Early Diagnosis of Hepatocellular Carcinoma Using Imaging Modalities

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Hepatocellular carcinoma (HCC) is one of the most frequent primary malignancies in the world, and, particularly, it is common in the Far East. In the world, more than one million new cases of HCC are seen each year. The prognosis of patients with HCC is extremely poor with an average survival of about six months following the diagnosis. In order to improve the prognosis of HCC, early diagnosis should be attempted utilizing mass screening methods. Screening of a high-risk population with alpha-fetoprotein (AFP) along with non-invasive medical imaging modalities will lead to early diagnosis of HCC and subsequent improvement of survival. Indeed, recent advances in medical imaging techniques have increased the rate of detection of small HCCs, and such imaging modalities include ultrasonography (US), radionuclide imaging (RNI), computed tomography (CT), magnetic resonance imaging (MRI), and angiography. Each imaging method is reviewed with special emphasis on the early diagnosis of HCC.

Key Words: Hepatocellular carcinoma, alpha-fetoprotein, hepatis B virus, imaging modalities.

Hepatocellular carcinoma (HCC) occurs frequently in the Far East and in some areas of Africa. In these regions, HCC is one of the major cause of cancer death (Kew and Geddes 1982; Yu 1985).

The most important factor in the high incidence of HCC in these regions is hepatitis B virus (HBV), which causes endemic viral hepatitis leading to chronic liver diseases. Cirrhosis following viral hepatitis is responsible for the subsequent development of HCC and indeed, cirrhosis is found in three-quarters of the patients with HCC (Beasley 1982; Prince and Alcabes 1982).

Prevention

There are more than 200 million individuals in the world infected with HBV (Hoofnagle and Alter 1984). HBV is a cause of chronic active hepatitis (CAH), cirrhosis, and HCC. One of the most important sources of HBV chronic carriers is perinatal transmission. The perinatal transmission of HBV to infants has been as high as 70% and at least 90% of these infected neonates become HBV chronic carriers. These carriers have a 25% risk of dying from chronic liver diseases such as CAH, cirrhosis, or HCC during their adulthood

(Beasley and Hwang 1984). Through immunoprophylaxis against HBV, transmission can be reduced to a 5 to 10% incidence (Beasley et al. 1983). Infants of mothers who are hepatitis B surface antigen (HBsAg) positive should receive hepatitis B vaccine and hepatitis B immune globulin (HBIG) at birth and repeated vaccines at ages 1 and 6 months. Early detection and treatment of HCC are important for the prolongation of survival, but at the same time, greater effort should be made towards the prevention of HCC by establishing passive and active immunization programs, in order to reduce HBV infection.

Mass Screening

These people who are HBV carriers, have a family history of HCC, have histories of previous transfusion or histories of liver disease, are considered to be at high risk for HCC. These individuals should be screened for elevated levels of alpha-fetoprotein (AFP). AFP, fetal α 1 globulin, is found often in the serum of patients with HCC. Serum AFP levels proved to be an excellent diagnostic tool for the detection of small HCCs which are usually asymptomatic. A sharp rise in serum AFP level in high-risk individuals is highly diagnostic for HCC. An additional screening tool is necessary for the high-risk population since approximately 35% of patients with HCC fail to demonstrate elevated serum AFP levels (Liaw et al. 1986). For this

group, noninvasive hepatic ultrasonography (US), which is sensitive in detecting small HCCs, should be supplemented. According to Tang *et al* (1980), early diagnosis only accounted for 0.4-0.9% in clinical cases, but it increased to 44.7-71.2% in a population screened with AFP.

