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Screening for hepatocellular carcinoma

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Summary

Introduction and purpose of the work. Hepatocellular carcinoma (HCC) is one of the most common malignant tumours all over the world. It is considered to be the sixth malignant tumour in terms of incidence. It is also characterized by high mortality rate, which, depending on the geographic region, gives the second or third place on the list of cancer related death. There are many known risk factors for the development of hepatocellular carcinoma, the most important of which is liver cirrhosis. Thus the cirrhotic patients are generally accepted for screening. Actually it is recommended to perform abdominal ultrasound every 6 months in this group. Other forms of screening are also tested.

Description of the current knowledge and conclusions.

Literature review provides indisputable evidences for the need of screening for liver cancer. Doubts remain only about the appropriateness of widening the screening group and possibly extending the scope of diagnostic tools.

The authors, by analyzing the available knowledge for hepatocellular carcinoma screening, consider the qualification of actually recommended screening tests to be insufficient in countries with high incidence. Relatively high incidence of HCC, even greater mortality in the context of all cancers, safety, low cost and universal access to ultrasound, should, in the opinion of the authors, be enough for the consideration to widen the screening guidelines in countries with high incidence of HCC. In countries with low incidence, e.g. in Poland, the screening in healthy population do not belong to the priority.

Key words: hepatocellular carcinoma, screening, liver cirrhosis, HCC

Introduction

Although the most common malignant neoplasm found in the liver are metastasis e.g. from colorectal cancer, hepatocellular carcinoma (HCC) is the most frequent primary malignant tumour of the liver. HCC is considered as the sixth in frequency cancer type but it is the third cause of cancer-related deaths in western countries [1] and second worldwide [2]. The simple conclusion is that it is a relatively common cancer but difficult to treat effectively. These in turn are the result of either too late diagnosis or lack of efficient treatment. Hepatocellular carcinoma is associated with a high rate of mortality because of early invasion, spreading out metastasis and lack of effective therapeutic modalities [3]. The authors of this paper ponder the importance of intensifying the screening procedure. If hepatocellular carcinoma in the cure statistics is a worse tumor than others, it should be sought out to detect it as early as possible. For this purpose, the authors reviewed valuable current literature to evaluate effects of screening for HCC.

High-risk group of hepatocellular carcinoma

The association between cirrhosis and hepatocellular carcinoma is well known. The vast majority of HCC develops on the basis of the liver cirrhosis. The other risk factors are: viral hepatitis B (HCV) and C (HCV), nonalcoholic fatty liver disease (NAFLD), type 2 diabetes, aflatoxin exposure, co-infection with multiple viruses (HBV, HCV and HIV), increasing age, male sex, positive family history of HCC, associated secondary alcohol abuse or NASH (nonalcoholic steatohepatitis) as a co-factor [1, 4, 5]. It is also dangerous to have HBV in the past, even in the absence of replication, virus is present in the human genome. Because the liver cirrhosis is not usually a primary disease but is a complication of other diseases, it

should be noted that the causes of cirrhosis include: alcoholic liver disease, hepatitis C, hepatitis B, NAFLD and metabolic syndrome, hereditary causes (e.g. hemochromatosis, Wilson's disease, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, alpha 1-antitrypsin deficiency, cystic fibrosis) chronic heart failure and finally cryptogenic [4, 6, 7, 8, 9, 10].
The most common causes of liver cirrhosis in the western countries are alcoholic liver disease, hepatitis B and NAFLD, while hepatitis B prevails in most parts of Asia and sub-Saharan Africa) [4, 8].

The particular risk factor usually leads to HCC by the cirrhosis, but not only this way. There is generally known that presence of HBV in human genome increase the HCC risk also in absence of cirrhosis. The level of viral replication determines the danger of carcinogenesis, however the lack of HBs antigen in HBV infection also is a condition of increased risk of HCC in non-cirrhotic livers. On the other hand the patients HCV RNA positive but without cirrhosis are not in the group of increased risk [11]. This situation turns totally when in chronic HCV infection the cirrhosis is developed. The risk of hepatocellular carcinoma is 2-4 times higher than in HBV related cirrhosis. Also high risk of HCC development is associated with hereditary hemochromatosis in the course of cirrhosis. Whilst this risk decreases respectively in cirrhosis caused by: chronic hepatitis B, alcoholic cirrhotics and advanced primary biliary cholangitis (presented in order of descending frequency) [12].
European Association for study of the liver (EASL) recommended screening in cirrhotic patients realised by the traditional transabdominal ultrasound performed every 6 months. Moreover, applicable guideline recommendations on surveillance of non-cirrhotic patients includes also adult Asian and African patients with hepatitis B virus carriers (HBV) who are with family history of HCC as well as with active viral replication. Hepatitis C virus (HCV) patients with bridging fibrosis (Metavir F3) are also recommended for the same screening by EASL [13].

