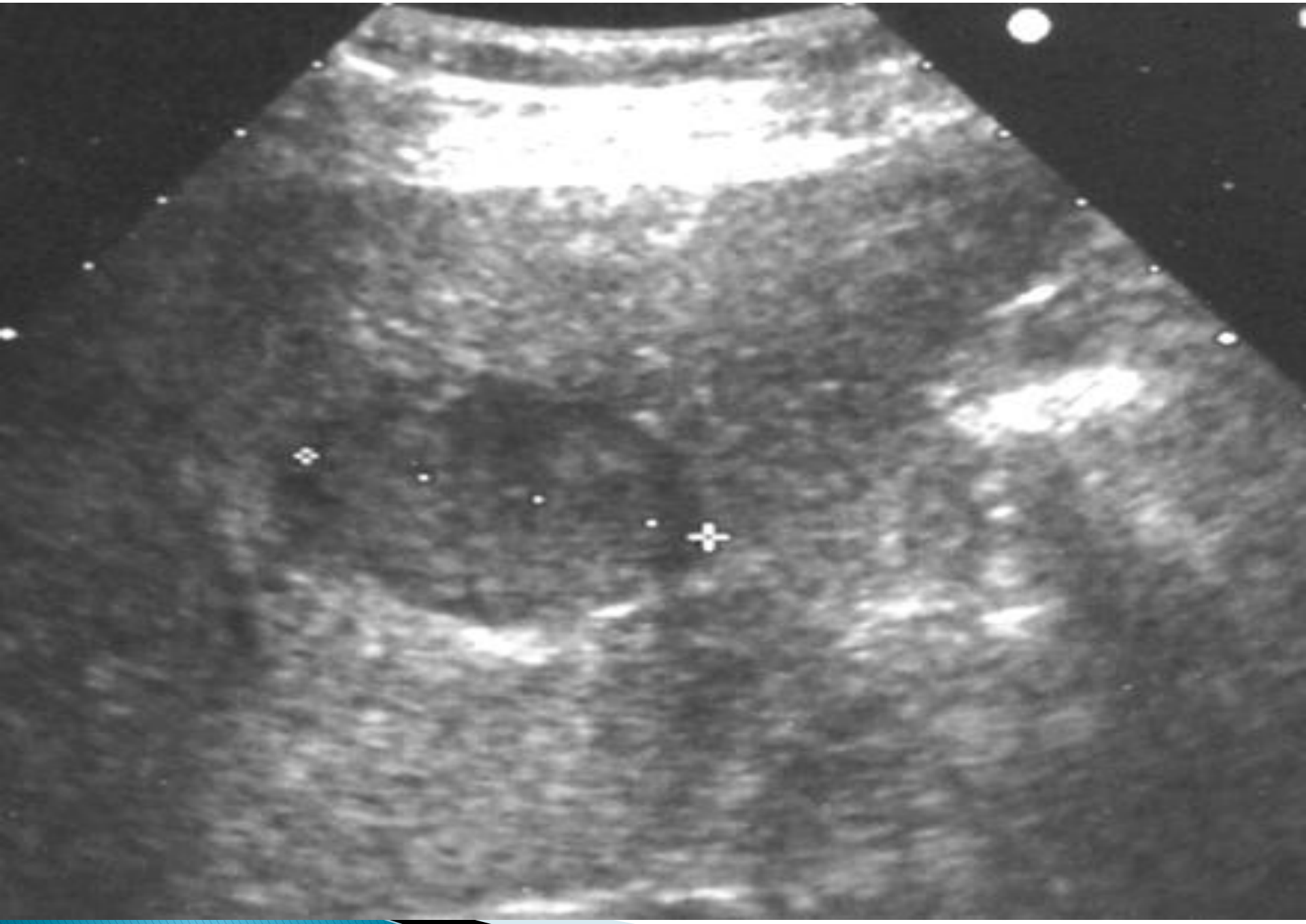
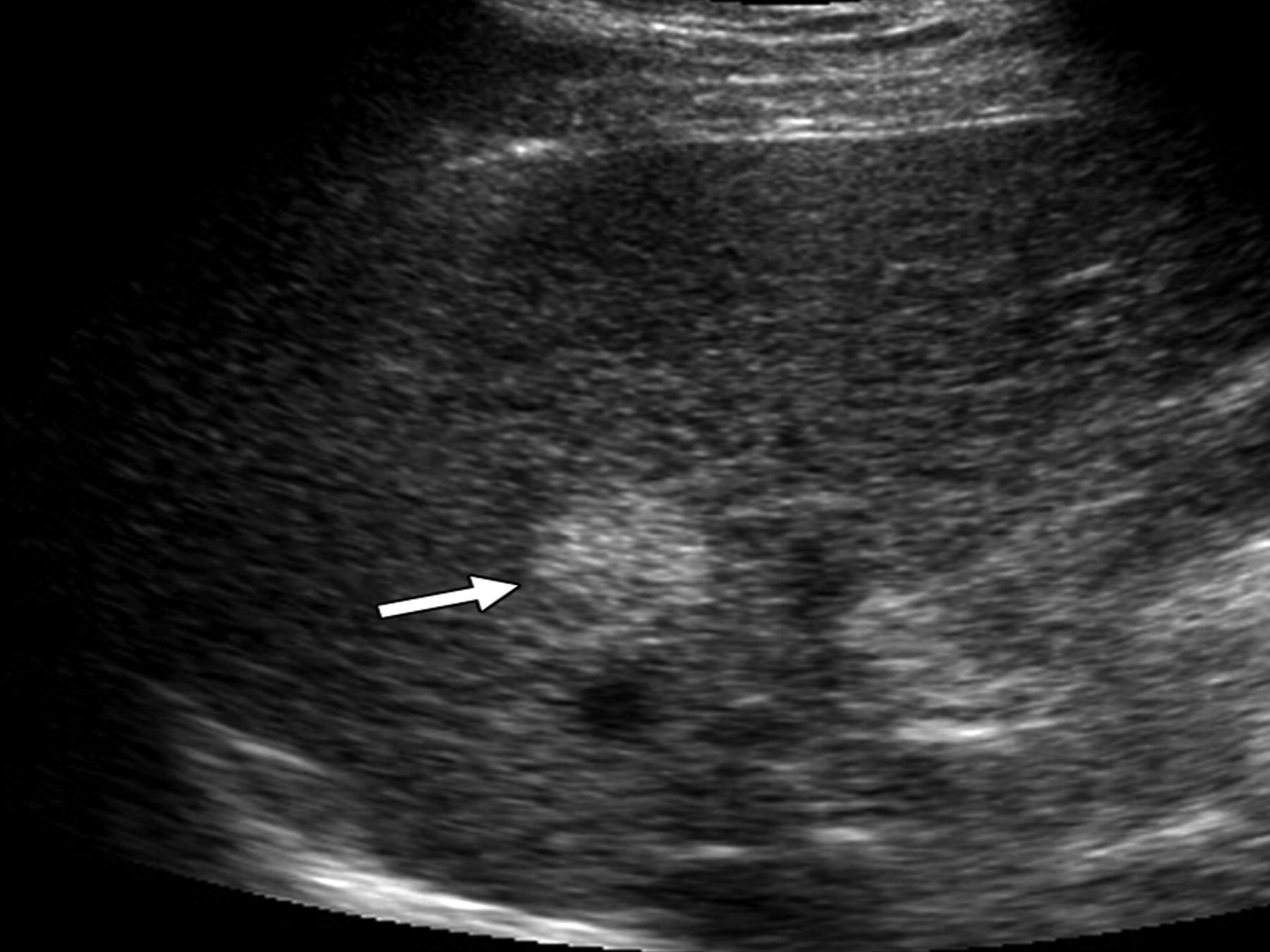
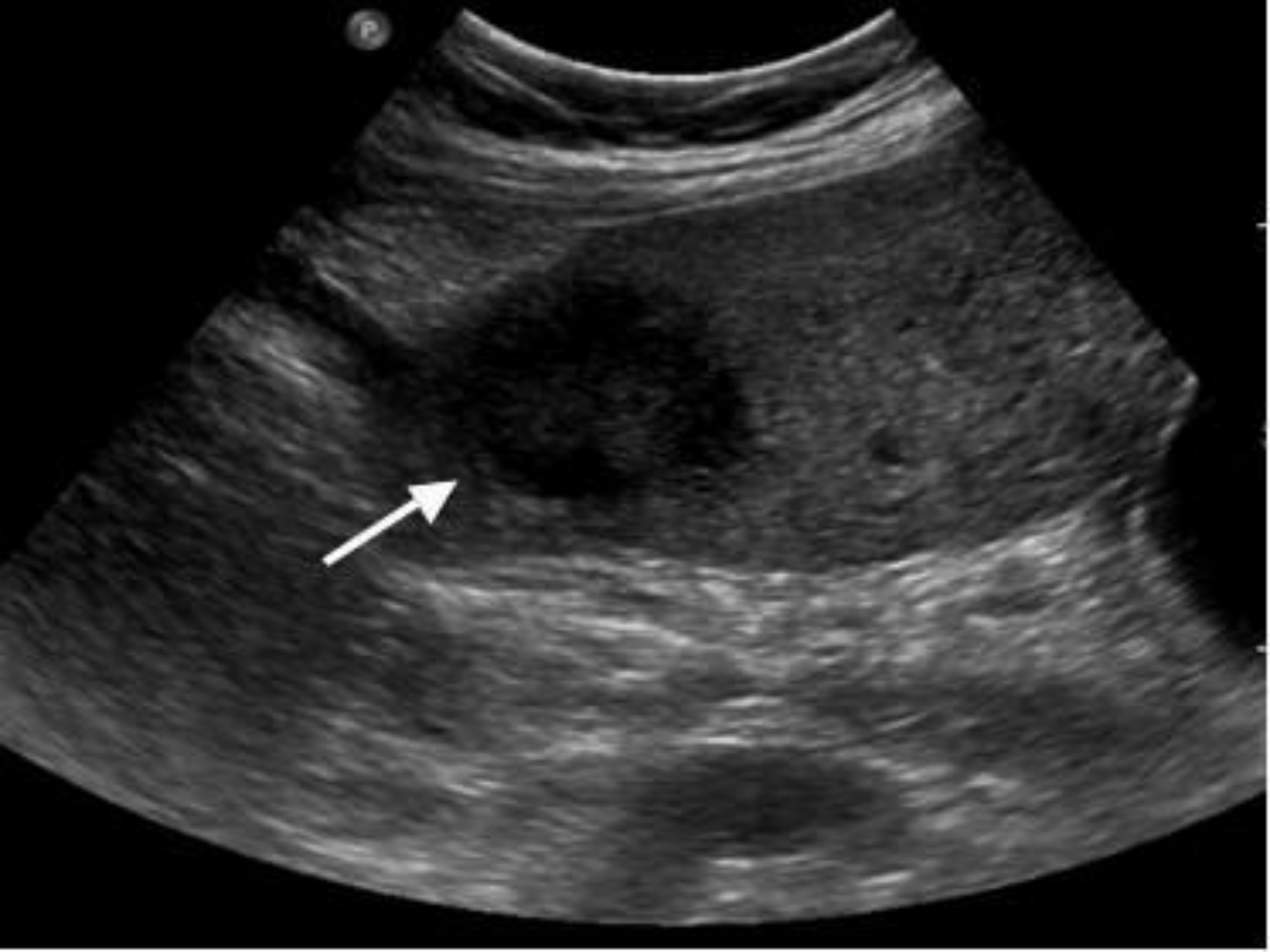
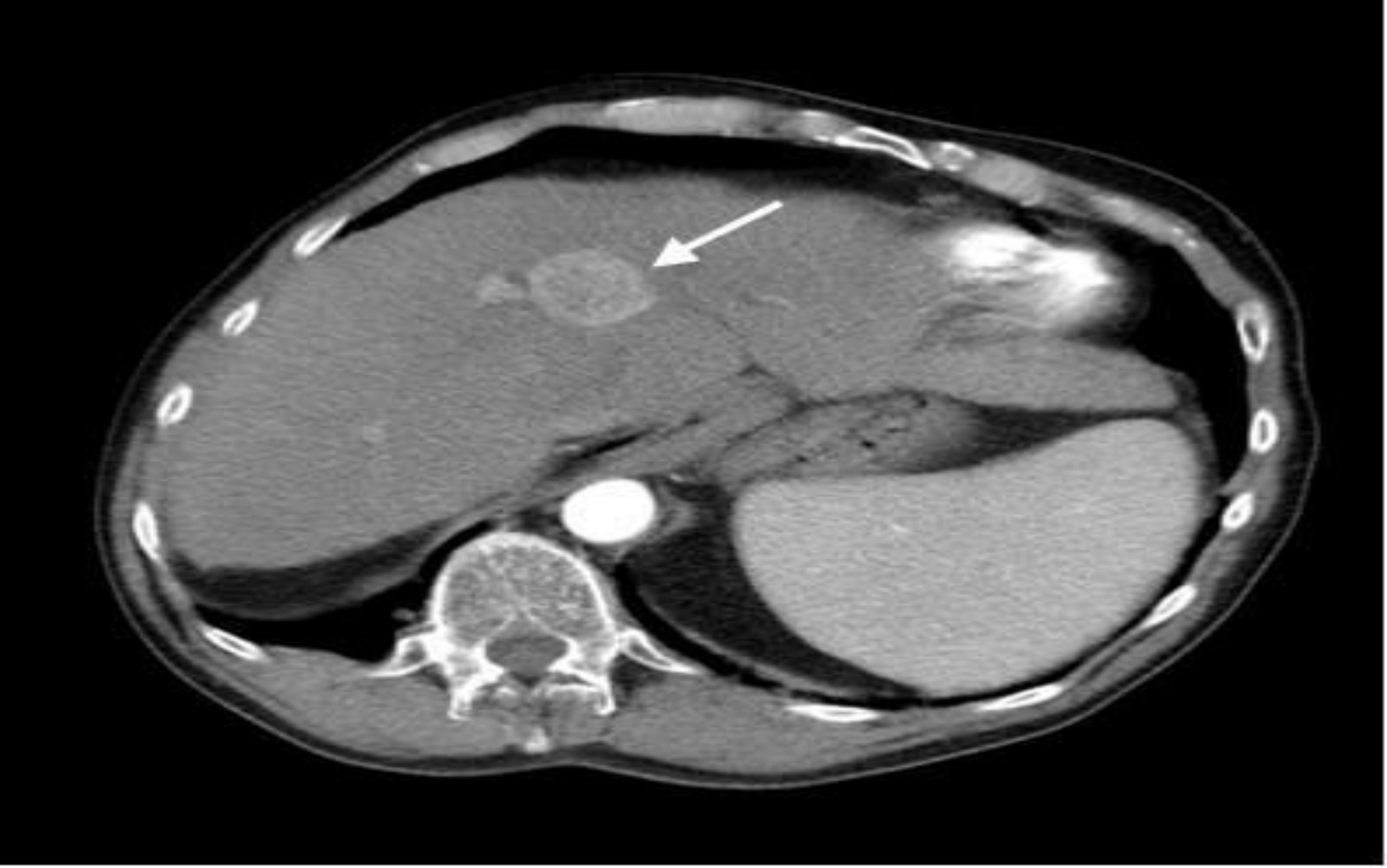
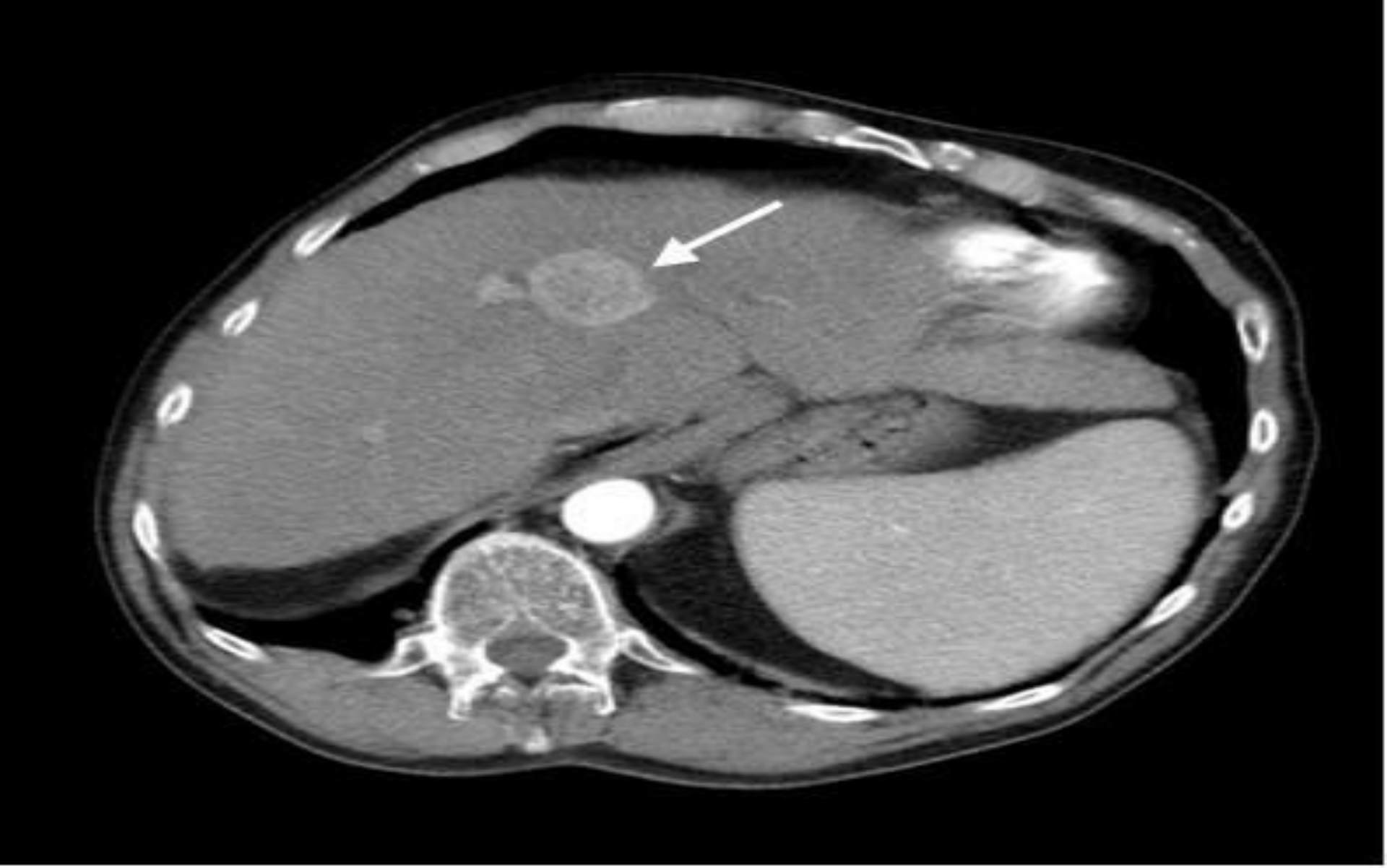










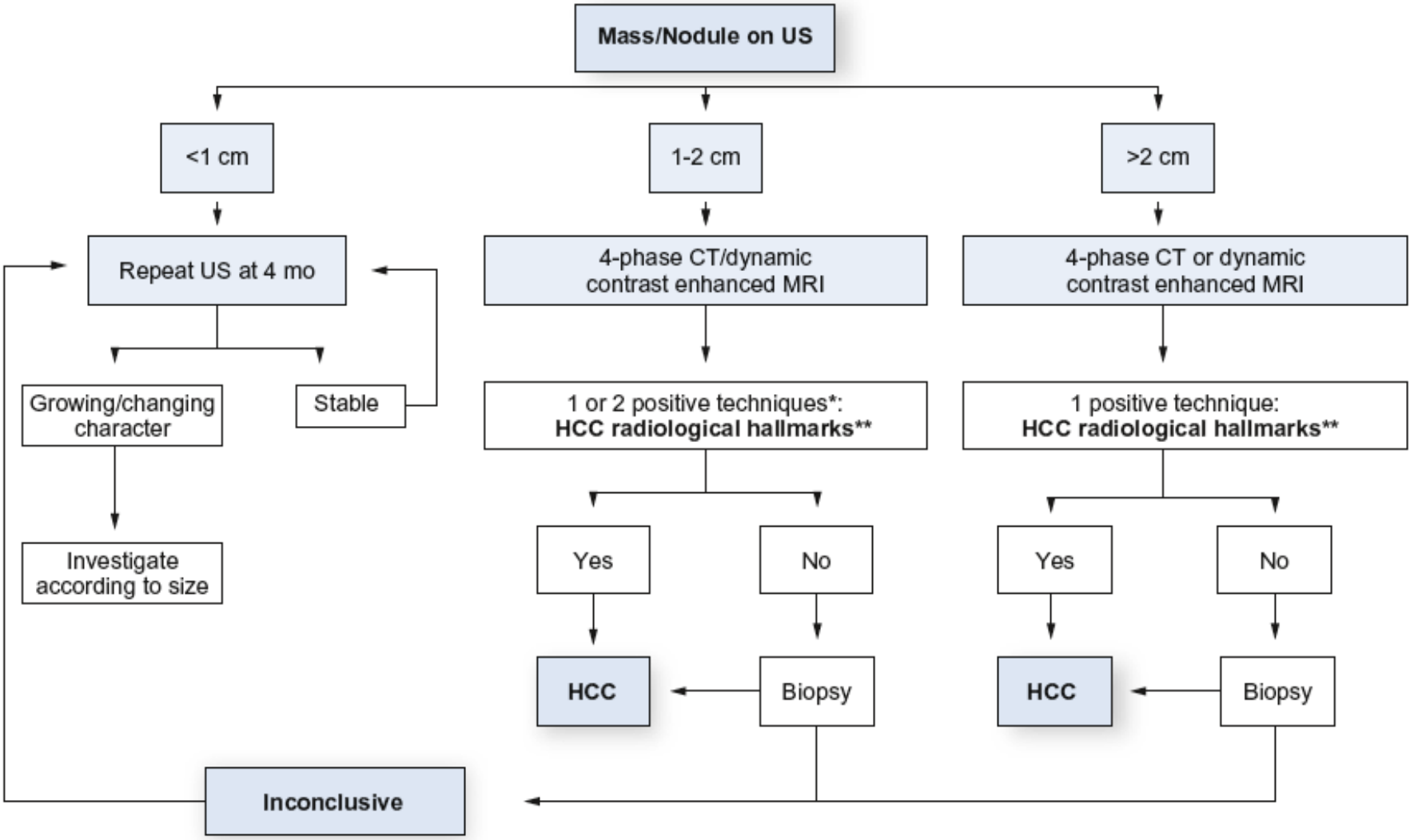
AFP

- As a serological test for surveillance, AFP has a suboptimal performance.
