Screening for hepatocellular carcinoma in cirrhosis

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1. Introduction

Hepatocellular carcinoma (HCC) has been recognized nowadays as the major cause of death in cirrhotic patients. Furthermore, epidemiological data, based on hepatitis C virus (HCV) epidemics and natural history of HCV infection, suggest that its frequency is increasing in U.S. [1] and that all western countries will probably face a rising epidemics of HCC in the next few years. For these reasons it is mandatory to establish a definite strategy for the early diagnosis of this neoplasm at a stage where curative treatments can be performed.

By definition, screening is the one-time application of a test for detecting a disease at an early stage, in order to increase the number of effective interventions. Surveillance is the repeated application of the test over time with the same objective. Both are considered effective if they are able to reduce the disease specific mortality [2]. Most of the published studies in the liver literature do not distinguish screening from surveillance but, when the target population is made by patients with chronic liver disease, they may include a first screening and a subsequent surveillance at different time intervals and the term ‘screening’ is commonly used to identify this policy.

HCC is a neoplasm presenting most of the characteristics that would suggest efficacy of screening: there is a well defined population at risk (cirrhotics); non-invasive, low cost, diagnostic tools (alpha feto protein, AFP and ultrasound, US) are available; curative treatments (percutaneous ethanol injection and thermoablation, surgical resection, liver transplantation) do exist and may provide excellent long term survival [3]. However, despite these premises and the large number of published studies in recent years, efficacy and cost/effectiveness of screening and surveillance of cirrhotics for the early diagnosis of HCC is still debated [4] and screening cirrhotics has not been implemented in any national heath policy program. There is now a general agreement that a randomized study, comparing outcomes in screened and non-screened patients, the only way for giving a definite answer to the question of efficacy and cost/effectiveness of screening, is at present unrealistic (and probably unethical), at least in developed countries, where the use of ultrasound is widespread. Rather, patients with chronic liver disease are routinely surveilled with US and AFP by referring hepatologists at time intervals ranging from 3 to 12 months, as a part of clinical and laboratory work up performed to follow the outcome of the disease. In a recent survey in United States [5] 84% of the respondents to a questionnaire mailed to American Association for the Study of Liver Diseases members were routinely screening patients with cirrhosis by AFP and US, in 99.7 and 93% of cases, respectively. One of the reasons for this policy is the believe that non-screening may pose malpractice liability; other reasons are that screening is cost-effective and prolongs survival. Screening of patients known to be affected by chronic liver disease has been therefore implemented in the current clinical practice, even in the absence or randomized trials, similarly to what occurred for cervical cancer screening in the past [6].

Therefore the question now is not whether to screen or not to screen, but rather: which is the target population? may patients with chronic liver disease be stratified and screened according to a different risk of developing cancer?, may different strategies of surveillance be applied in relation to this risk? which are the best tools for screening and surveillance? which are the correct methods for confirming a positive result of the screening test? In other words, can we improve the efficacy and cost/effectiveness (if any) of this practice?

Answers to these questions are difficult, since current data emerging from the literature are based on cohort studies [7–12], on case/control retrospective [13–15] or prospective studies [16,17] analyzing for comparison contemporaneous non-randomized controls, or on decision analysis models [18]. Furthermore the screened populations are heterogeneous, including patients with chronic hepatitis with or without cirrhosis, mainly of viral origin. The impact of screening other disease conditions, which seem to have...
a strong impact on HCC development in certain areas, such as non-alcoholic fatty liver disease [19,20], is less defined. The poor literature assessing treatment efficacy further complicates the analysis.

The present review tries to get answers from the tremendous body of data coming from the above mentioned and many other published studies, which deal with different issues related to screening patients with chronic liver disease. They include: the analysis of risk factors, the evaluation of performance of screening tests and the schedule for their application, and the assessment of efficacy and cost/effectiveness of screening programmes.

2. Risk factors

Incidence of HCC shows a different geographical distribution worldwide (Table 1) [21], reflecting different risk factors. This may influence the adoption of a screening policy and the screening strategy.

