Surveillance for hepatocellular carcinoma… A hotly debated issue

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Abstract

The question of screening for hepatocellular carcinoma and particularly the surveillance of patients with cirrhosis remains hotly debated. Indeed, even if well defined groups at risk and accurate tools of early diagnosis exist, the impact of screening on the survival improvement has not yet been completely demonstrated. Moreover, the prevalence of hepatocarcinoma and the aetiologies of cirrhosis differ according to regions resulting in recommendations that should be adapted to each country. The purpose of this review is to summarise the data of the literature and to provide adapted recommendation for our country. (Acta gastroenterol. belg., **2004**, 67, **255-264**).

Key words : hepatocellular carcinoma, screening, surveillance, cirrhosis.

"Screening" has been defined as *"… the routine investigation of an apparently healthy population to detect an unsuspected condition for which treatment would be beneficial"* (1).

The confusion should actually be avoided between the terms *"screening"* and *"surveillance"*. As defined by Collier and Sherman, *"…Screening is the one time application of a test that allows the detection of the disease at a stage when intervention may significantly improve the natural course and outcome. In contrast, surveillance is the repeated application of such tests over time"* (2). Several studies of the literature entitled *"screening for hepatocellular carcinoma"* refer in fact to the initial work-up of patients with cirrhosis or chronic viral hepatitis (3-6). These studies have shown that in a population of cirrhosis or severe chronic hepatitis, the initial work-up could identify hepatocarcinoma (HCC) in a range of 7.7% (4) to 18.5% (5). The following review and recommendations will address specifically to the «surveillance» for hepatocellular carcinoma, that is to say a regular, repeated screening.

Surveillance for HCC in high-risk populations has become a popular clinical practice in western countries. Ninety-six per cent of french specialists in hepatogastroenterology (7) and 84% of physician members of the *American Association for Study of the Liver Disease* (8) routinely screened their patients with cirrhosis for HCC. Nevertheless up to now, it has not been fully demonstrated that primary liver cancer ideally fulfils the accepted rules justifying surveillance. According to the World Health Organisation (9,10), surveillance programs should fulfil the following criteria :

- The disease is recognised as an important public health problem.
- Populations of high-risk patients can be identified.
- The clinical stage of the disease is preceded by a period of latency when the disease is detectable.
- Effective, safe and financially acceptable tools of early detection are available.
- Curative treatment exists at an early stage resulting in survival improvement.

If it is widely accepted that surveillance for HCC fulfils the first 4 criteria, the last one, however, remains hotly debated.

The disease is recognised as an important public health problem

Primary liver cancer is obviously an important public health problem in the Far East and Sub-Saharan Africa where it accounts for one of the most frequent cancers due to endemic hepatitis B infection. In these regions, the mortality by HCC is about 100 per 100,000 inhabitants (11,12). It is estimated that more than 40% of world's cases of HCC occur in China alone (11) and that is this country, the absolute risk of dying form HCC before age 70 is approximately 3% in the general male population and 25% in the hepatitis B-Carrier male population (13). With the advent of effective hepatitis B vaccines, it is likely that the incidence of HCC will markedly decrease over the next decades in these high-incidence areas.

Conversely, HCC is a hitherto relatively rare cancer in western countries. In Belgium, statistics from the *National Cancer registry* for the 1993-1995 period showed that the annual incidence of cancer classified as ICD 155 (International Classification of Disease – 7th revision) including primary liver, gallbladder and bile duct cancers was 4.9/100,000 in men and 5.2/100,000 in women. According to these statistics, the annual incidence of HCC is in a range of 2-3 per 100 000 habitants making of Belgium a low-incidence area for HCC. Recent trends published for Europe even demonstrated that the mortality from HCC was decreasing in Belgium between 1975 and 1995 (14). At first glance, it seems therefore not justified to launch large and costly programs of surveillance for HCC in Belgium. However, these statistics have to be cautiously considered. Indeed