Results of studies
Patients with cirrhosis as a risk factor for the development of hepatocellular carcinoma are subject to special surveillance, what was mentioned previously. It is realized by the traditional abdominal ultrasound examination performed every 6 months [13]. Some investigators also suggests the screening including the general population. One of Taiwanese researchers proposal is to perform ultrasound examination after 50 years of age every 2 years. Longer intervals than in cirrhosis are due to lack of abnormalities that may be responsible for diagnostic difficulties (similarity of regenerative nodules to HCC and precancerous dysplastic forms). In addition, the risk of that cancer is much lower in the general population than in cirrhotic individuals. Because the risk is increased with age progression, the lower limit for screening is suggested at the age of 50 years. It has been shown that this type of screening is the most cost-effective [14].
Group of 2293 both sexes Thai patients, aged 20-65 years, who were serologically positive for hepatitis B surface antigen was observed in screening examination – ultrasonography and serum alpha-fetoprotein (AFP) assay every 6 months. 3.3% of examined population were diagnosed with liver cirrhosis, all of which were from Child-Pugh class A. Decompensated cirrhosis was the exclusion criterion. The presented study proved the usefulness of ultrasound screening but not AFP. Ultrasound studies allowed to find 7 cases of HCC at initial screening. 10 additional cases of HCC were diagnosed during follow-up time (median 42, and maximal 48 months period). Authors estimated the ultrasound sensitivity in HCC diagnosis at the level of 94%, whilst the specificity 82%. Whereas the sensitivity and specificity of AFP were 41%

and 98%, respectively (at a cut-off value of ≥ 20 mg/L). Moreover all of HCC patients diagnosed were in the age of 40 and more years old, irrespective of hepatitis B duration [15].
Smaller number of patients were evaluated in the US study conducted between 2004 and 2010. 446 patients with Child A/B liver cirrhosis were prospectively evaluated in surveillance program using ultrasound and AFP in period of 4-6 years (with median follow-up of 3,5 years). HCC was diagnosed in 41 patients. 30 of them had early stages of cancer. The estimated annual incidence was 2,8%, whilst cumulative 3-year rate od 5,7% and 9,1% in 5 year incidence. Contrariwise to applicable standards, higher sensitivity of AFP over ultrasound was reported and their values were respectively: 44% and 66%, wherein specificity was comparable (92% versus 91%) [16]. However, the development of transabdominal ultrasound imaging techniques has improved considerably over the past decade, and even more importantly, the ability and skills of ultrasonographers have improved [17].
African studies showed hihger predisposition to HCC in HCV-related cirrhosis in men (twice more than in woman) and in the age after 60 years old [18]. These observations confirm the well-known fact of the relationship between the age and increased risk of cancer development [8, 14, 18] and also emphatically showed the difference between males and females in HCC incidence [5, 10].
An optimal approach in a diagnostic and therapeutic procedures should assume to detect liver changes, when the disease can be fully curable, when the tumours are small and can be removed by surgical procedures. Even better method would be to detect changes in the liver at the stage of dysplastic nodules, which may be subject to cancer transformation [19]. Epidemiological studies, evaluating the fate of patients with hepatocellular carcinoma who have not undergone radical treatment, show very high mortality (5-year survival less than 5%). 5-year survival of patients in the early HCC stages receiving potentially curative therapy is estimated at the range between 40-70%, what can also be considered insufficient [20].
A standard ultrasound may not be sufficient to properly visualize the character of lesions. Diagnostic difficulties depend not only on differentiation between malignant and benign lesions, but most often hepatocellular carcinoma imitates regenerative nodules seen in cirrhosis. Thus the studies over the implementation of additional contrasts in screening programs are undertaken. Substantially helpful may be perfluorobutane allowing to identificate HCC in the liver nodules by defect reperfusion [21, 22]. However, additional imaging tests, such as computer tomography (CT) or magnetic resonance imaging (MRI), in turn have a number of false positive results, are considered to be harmful to health (X-rays, contrast agents). Most of all, they are expensive, not so common comparing to ultrasound and in case of MRI time-consuming. The above mentioned features are not suitable for screening tests [20].
Current data from the United States published in this year (2017) indicate a reduction in the incidence of liver cancer. However, the position on the list of most common cancers and the position on the death-related cancers list remain for years on the same site. Mortality in Caucasian race due to the liver cancer is the smallest comparing to the others. It is a result of lower incidence but also higher socioeconomic status in that group [23]. The worse socioeconomic status often involves less knowledge of health hazards, access to inferior food, poor food storage. Thus liver cancer is more often and usually later diagnosed than in groups with higher social and economic status [23, 24, 25]. In a study of 820 patients with chronic hepatitis B, after 5 years of follow-up, 4.4% patients were diagnosed with hepatocellular cancer. After 10 years, HCC was confirmed in 6,3% of population. Viremia was closely correlated with the risk of development hepatocellular carcinoma and was an independent risk factor for its development [26]. A study of 1429 patients showed HCC in 150 patients after 10 years of observation [27]. In a study evaluating the risk of hepatocellular carcinoma