- Reasons for the suboptimal performance of AFP as a serological test in the surveillance mode are twofold.
- Firstly, fluctuating levels of AFP in patients with cirrhosis might reflect flares of HBV or HCV infection, exacerbation of underlying liver disease or HCC development.
- Secondly, only a small proportion of tumors at an early stage (10–20%) present with abnormal AFP serum levels, a fact that has been recently correlated with a molecular subclass of aggressive HCCs (S2 class, EpCAM positive) .
- When used as a diagnostic test, AFP levels at a value of 20 ng/ml show good sensitivity but low specificity, whereas at higher cut-offs of 200 ng/ml the sensitivity drops to 22% with high specificity .

Other Biomarkers

- All other serum markers have usually been evaluated, alone or in combination, in a diagnostic rather than surveillance setting .
- DCP, measured with a first generation assay, did not offer substantial advantages with respect to AFP . In addition, DCP levels have been associated to portal vein invasion and advanced tumor stage, a fact that prevents the usage of this marker for early detection.
- A similar situation occurs with AFP-L3 fraction levels .
- In conclusion, US can be seen as the most appropriate test to perform surveillance. The combination with AFP is not recommended, as the 6–8% gain in the detection rate does not counterbalance the increase in false positive results, ultimately leading to an about 80% increase in the cost of each small HCC diagnosed .

Diagnostic algorithm and recall policy.

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