Exhaustive knowledge of individual risk factors for developing HCC would allow the best selection of the target population for screening. Many data about this issue have been produced through multivariate analyses of current clinical, biochemical and virological markers of the screened populations, with non-homogeneous results.

Regarding gender and age [22], there is a quite general agreement that males show a higher risk [12,17,23]. Older age probably only reflects a longer exposure to predisposing factors, thus increasing the probability of malignant transformation. In most studies it proves significant only at univariate analysis. The same consideration can be applied for biochemical markers related to liver function, analyzed as single factors or included in the Child Pugh classification [17]. Furthermore, most studies exclude advanced cirrhosis and do not allow the analysis of their impact on HCC development.

<table>
<thead>
<tr>
<th>Country</th>
<th>Age adjusted per 100,000</th>
<th>Cumulative rate (0–74)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>France</td>
<td>5.89</td>
<td>0.99</td>
</tr>
<tr>
<td>Germany</td>
<td>3.94</td>
<td>1.53</td>
</tr>
<tr>
<td>Italy</td>
<td>8.41</td>
<td>3.08</td>
</tr>
<tr>
<td>Spain</td>
<td>5.78</td>
<td>2.46</td>
</tr>
<tr>
<td>Switzerland</td>
<td>6.26</td>
<td>1.49</td>
</tr>
<tr>
<td>UK-England-Wales</td>
<td>1.71</td>
<td>0.84</td>
</tr>
<tr>
<td>US White</td>
<td>2.39</td>
<td>1.02</td>
</tr>
<tr>
<td>US Black</td>
<td>4.85</td>
<td>1.58</td>
</tr>
<tr>
<td>China</td>
<td>33.67</td>
<td>11.42</td>
</tr>
<tr>
<td>India</td>
<td>2.77</td>
<td>1.28</td>
</tr>
<tr>
<td>Japan</td>
<td>32.79</td>
<td>8.00</td>
</tr>
</tbody>
</table>

From Parkin et al. [21].

Comparison of etiologic factors for chronic liver disease is a more complicated issue, since the series in the literature are heterogeneous and often they include only selected populations (hepatitis B virus, HBV or hepatitis C virus, HCV carriers) and patients affected by chronic hepatitis with and without cirrhosis. Hepatitis B surface antigen + ve patients are at higher risk in some series [16,24], but not in other [25], where the HCV status (and not the HBV) is one of the most important risk factor. These authors found that anti-HCV positivity, prothrombin activity 75% or less, platelet count less than 75,000 and age 55 years or older allow the construction of a model which accurately discriminates a high risk from a low risk group (30.1 versus 2.3% at 4 years, P < 0.0001). These results however may be influenced by selection of patients enrolled into the study [26]. HBV infection has also been reported to be associated to a higher risk of developing the infiltrating form of HCC [27]. Association of different etiological factors (previous HBV infection in HCV carriers, HCV and alcohol) has been emphasized as responsible to significantly increase the risk of HCC [21,28], to anticipate its development and to be associated to multinodular HCC [29]. The role of HCV genotypes is controversial, but evidence for a significant influence on HCC development is insufficient [30,31]. The contribution of other etiological factors for chronic liver disease to the risk of HCC is recognized [19,20] but its magnitude has not been fully compared to that of hepatitis B and C viruses.

The role of AFP elevation at baseline as a prognostic marker is still debated. It proved significantly and independently associated to a higher risk in most studies [9,10,12,17,23] but not in all [24].

Other factors related to the pattern of liver tissue, such as the ultrasonographic appearance (hypoechoic nodular pattern and the irregularity of parenchymal echo pattern) [32,33], histologic staging [21], liver cell dysplasia [34,35] and irregular liver regeneration [36] may predict HCC. However these factors, probably because their undefined observer variability, and invasiveness (biopsy) are not routinely utilized in the clinical practice. The influence of other patterns derived from pathology, such as the degree of fibrosis or fatty infiltration, have been less investigated.