HEPATIC IMAGING MODALITIES

The selection of imaging modalities in the detection of HCC has to be tailored to each patient who has already been screened with serum AFP level measurement or US. Two clinical cases are illustrated here.
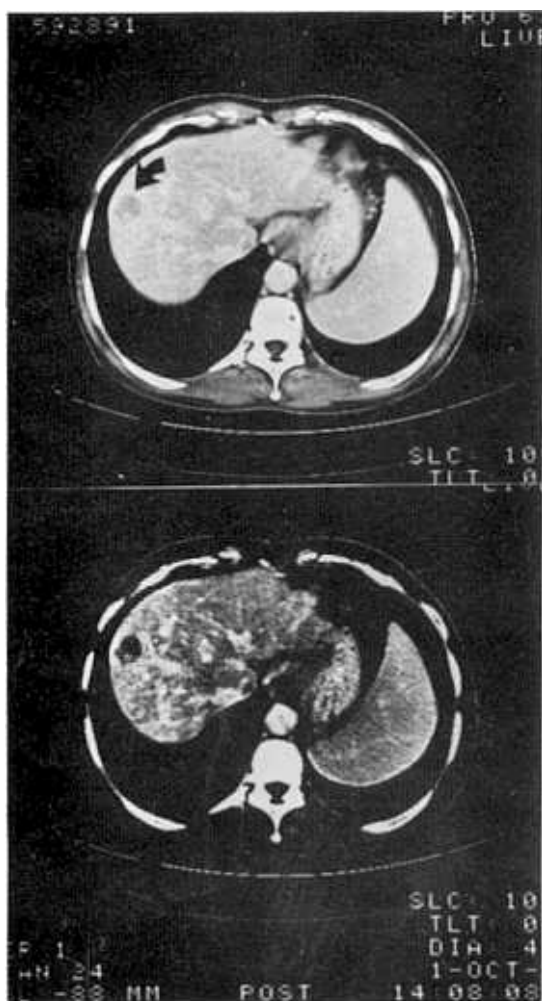

Fig. 1. Ct scans with two different windows show a small HCC (2.0 cm in diameter) in the right hepatic lobe (arrow) and splenomegaly.

The first case is a 44-year-old pulmonist from the Far East. She had several episodes of esophageal variceal bleeding from HBV induced cirrhosis of the liver. She was screened for HCC with serum AFP measurements every 3-6 months. When she had an elevated serum AFP level of 60ng/ml, hepatic US and CT were performed. US showed cirrhosis of the liver and splenomegaly but failed to show HCC. CT, however, revealed a 2 cm lesion at the lateral margin of the right hepatic lobe near the diaphragm (Fig. 1). Following a hepatic angiogram (Fig. 2), the patient underwent an intra-operative US which revealed a small HCC close to the hepatic veins and severe cirrhosis. The lesion was felt to be unresectable, and only a biopsy was obtained. She was then treated with intrahepatic arterial administration of I-131-Ethiodol in an attempt to deliver high internal radiation. She was not a candidate for chemotherapy since she was severely pancytopenic due to hypersplenism. The HCC was resected two months later when the lesion became smaller in size with more than 50% shrinkage. Serum AFP level has returned to normal following the surgery and she is doing well at present with more than one year follow-up.

The second case was a 74-year-old alcoholic male who was evaluated for HCC with US and CT scans in Florida (Fig. 3). Due to massive ascites and severe cirrhosis with distorted hepatic parenchyma, the scans were interpreted as free of mass lesion. Then the patient was re-evaluated at Thomas Jefferson University Hospital. ^{99m}Tc Sulfur Colloid scan showed multiple
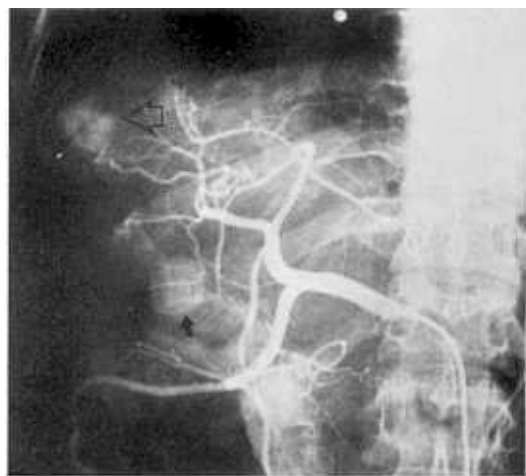

Fig. 2. Selective hepatic arteriogram on the same patient as in Fig. 1 depicts a vascular HCC (open arrows) and a gallstone (solid arrow).

nonspecific defects, and a few defects were radiogallium avid on ^{67}Ga-Citrate scintiscan (Fig. 3). A large hypervascular HCC in the left lobe and multiple small HCCs in both lobes were found on hepatic angiogram. Following this, the patient deteriorated rapidly.