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it is acknowledged that the statistics from the *National Cancer Registry* are inaccurate due to a low-rate of reporting cases, and epidemiological figures from neighbouring countries exhibiting comparable pattern of chronic liver diseases have clearly shown a rapid increase in the incidence of primary liver cancer particularly in the male population. In France, the mortality rate due to HCC has increased from 3 per 100,000 to 11 per 100,000 from 1979 to 1993 in the male population (15), in United Kingdom, the equivalent figure has shown a progressive increase from 2 per 100,000 to 3.5 per 100,000 from 1980 to 1994 (16), and in Sweden, primary liver cancer in the general population has increased from 1.9 per 100,000 to 7.6 per 100,000 during the last 20 years (17). It is likely that the increase in the incidence of HCC follows the epidemic of hepatitis C virus infection that occurred in late sixties and early seventies. The same phenomenon has been first observed in Japan where the epidemic of hepatitis C occurred earlier, probably after the end of World War II. In the Japanese male population, deaths by HCC have steadily grown from less than 10 per 100,000 in 1950 to 40 per 100,000 recently, whereas the incidence of HCC related to HBV infection remained stable (18). In the United States, the incidence of histological proved hepatocellular carcinoma increased form 1.4 per 100,000 for the period 1976-1980 to 2.4 per 100 000 for the period 1991-1995 (19). Epidemiological analyses have shown that hepatitis C virus infection accounted for most of this increase, while the rates of primary liver cancer associated with alcoholic cirrhosis and hepatitis B infection remained stable (20).

Populations of high-risk patients can be identified

Risk factors for HCC have been clearly identified : cirrhosis regardless of the aetiology, chronic HBV and HCV infections, alfatoxin exposure, haemochromatosis, hereditary tyrosinemia. Hepatocarcinoma typically does not occur in the absence of cirrhosis. Cirrhosis is present in more than 80% of the cases in most series of HCC (21) and exceeds 90% in frequently quoted studies aimed at determining the prognosis of HCC (22,23). In some surgical series, non-cirrhotic patients account for more than 20% but this only reflects the fact that non-cirrhotic patients are more likely to undergo hepatic resection. Moreover, the majority of HCC developed on non-cirrhotic livers occur when underlying chronic liver lesions are present including portal inflammation, fibrosis, steatosis and iron overload (24,25,26). The oncogenic role of HBV in the emergence of HCC on non-cirrhotic liver as been widely assessed. In European (25,26) and Japanese series (24) of HCC developed on non-cirrhotic livers, hepatitis B virus infection appear to be a significant albeit small risk factor (less than 20%). Conversely, in endemic areas of hepatitis B infection, the prevalence of HBsAg was similar (more than 50%) in HCC occurring on cirrhotic and non-cirrhotic livers (27,28). In a Japanese prospective study on the incidence of HCC in chronic viral hepatitis without cirrhosis, HCC was detected in 10.4% of 124 chronic hepatitis C and in 3.9% of 127 chronic hepatitis B after a mean follow-up of 70 months (29). Interestingly, at the time of the emergence of HCC, cirrhosis was present in 92.3% of the hepatitis C but only in 60% of the hepatitis B cases. These studies suggest that in chronic hepatitis C, HCC develops only at a stage of cirrhosis or extensive fibrosis whereas in chronic hepatitis B, the occurrence of HCC is possible without extensive fibrosis suggesting an oncogenic potential of the virus (29).

Finally, it must be pointed out that the combination of different risk factors has a cumulative impact on the incidence of primary liver cancer : alfatoxin exposure in endemic regions for hepatitis B infection (30), HBV and HCV coinfection in european patients (31), HBV and HCV infections in alcoholic cirrhosis (32). A Swedish national survey showed that the incidence ratio for HCC was 40.7 in the presence of cirrhosis, 118.5 in the presence of cirrhosis and chronic viral hepatitis and 171.4 in the presence of cirrhosis, chronic viral hepatitis and alcoholism (33).

An exhaustive survey of the literature shows that the annual incidence of HCC in cirrhosis ranged from 1.4% to 6.5% with a median of 3.9% (Table 1). The lower rates were observed in studies including compensated cirrhosis (43,46,48) or mixing cirrhosis and chronic hepatitis (45). The level of α-foetoprotein at the time of entry in the surveillance program appeared to be the strongest predictive factor for the further emergence of HCC. In most studies, the cumulative incidence of HCC was more than doubled in patients with aFP level exceeding the defined cut off level ranging from 5 to 50 ng/ml (Table 2). In only one large series of hepatitis C virus-related cirrhosis, aFP level at entry was not predictive of HCC emergence in the following years (48). In this series however, patients with aFP above 50 ng/ml were excluded. In chronic viral hepatitis without cirrhosis, the annual incidence of HCC is less than 1% for chronic hepatitis B (54-57) and about 1.5% for chronic hepatitis C (38, 56). For chronic hepatitis B, familial clustering (58) and positivity for HBe Ag (57) are associated with an greater risk of HCC.