More recently, tissue markers related to hepatocyte proliferation rate (immunostaining of proliferating cell nuclear antigen) [37,38], evaluation of hepatocyte argyrophilic nucleolar organizing region quantity [39] or nucleolar hypertrophy [40] have been proposed as powerful markers for identifying patients at higher risk. Unfortunately these markers can be obtained only invasively and the need for a biopsy it is questionable in the majority of cirrhotic patients in whom the diagnosis is already evident.

3. Screening tests and schedule for surveillance

Diagnostic tools employed in screening programmes must be simple, not expensive, not invasive, well accepted by
the target population. They also must have a good sensitivity and specificity. Serum AFP and US, which have been used in most studies, satisfy nearly all these requisites but their diagnostic accuracy has been largely debated and this issue has been thoroughly analyzed in the paper of Gebo et al. [4].

3.1. Serum markers

It was reported long time ago [41] and confirmed in recent studies [42] that AFP, at a cut off value of 20 ng/ml, has a low sensitivity (< 50%) for the diagnosis of HCC and only rarely (17.7–26.1%) shows values > 200 ng/ml, which may strongly suggest HCC. Other studies [16,43–49], conducted in Europe and Asia and a few studies from Australia and United States, show that, with a threshold of 400 ng/ml, the sensitivity ranged from 0 to 64% and, with a threshold of 10–19 ng/ml, from 45 to 100% [4]. The detection of HCC based on a significant rise of AFP (> 200 ng/ml) in the absence of a positive US is exceptional [17].

In conclusion there is now general agreement that AFP alone should be used only in population based screening programmes [50] and not for screening patients with chronic liver disease (clinical based screening programmes).

Other serological markers have been proposed (MAGE-4 protein, Des-gamma-carboxy prothrombin, urinary TGFbeta1, IL2 receptor, the latter showing a very high sensitivity – 99%) [47,51–53], but none of them has ever entered into the current clinical practice.

3.2. Imaging techniques

It is almost impossible to evaluate the actual sensitivity of US and other imaging techniques from the published studies on screening and surveillance, since the gold standard remains undefined. However the analysis of these studies by Gebo et al. [4] graded the evidence for the use of US in this setting as a weak evidence. It must be outlined that in a study prospectively comparing US and computed tomography (CT) in a screening programme [54] the sensitivity of CT (88%) was significantly higher than that of US (59%).

Apart from the issue of screening, literature about diagnostic accuracy of imaging techniques is redundant, but its quality is generally poor, due to frequent incorporation bias and the retrospective nature of most studies. More correct studies have been performed in recent years using explanted livers as a gold standard [55–60] (Table 2). Some of these studies report disappointing sensitivities ranging from 53 to 65% for US, CT, magnetic resonance imaging (MRI) and Lipiodol CT. To explain these poor results it must be outlined that liver explants were not contemporaneous to the imaging techniques, but done within 6 months from them. Better results have been obtained more recently by Yao et al. [58], giving a sensitivity of 79.4% for US, of 81.6% for CT and 88.9 for MRI in the diagnosis of the main lesion before liver transplantation. These results probably reflect the bigger size of lesions in this study and in fact the sensitivity of the techniques in the detection of small satellite nodules was very low (27.6–42.9%). Finally, a higher sensitivity for US (89%) was very recently reported in comparison to CT and MRI (67 and 56%, respectively) [59]. These authors also demonstrated that positron emission tomography (PET) has no value in the diagnosis of HCC. Very recently MRI angiography has shown a high sensitivity in detecting early HCC prior to liver transplantation [60].

In conclusion, even though these studies have not been designed to assess the performance of screening tests, we can argue that the sensitivity and specificity of imaging techniques currently used in screening programmes is far from ideal for a correct diagnosis and staging of HCC at an early stage but data for replacing US with another test are insufficient.