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In recent years, there has been rapid development of various medical imaging modalities in the evaluation of focal hepatic lesions, and the proper selection of these imaging modalities is somewhat confusing. Therefore, understanding the pros and cons of each imaging modality is essential for the early detection of HCCs.

Ultrasonography (US)

Us is one the most frequently used imaging modalities for HCCs because of its low expense, short examination time, and use of nonionizing radiation. Therefore, US is best suited for a mass screening purposes. US offers an anatomical definition of the hepatic and portal veins and extrahepatic structures in addition to tumor characteristics (Okuda 1981).

HCCs are observed as hypoechoic, isoechoic, and hyperechoic on US examination. Most small HCCs evolve progressively from a hypoechoic to an isoechoic lesion. The isoechoic lesion can be missed easily on US. Small HCCs located at the perphery, especially near the diaphragm are overlooked frequently. Also an HCC arising from a severely cirrhotic liver is difficult to discriminate from abnormal liver parenchyma (Case 1). Real-time US with an elec-
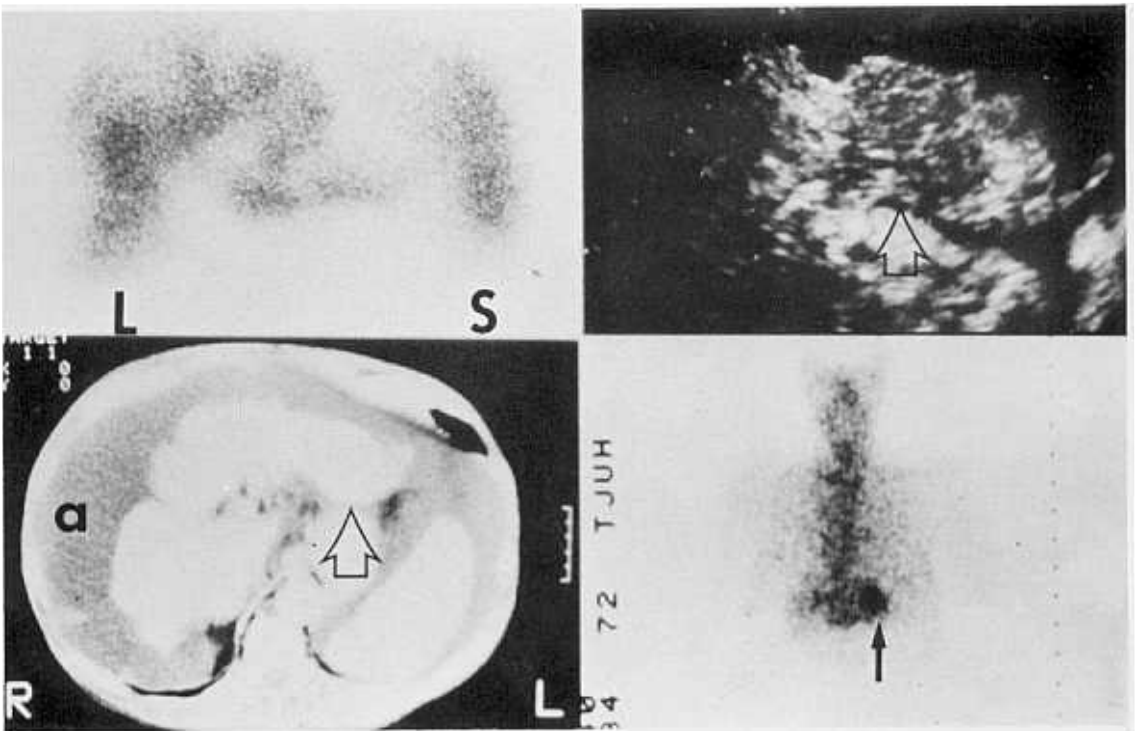

Fig. 3. ^{99m}Tc-SC scan (left upper) reveals multiple defects. (L: Liver, S: Spleen)
US (right upper) shows an irregular hypoechoic lesion (open arrow) CT scan (left lower) demonstrates ascites (a) and an ill-defined lesion (open arrow)
[67]Ga scan of head, neck, chest and abdomen (right lower) shows intense uptake by a hepatoma (arrow) in the left lobe and multiple small increased uptake in the liver.

tronically activated high-resolution linear-array transducer is a very sensitive method for detecting small HCCs less than 3.0m (Fig. 4) (Shue *et al.* 1984). One major drawback of US is operator variability.