development in group of 980 hepatitis C related cirrhotic patients, after little over 4 years, HCC was observed in 142 patients [28].
As mentioned previously, the strongest risk factor for the development of hepatocellular carcinoma is the hepatitis C related cirrhosis [12]. Even complete cure of the hepatitis C infection does not reduce the risk [29] and there are also the assumptions that this therapy may even increase the risk of liver cancer [30, 31].
Analysis performed in United States of America on 1500 HCC patients reported between October 2005 and December 2011 revealed 1201 cirrhosis related HCC. Moreover, in those group, 296 people did not know they had liver cirrhosis. Thus authors conclude that cirrhosis is under-recognised in patients subsequently diagnosed with hepatocellular cancer [32]. Although screening for hepatocellular carcinoma (HCC) is recommended in high-risk patients, many studies found underutilization in clinical practice. Most studies performed in United States of America found surveillance rates below 30% [33].
The major risk factor for the development of hepatocellular carcinoma is cirrhosis, especially, HCV related, as previously mentioned. Patients with confirmed hepatocellular carcinoma in 80-90% of cases are cirrhotics initially [20]. The suggested process of carcinogenesis in hepatocellular carcinoma developed from liver cirrhosis includes successive stages. They include mentioned previously the regenerative nodules, through the nodules with low grade dysplasia, followed by high-grade dysplasia nodules and subsequently nodules with focal cancer, which finally become HCC [19].
High mortality of HCC is caused by late diagnosis and the lack of effective therapy in advanced disease. In nonadvanced hepatocellular carcinoma the clinical presentation is very poor. The main symptoms of HCC declared by the patients was abdominal pain and was found in just over half of people affected by hepatocellular carcinoma. The second most common ailment was altered general health, presented in 40% of HCC patients [3]. These makes the HCC in early stages poorly symptomatic condition and difficult to discover in curable period.

Although nonalcoholic fatty liver disease does not carry so much risk of HCC development as other causes, it is an epidemiologically significant problem for carcinogenesis. NAFLD, usually being the result of metabolic syndrome manifestation, affects the people around the world to a percentage reaching almost 25% of the adult population worldwide. Despite the low risk of developing HCC individually, the growing number of people with visceral obesity causes that the metabolic syndrome in western countries slowly becomes one of the most common cause of hepatocellular carcinoma [34, 35, 36]. There is estimated that 4-22% of HCC cases in the western countries are related to NAFLD [35]. Liver steatosis is also a condition that has characteristic ultrasound features and thus is helpful in the diagnostic process. Moreover ultrasound examination is helpful to find potential abnormalities in the other organs in abdominal cavity. Thus it presents additional advantages.
Low price and easy availability could make AFP also useful as a screening tool in liver cancer. AFP in HCC is very helpful test, but its value is limited. Not every human being suffering because of hepatocellular carcinoma has AFP increase in the body. However, it is common phenomenon in chronic liver disease to increase alpha-fetoprotein levels despite the absence of malignancy. There is necessary in differential diagnosis to consider the extrahepatic causes of increased AFP, e.g. germ cell tumour [37].
It has been shown usefulness of screening for colorectal cancer (CRC). Thus reduced incidence of this tumour has been demonstrated [38, 39]. Because the risk of cancer development is increasing with age, it has been established that every person aged 50-65 years should have done colonoscopy. Families with colorectal cancer (in first degree relative) are

advised to perform the first examination after age of 40, and in individuals with proven genetic predisposition even earlier [40].
Evaluating availability, price, ease of use, preparation, and finally its non invasiveness and safety, abdominal ultrasound when comparing any of these features, dominates over colonoscopy. Thus it is enough for the consideration to widen the screening guidelines in countries with high incidence of HCC. An additional value of this test is the possibility of detecting other abnormalities besides liver tumours, e.g. kidney disease, urinary bladder, gallbladder, spleen, evaluation of blood vessels and lymph nodes etc.
Epidemiological data indicate that in the Central and Eastern European countries, also in Poland the incidence of HCC is one of the lowest in the world, and non-cirrhotic related cases are sporadic [37]. In countries with low incidence of HCC, e.g. in Poland, the screening in healthy population do not belong to the priority.

Recapitulation
In conclusion, the main attention should be paid to the observance of already existing recommendations for screening. Subsequently consideration should be given to extending the indications. Screening in healthy populations with low incidence of hepatocellular carcinoma, eg in Poland, should not be considered as a priority.

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