3.3. Screening schedule

The choice between different schedules for the application of screening tests is relevant from an economical point of view. The screening intervals currently applied in

<table>
<thead>
<tr>
<th>Authors</th>
<th>US</th>
<th>Tc</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller et al. [55]</td>
<td>–</td>
<td>–</td>
<td>68</td>
</tr>
<tr>
<td>Taourel et al. [56]</td>
<td>–</td>
<td>–</td>
<td>53</td>
</tr>
<tr>
<td>Gambarin-Gelwan et al. [57]</td>
<td>58</td>
<td>94</td>
<td>91</td>
</tr>
<tr>
<td>Yao et al. [58]a</td>
<td>79.4</td>
<td>–</td>
<td>87.6</td>
</tr>
<tr>
<td>Yao et al. [58]b</td>
<td>34.3</td>
<td>–</td>
<td>27.6</td>
</tr>
<tr>
<td>Llovet et al. [60]</td>
<td>–</td>
<td>–</td>
<td>100</td>
</tr>
<tr>
<td>Teefey et al. [59]</td>
<td>89</td>
<td>51–45c</td>
<td>67–56c</td>
</tr>
</tbody>
</table>

a Main lesion.
b Satellite nodule.
c Data refer to different readers.
most programmes have been established on the basis of the volume doubling time of HCC [17,29,61]. A 6-month schedule has been generally used in most programmes, but 4-month [42] or 12-month intervals have also been used [8]. A prospective comparison of different schedules is lacking in the literature. In a retrospective analysis [15] semiannual and annual surveillance have been demonstrated to equally improve the survival of cirrhosis with HCC. The tumor size was however slightly smaller (<1 cm) in individuals under semiannual surveillance and these results confirm the findings of a prospective study on the impact of screening on gross pathology of HCC [29]. The heterogeneity of the screened population and the related variability of risk factors may however influence these findings, since different growth patterns in relation to risk factors have been hypothesized (but not definitely demonstrated) in some studies [29,62].

3.4. Diagnostic confirmation and recall procedures

Methods for diagnostic confirmation and recall procedures have not been unequivocally defined in published studies dealing with screening. This issue has then been thoroughly addressed in the final document of the 2000 EASL Conference [63] (Fig. 1). According to this document, the US detection of a liver nodule during follow up should raise the suspicion of HCC. The subsequent policy has to be modulated according to the size of the detected nodule. Since about half of nodules less than 1 cm in diameter may not correspond to HCC and current therapy is really altering outcome [64]. However, regarding this point, the final document of the EASL conference on HCC [63], a milestone in the clinical management of HCC, has defined as ‘curative’ treatments surgical resection, liver transplantation and percutaneous techniques, since they achieve a high rate of complete responses in properly selected candidates. Efficacy of screening should be discussed in this context.

Apart the reduction of disease-specific mortality derived from the application of these treatments, other related outcome measures can be analyzed in order to assess the efficacy of screening. They include the number and size of detected HCC and the eligibility for curative treatments. Unfortunately these outcomes have been evaluated only in a few case/controls studies [13–17] and decision analysis models [18]. Control groups are however heterogeneous, since they include symptomatic patients or patients diagnosed at a subclinical stage but outside regular screening programmes.

4. Efficacy and cost effectiveness of screening/surveillance

The essential pre-requisite of a screening strategy, which implies its possible efficacy, is the availability of an effective treatment for the disease condition to be diagnosed though the screening. This is a crucial point for HCC: are current treatment strategies truly effective? Even in this case the lack of randomized controlled trials for most of the treatment currently applied for HCC affects a definite conclusion, and still recently some authors question whether current therapy is really altering outcome [64]. However, regarding this point, the final document of the EASL conference on HCC [63], a milestone in the clinical management of HCC, has defined as ‘curative’ treatments surgical resection, liver transplantation and percutaneous techniques, since they achieve a high rate of complete responses in properly selected candidates. Efficacy of screening should be discussed in this context.