However, overall accuracy for ultrasonic detection of HCCs is over 90% (Tanaka *et al.* 1986). Currently, portable US is popular especially in Japan, and realtime US may play a role as stethoscope for hepatologists
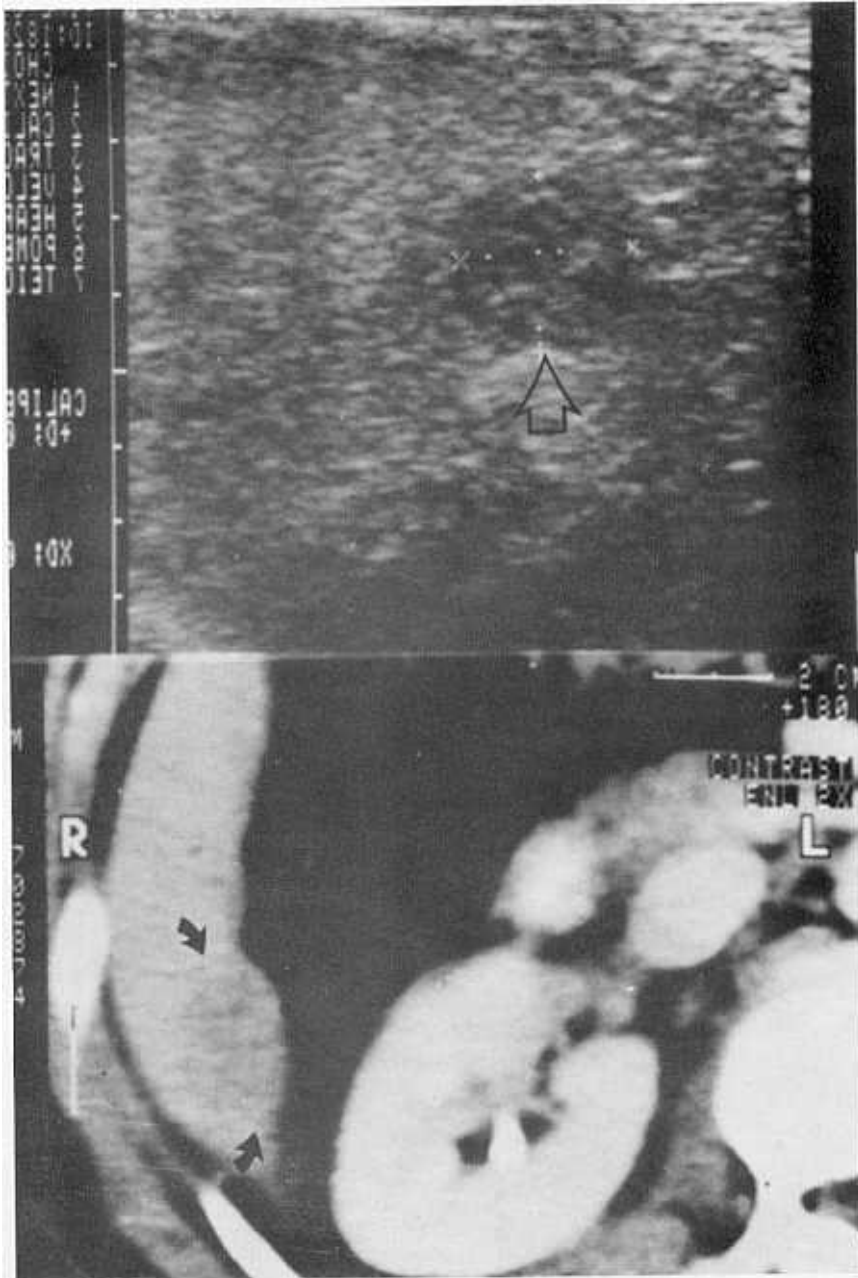

Fig. 4. US scan (top) on an asymptomatic patient reveals a small HCC (2.0cm) which was resected. CT scan (bottom) on the same patient shows a small HCC located at the right hepatic tip.

(Okuda 1981).

