

# Medical Writers' Circle

a series of articles

written by medical  
professionals about  
the management  
and treatment of  
Hepatitis C

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## Screening for Hepatocellular Carcinoma

Patients who have chronic hepatitis C have a risk of developing hepatocellular carcinoma (liver cancer). This form of liver cancer is different from cancer that starts elsewhere in the body, and spreads to the liver. Hepatocellular carcinoma starts in the liver. Not all patients with hepatitis C have an increased risk of cancer. Patients who have advanced disease, namely cirrhosis get liver cancer with a frequency of about 5%/year. Patients who do not have cirrhosis rarely get liver cancer.

Liver cancer grows silently and does not cause symptoms until the disease is advanced, at which time there is little hope of cure, and life expectancy is usually in the range of a few months. Therefore, the only hope of effective treatment of this cancer lies in early detection, or screening.

Strictly speaking, screening refers to testing of an at-risk population, who have no external indications of the disease, either on history, on examination or by laboratory tests. The objective of screening is not just early detection, but a reduced death rate from liver cancer. It is not sufficient to find a small cancer if treatment does not cure

patients or at least significantly prolong life. Although there are many studies apparently showing that screening does prolong life these studies suffer from what is called lead-time bias. Essentially, this is a bias in which life is apparently prolonged, but in reality, because the diagnosis is made early, only the period between diagnosis and death is prolonged. The death rate may not be truly reduced.

So far, there are no studies that conclusively prove that screening hepatitis C patients at risk for liver cancer will reduce the death rate. This is because no studies have been undertaken. Such studies require many thousands of patients who must be followed over a long time. Nonetheless, potentially curative treatments are more frequently possible in cancers detected early, so an improvement in the death rate is likely.

There are two tests commonly used to screen for liver cancer. One is a blood test, called the alphafetoprotein, and the other is an ultrasound examination of the liver. Both tests have advantages and disadvantages. The alpha-fetoprotein is easier to do and less expensive. However, it is not very accurate. There is a high rate of false-positive tests, and a high rate of

false-negative tests. Over all the predictive accuracy is only about 15%. Ultrasound is better, but is more expensive. In addition, ultrasound is very operator-dependent. This means that unlike regular X-rays, the ability of the person doing the ultrasound is important. The quality of ultrasound examination is very variable. Furthermore, in the presence of cirrhosis ultrasound becomes even less reliable, missing a significant number of cancers. Nonetheless, these two tests are widely used. Other forms of X-ray, such as CAT scans or MRI are even more expensive, but have not clearly been shown to be more accurate than ultrasound.

New screening blood tests are under study. These include tests for proteins called alpha fucosidase, desgamma-carboxy prothrombin and a sub-fraction of alphafetoprotein call L3. None of these tests have yet been conclusively shown to be superior to ultrasound and are not widely available.

Most often screening tests are repeated every 6 months. However, there is no data to show that this is an appropriate time interval. Some believe that 12 monthly screening is just as effective as 6 monthly, and of course, costs less.

The optimal next steps to investigate an abnormal screening test result has not been defined, particularly if the abnormal result is from an ultrasound. Most would do a CAT scan, and some would also do an MRI. However, all these methods have false-positive and false-negative results. The smaller the lesion found by various imaging tests, the more likely is it that the lesion is not cancer, but perhaps a so-called

of liver cancer, and to only screen that group. Such methods are under study, and are not yet in general practice.

One of the major problems with this form of investigation and management is that one can never prove that a cancer does not exist. A negative X-ray result may be because there is no cancer present, but may also be because the test is insufficiently sensitive to confirm the presence of cancer. Thus one

present or not. Thus, if a biopsy or ultrasound or blood test show cirrhosis the decision whether to screen or not is easy. The decision is more difficult in patients who have had a biopsy that shows less severe disease than cirrhosis. These patients will, if not treated, progress to cirrhosis over time. The early stages of cirrhosis will be completely undetectable, yet the cancer risk will increase.

To deal with this problem

lesions, but will not fulfill its promise of reducing the death rate for the disease. ■



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cirrhotic nodule, or a dysplastic nodule. These are not cancer and may never develop into cancer, and should not be treated (since treatment carries risks). However, at the same time we do not want to miss a small, eminently treatable cancer. One compromise is to simply observe small lesions (say smaller than 2 cm in diameter) and repeat the X-ray (CAT scan or MRI) after a 3-4 month interval. Lesions that get bigger are likely to be cancer. Lesions that do not grow should continue to be followed.

Another approach is to treat the lesion by the least invasive method, usually alcohol injection or radiofrequency ablation (using heat to cook the cancer). However, although these methods have fewer complications than surgery, they may still cause problems.

Still others have taken the approach that it may be possible to predict which patients with cirrhosis are at highest risk

can never be certain that a negative test is truly negative, and once the suspicion of cancer has been raised the patient is condemned to an unending series of radiological examinations, until either the patient or the doctor gets tired of the process.

Not every one with hepatitis C and cirrhosis needs to undergo screening. If, for example the patient is too old or too infirm to undergo an attempt at curative therapy for liver cancer there is no point in screening. Patients who do not have cirrhosis have a negligible risk of developing liver cancer and do not need screening. However, it may be difficult to make the diagnosis of cirrhosis. Moderately advanced cirrhosis can be diagnosed by blood tests and ultrasonography. Early cirrhosis is completely silent, and can only be detected by biopsy. However, patients cannot undergo frequent biopsy simply to find out whether cirrhosis is

some have suggested that even patients with stage III fibrosis (so-called bridging fibrosis, a degree of scarring that is advanced, but not yet cirrhotic) should also undergo screening. However, this makes screening economically unattractive because of the large number of patients who will be screened unnecessarily.

Finally, screening for liver cancer requires resources. These include not only that the screening tests be available, but that an adequate radiology facility exists to undertake the necessary follow-up X-rays, and that an established treatment facility should include hepatologists (experts in liver disease), expert surgeons (liver surgery is not for everyone) and interventional radiologists (radiologists who perform procedures with catheters and needles). A liver transplant program should also be accessible. In the absence of such facilities screening will find early

# Medical Writers' Circle

*is a program of the Hepatitis C Support Project.*

The Mission of the Hepatitis C Support Project is to offer support to those who are affected by the hepatitis C virus (HCV) and HIV/HCV coinfection.

Support is provided broadly, through information and education, as well as access to support groups. The (Project) seeks to serve the HCV community as well as the general public.

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