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4.1. Stage of HCC detected during screening

Several studies [14–17], even without a control group [7,8,10,12] report that screening allows the detection of a high number of small unifocal HCC (Table 3). The rate of unifocal HCC <3 cm in diameter was 75% in screened patients versus 15.5% in non-screened in the series of Solmi et al. [16] and 75.8 versus 37.4% in that of Trevisani et al. [15]. The mean volume of the HCC nodules was 20.1 cm³ in screened versus 12.5 cm³ in non-screened in our series [17]. The mean diameter was 3.5 versus 8.1 cm (P < 0.0001) in the series from Hong Kong [14] and 2 versus 6 cm (P < 0.001) in the series of Trevisani et al. [15]. The rate of unifocal HCC was 80.4% in screened versus 52.9% in non-screened (P < 0.001) in our series [17]. Regarding

* Available for curative treatments if diagnosed with HCC
** AFP levels to be defined
*** Pathological confirmation or non-invasive criteria (Table 1)

Fig. 1. Diagnostic confirmation of HCC and recall procedures according to the 2000 EASL conference.
the correct assessment of the stage of HCC, however, it must be underlined that unifocality at first detection with US do not correspond with the staging of the disease with other imaging techniques [17,29] and that the number of satellite nodules missed by all imaging techniques is very high when compared with findings in explanted livers [58].

4.2. Eligibility for local or surgical treatments

Outcomes of screened patients, and particularly this point, have been less investigated in most of the published studies (Table 3). In the old studies [7,8,10,11] there is a great variability of results, from 14% of operable cases in the series of Colombo et al. [8] to 82.5% of treated patients of Oka et al. [7], reflecting a different approach to the selection of treatment procedures. In the series of Zoli et al. [12] 58% of HCC detected during screening were treated. Yuen et al. [14] reports a rate of surgical resection and transarterial chemoembolization in 26.8 and 45% of screened patients versus 7.9 and 32.3%, respectively of non-screened. It must be remarked that in these series orthotopic liver transplantation, the most important curative treatment for HCC, was not considered. In our series [17] the rate of treated HCC was 69% in screened versus 59% in non-screened, while the rate of curative treatments was 47.5 versus 31.7% (P < 0.01). It is worth to remark that in this study it was first reported a significant increase in the rate of patients included in the waiting list for liver transplantation in screened patients (26 versus 13%, P < 0.01), even though only six out of 11 patients could be subsequently transplanted because of the growing of the tumor in the waiting time. In the retrospective analysis of Trevisani et al. [15], 68.5% of HCC detected with screening at 6 months intervals were potential candidates for orthotopic liver transplantation versus 32.3% of non-screened (P < 0.001).

This has been further confirmed in the series of Velazquez et al. [24] where the rate of transplanted patients was 28.9%.

4.3. Survival

The decision analysis model of Sarasin et al. [18] concludes that screening at 6 months intervals provides a negligible benefit in life expectancy (<3 months). This study however do not consider liver transplantation as a therapeutic option for screened patients. Human studies analyzing survival generally report a better figure for screened patients. The retrospective series from Hawaii [13] and from Hong Kong [14] report significant longer survivals for screened versus non-screened (P = 0.009 and P < 0.0001, respectively). In our prospective series survival of patients with HCC detected during screening proved significantly longer (P < 0.02) than that of unscreened patients: the 3 year survival rates were respectively 45 and 31.7% (median survival 30 versus 15 months) and transplanted patients were the longest survivors. Trevisani [15] reports a better survival (P < 0.001) only in the subgroup of screened patients with compensated cirrhosis.

The lead time bias has to be considered when comparatively assessing outcomes measures, particularly in retrospective studies. This can be partially corrected by the length of the follow up or by mathematical methods [65]. Better survival is maintained in the study of Trevisani et al. [15] even after adjustment of this bias. This bias is also compensated by the consideration that in some studies [16,17] control patients were not totally non-screened, since in most cases they were submitted to random US examinations outside screening programmes. Another important bias for the analysis of survival in retrospective studies may derive from the lack of pre-defined criteria for treatment allocation following the detection of HCC.