Portable real-time US during surgery for preresection evaluation is an indispensable procedure in the resection of a small HCC (Igawa et al. 1985), and it should be used as a routine procedure. US-guided puncture using a very thin 22 gauge biopsy needle and a specially designed transducer is a well accepted method in the diagnosis of HCC, although the diagnostic accuracy of needle aspiration cytology is inferior to biopsy.

Radionuclide Imaging (RNI)

In general, RNI is not a reliable detection technique for small HCCs. The preference for RNI is based on its high sensitivity, short imaging time, reproducibility, operator independancy, low radiation dose and low cost. ^{99m}Tc Sulfur Colloid (TcSC) scanning is easy to perform, and the sensitivity of the imaging is similar to CT for focal hepatic lesions (85-95%) (Snow et al. 1979; Grossman et al. 1977). However, CT is more specific than the TcSC imaging. Planar imaging with TcSC cannot recognize an HCC smaller than 2.0cm in diameter even using state-of-the-art gamma scintillation cameras. Resolution, however, has improved since the development of the new technique called single photon emission computed tomography (SPECT) (Kudo et al. 1986). Using multiple projectional images (64 or 128) and back projection algorithm, tomographic images in transverse, sagittal and coronal sections are generated in SPECT.

The avidity of radiogallium (^{67}Ga-Citrate) for HCC is well recognized (James et al. 1974; Bekerman et al. 1984). One of the most difficult problems in hepatic imaging is the detection of HCC in the presence of cirrhosis, and ^{67}Ga planar or SPECT can be the most reliable noninvasive method in the diagnosis of HCC in the cirrhotic liver (Fig. 5). A small number of patients with small HCCs, less than 5.0cm in diameter, were evaluated with various imaging modalities at Yonsei University by the author et al, and ^{67}Ga SPECT is a very sensitive method in the detection of small HCCs (Table 1).
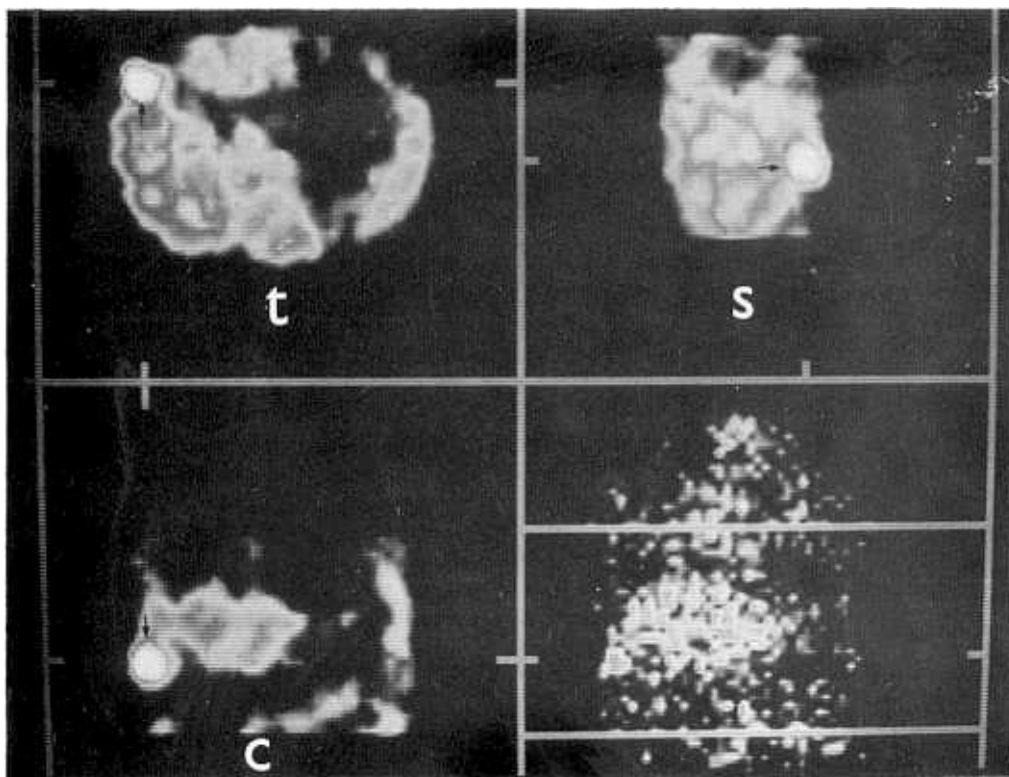

Fig. 5. ^{67}Ga SPECT in transverse (t), Sagittal (s), and coronal (c) sections depict a small HCC (small arrow) which was not visualized on US because of superimposed cirrhosis.