### Table 3

<table>
<thead>
<tr>
<th>Authors</th>
<th>No screened patients</th>
<th>HCC detected by screening</th>
<th>% small HCC detected in screened pts</th>
<th>% small HCC detected in unscreened pts</th>
<th>P</th>
<th>Eligibility for treatment in screened pts (%)</th>
<th>Eligibility for treatment in control pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oka et al. [7]</td>
<td>140</td>
<td>40</td>
<td>65.0 (unifocal Ø ≤2 cm)</td>
<td></td>
<td></td>
<td>82.5</td>
<td></td>
</tr>
<tr>
<td>Cottone et al. [10]</td>
<td>147</td>
<td>30</td>
<td>53.3 (unifocal Ø ≤3 cm)</td>
<td></td>
<td></td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>Pateron et al. [11]</td>
<td>147</td>
<td>30</td>
<td>53.3 (unifocal Ø ≤3 cm)</td>
<td></td>
<td></td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td>Zoli et al. [12]</td>
<td>164</td>
<td>34</td>
<td>76.0 (unifocal Ø &lt;4 cm)</td>
<td></td>
<td></td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Solmi et al. [16]</td>
<td>360</td>
<td>24</td>
<td>75.0 (unifocal Ø ≤3 cm)</td>
<td>15.5 (unifocal Ø ≤3 cm)</td>
<td>&lt;0.0001</td>
<td>73.9</td>
<td>40.8</td>
</tr>
<tr>
<td>Fasani et al. [20]</td>
<td>1584</td>
<td>178</td>
<td>50.0 (Ø &lt;3 cm)</td>
<td></td>
<td></td>
<td>52.4 (unifocal Ø ≤3 cm)</td>
<td></td>
</tr>
<tr>
<td>Yuen et al. [14]</td>
<td>142</td>
<td>142</td>
<td>40.1 (Ø &lt;3 cm)</td>
<td>4.9 (Ø &lt;3 cm)</td>
<td>&lt;0.001</td>
<td>73.9</td>
<td>40.8</td>
</tr>
<tr>
<td>Bolondi et al. [17]</td>
<td>313</td>
<td>61</td>
<td>80.4 (unifocal)</td>
<td>52.9 (unifocal)</td>
<td>&lt;0.001</td>
<td>69</td>
<td>59</td>
</tr>
<tr>
<td>Trevisani et al. [15]</td>
<td>215</td>
<td>155</td>
<td>75.8 (unifocal Ø ≤3 cm)</td>
<td>37.4 (unifocal Ø ≤3 cm)</td>
<td>&lt;0.001</td>
<td>69</td>
<td>59</td>
</tr>
<tr>
<td>Velazquez et al. [25]</td>
<td>463</td>
<td>142</td>
<td>50 (unifocal)</td>
<td>50 (unifocal)</td>
<td>79 (2–3 nodules)</td>
<td>50 (unifocal)</td>
<td></td>
</tr>
</tbody>
</table>
This may account for the scarcity of liver transplantation in the retrospective series.

5. Cost/effectiveness

Actual measurement of cost is a major area of methodological inconsistency in cost/effectiveness analysis. The calculation of charges for diagnostic and interventional procedures is more simple, since they are the only objective parameters available and may be comparable in different countries. On this basis, the cost per each additional life-year gained ranged between 48,000 and 284,000 US dollars in the model of Sarasin et al. [18] (which does not consider liver transplantation), but it may be lower (26,000–55,000 US dollars) in ‘ideal’ candidates with a predicted cirrhosis-related survival rate above 50% at 5 years. In the view of transplantation, estimated medical charges suggest that 285,294 US dollars are required per ‘cured’ case [66]. Assuming that this cure is associated to 75–85% chance for high-quality 10 year survival (an optimistic view for HCV carriers) the charges approximate 35,000–45,000 US dollars/quality adjusted life-year [66], which are slightly higher in comparison to those for breast cancer screening [67]. The actual cost per additional life-year gained were analyzed in the series from our group [17] and they resulted 112,993 US dollars per year of life saved, much more than that for breast cancer. These estimated costs imply that the adoption of a screening programme for HCC in the daily practice in each country must take into account the relative importance of the disease in the country (prevalence, socio-economic impact, etc.) in order that such programme do not consume resources out of the importance of the disease in the country.

6. Other issues emerging from screening

The detection of a nodule in a cirrhotic liver does not always correspond to the diagnosis of HCC. This is a typical figure of the ‘overdiagnosis’ problem resulting from screening programmes and may produce a cycle of increasing diagnostic and even interventional procedures without a definite advantage. This point has always been poorly analyzed, even in recent studies about screening, in which the rate and the subsequent management of suspected but not confirmed nodules is not reported. The rate of nodules in which a definite diagnosis of malignancy cannot be reached may be in fact as high as 17% [17] and may be due to dysplastic nodules [68] or other benign and malignant conditions which may arise in cirrhotic livers similarly to normal livers. A recent study reports a diagnosis different from HCC in 7.5% of nodules detected during screening and submitted to guided biopsy [42]. These lesions are mainly dysplastic nodule or, in some cases, non-Hodgkin’s lymphoma (1.8% of cases, which is however the highest rate in all published cohorts). Non-Hodgkin’s lymphoma has been described with increasing frequency in patients with chronic HCV infection and its treatment is different from that of HCC. It is not clear whether this condition can be differentiated from HCC by imaging techniques and this opens new questions about the method for confirmation of a positive screening test. This problem further support the need that the evaluation of these patients should be done within expert units with state of the art technologies.

7. Conclusion

Screening and surveillance with US and AFP is now a well established practice in the clinical management of patients with chronic liver disease, both in western countries and in Asia. Follow up schedules are variable, according to centers’ or individual hepatologists’ policy, but intervals around 6 months are most frequently used. This has allowed for a great improvement of our knowledge on incidence and risk factors for HCC, but answers to questions put at the beginning of this review remain uncertain.

At present, the target population should be made by patients with established cirrhosis, whatever the etiology. The challenge is to detect, confirm and stage early stage disease. Therefore only individuals who would be treated if diagnosed with HCC should enter into surveillance and surveillance should be stopped if severe associated conditions or liver failure precluding treatment appear during screening.

Screening patients with chronic viral hepatitis is questionable, since the incidence of HCC in chronic hepatitis is significantly lower [23] than in cirrhotics. Chronic hepatitis and cirrhosis, however, are not two distinct diseases but the same disease at different evolutive stages and a differential diagnosis between the two conditions is difficult at an early stage with current diagnostic methods, including biopsy [69].

More targeted screening strategies, based on stratification of patients according to the risk, would be an attractive perspective in term of health economics, but they are limited by the great number and the variability of risk factors, which make difficult to provide an individual risk score equally efficient in different geographical areas. Furthermore, some risk factors (older age and advanced cirrhosis with functional impairment) affect patients with a lower chance to benefit from curative treatments. Different screening schedules based on risk factors are not conceivable, since there is no definite demonstration that a lower risk of developing HCC implies a less rapid evolution of the tumor.

Regarding screening tests, at present there is not enough evidence for changing those currently used (AFP and US) even though their diagnostic accuracy is far from ideal. Spiral CT has probably a higher sensitivity than US in the detection of nodules during screening [54], but the additional cost should be justified by a thorough
cost/effectiveness analysis before clinical implementation. Harmonic US imaging [70] and MRI angiography are new perspectives which should also be evaluated in this setting. It must be underlined that accuracy of imaging techniques is strictly dependent from the expertise of the operators and their clinical background: this may rise questions about screening programmes disseminated in primary health care structures and not restricted to referral centers [26].

Finally, regarding screening efficacy, literature provides enough evidence that the number of patients eligible for curative treatment is increased by screening. Having reached this point, improvement of survival strictly depends on efficacy of treatments. To my interpretation, the most interesting result emerging from recent studies [15,17] is that the rate of HCC that could benefit from orthotopic liver transplantations may be significantly increased by screening programmes. Survival of transplanted patients greatly contributed to the overall survival increase in the series from our group [17], where definite criteria for transplantation were included in the study design. Conversely, a pre-defined treatment allocation of incidental HCC was not done in the majority of prospective studies about screening, and in fact the actual number of transplantations has been very low in all series, reflecting the confusion of criteria for post-transplantation will be the challenge for future research.

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References