Table 1. Detection rate of small HCCs (Less than 5cm)

Modality	Detection Rate	Percentage
Ultrasonography	11/16	68.8%
Computed Tomography	14/16	87.5%
[67]Ga Planar	9/16	56.3%
[67]Ga SPECT	13/16	81.3%
Angiography	15/16	93.8%

Computed Tomography (CT)

X-ray CT produces images based on the varying densities within the liver due to the different absorption co-efficients of normal and abnormal tissues. Typically, HCCs appear as areas of low attenuation and CT is highly diagnostic for HCCs (Figs. 1 & 4) (Itai et al. 1979). Occasionally, HCCs may be isodense with normal hepatic parenchyma, and such lesions will be missed on CT unless one uses a manipulation technique such as contrast enhancement. To improve sensitivity, intravenous bolus injections of contrast material may be combined with rapid scanning in a single plane (CT angiography or dyamic CT scanning). Contrast enhanced CT is also performed following intraarterial infusion in order to reveal the vascular architecture or filling pattern of hepatic tumors. Small HCCs or daughter nodules could not be detected by conventional CT, but small lesions were identified on Lipiodol or Ethiodol enhanced CT as the oily contrast agent is selectively retained within the tumor vessels of HCC (Bruneton et al. 1988). This method was superior to hepatic angiography in detecting very small HCCs or nodules (Ohnishi et al. 1985). In this technique, about 10ml of Ethiodol or Lipiodol are slowly injected into the hepatic artery proper and a CT scan is done about 10 days later. The oily dye remains in the vascular HCC, enabling detection of a lesion as small as 3mm by Lipiodol enhanced CT, while Lipiodol is cleared quickly by normal hepetic parenchyma (Nakakuma et al. 1985). Also Ethiodol or Lipidol is utilized in therapeutic protocols where it is mixed with chemotherapeutic agents (Konno et al. 1984) or labeled with I-131 (Kobayashi et al. 1986; Park et al. 1986).

Magnetic Resonance Imaging (MRI)

MRI is the most recent development of medical imaging modality. Theoretically, MRI is able to provide superior contrast resolution in soft tissues; therefore, one would expect increased detectability of small HCCs. In hepatic imaging, MRI is in its infant stage, and only limited experiences on the detectability of HCC are available at present (Glazer 1988).

Itoh et al (1987) found an 84.6% detection rate with MRI for small HCCs less than 2cm while in the study of Ebara et al (1986), the sensitivity was only 33.3% for small HCCs less than 2cm. The role of MRI in the detection of small HCCs needs to be studied further.

MRI does provide important tumor characteristics of HCC such as pseudocapsules, internal septa, tumor thrombi, and daughter nodules, and MRI is expected to be used more in the future since nonionizing radiation, a magnetic field, is used in MRI. At present only limited numbers of MRI are available, and MRI is an expensive imaging modality.

Hepatic Angiography

Angiography (Fig. 2) far exceeds the sensitivity of CT in detection of HCCs, and HCC especially shows arterial tumor vessels with vascular lakes and channels on the arteriogram. A small HCC, however, does not exhibit these angiographic features but only localized stains in the capillary phase. Therefore, a special technique called infusion angiography should be used to enhance stains by small HCCs (Takashima and Matsui 1980; Sumida et al. 1986). Hyperplastic cirrhotic nodules also show stains mimicking small HCCs. For differential diagnosis between a small HCC and a regenerating nodule, ^{67}Ga SPECT or Ethiodol enhanced CT may be useful. Hepatic angiography is routinely performed on surgical candidates to clearly demonstrate the pertinent vascular anatomy and characterization of the HCC. Selective hepatic vein involvement. Hepatic angiography is often indicated for those with suspected HCC and those needing therapeutic intervention of infusion chemotherapy or embolization.

In conclusion, mass screening of a high-risk population and the recent development of various imaging modalities described above have made it possible to diagnose small HCCs of 1 to 2 cm in diameter. However, future efforts should be made towards the prevention of HCC by controling HBV transmission

in order to limit the number of people suffering from HCC.

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