In Belgium, surveillance for HCC addresses almost exclusively to patients with cirrhosis. It is widely accepted that in Belgium like in other countries from central and northern Europe, the main aetiological factors of cirrhosis and HCC remains excessive alcohol consumption (11). In a recent cohort of 411 consecutive Belgian patients with cirrhosis, the main aetiologies of cirrhosis were alcohol abuse in 63% and chronic hepatitis C virus infection in 20% (59). The fact that alcohol is the main aetiology of cirrhosis in Belgium is not without consequence for the success of a surveillance program. Indeed, patients with alcoholic cirrhosis are obviously less observant than patients with cirrhosis of viral

Table 1. — **Annual incidence of HCC in cirrhosis**

First author (ref.), *country / year*	Main etiology	N. cirrhosis	N. HCC	Annual incidence
Kobayashi (34), *Japan / 1985*	Viral	95	8	2.4%
Oka (35), *Japan / 1990*	Viral	140	40	6.5%
Colombo (36), *Italy / 1991*	Viral	417	29	3.2%
Imberti (37), *Italy / 1993*	Viral	200	38	5.1%
Tsukuma (38), *Japan / 1993*	Viral	240	28	4.1%
Ikeda (39), *Japan / 1993*	Viral	795	221	4.5%
Sato (40), *Japan / 1993*	Viral	361	56	5.1%
Cottone (41), *Italy / 1994*	Viral	147	30	3.8%
Pateron (42), *France / 1994*	Alcoholic	118	14	5.8%
Fattovich (43)*, *Europe / 1995*	Viral Only hepatitis B	349	32	1.5%
Zoli (44), *Italy / 1996*	Viral	164	34	6%
Solmi (45)**, *Italy / 1996*	Viral	254 (+ 106 chr.hep.)	24	1.4%
Fattovich (46)*, *Europe / 1997*	Viral Only hepatitis C	384	29	1.4%
Serfaty (47), *France / 1998*	Viral	103	11	3.3%
Degos (48)*, *France / 2000*	Viral	416	60	2.7%
Bolondi (49), *Italy / 2001*	Viral	313	61	4.1%
Caturelli (50), *Italy / 2002*	Viral	1599	269	4%
Velazquez (51), *Spain / 2003*	Alcoholic	463	38	2.9%
Henrion (52), *Belgium / 2003*	Alcoholic	293	17	2%

* Only compensated cirrhosis.
** This study included 106 chronic hepatitis without cirrhosis ; twenty-three of the 24 HCC occurred in cirrhotic patients.

Table 2. — **Incidence of HCC in cirrhosis according to a defined cut-off level of a-foetoprotein**

			Cumulative incidence OF HCC		
First author (ref.), *country / date*	N. Cirrhosis	Follow-up duration (Years)	Less than cut-off (CI / N. cirrhosis)	Cut-off level of αFP	More than cut-off (CI / N. cirrhosis)
Colombo (36), *Italy / 1991*	297	3	2% / 185	20 ng/ml	29% / 42
Imberti (37), *Italy / 1993*	200	8	11% / 151	20 ng/ml	39% / 46
Ikeda (39), *Japan / 1993*	795	10	25% / NR	10 ng/ml	65% / NR
Sato (40), *Japan / 1993*	361	3	8% / 285	30 ng/ml	43.5% / 76
Cottone (41), *Italy / 1994*	144	8	17% / 123	50 ng/ml	43% / 21
Oka (53), *Japan / 1994*	253	5	26% / 185	20 ng/ml	46% / 68
Bolondi (49), *Italy / 2001*	313	5	28% / 258	20 ng/ml	63% / 55
Velazquez (51), *Spain / 2003*	463	4	10.5% / 320	5 ng/ml	24.5% / 143

Abbreviations : CI : cumulative incidence of HCC ; NR : not reported.

origin (52). If alcohol abuse remains the main cause of cirrhosis in Belgium, the increasing role of hepatitis C virus infection in the emergence of HCC appears however clearly during recent years. In the same study of 411 Belgian patients with cirrhosis mainly of alcoholic origin (63%), the main risk factor in 57 consecutive cases of HCC was hepatitis C virus infection in 44% followed by alcohol in 33% (59). These results must be compared with the figure observed in a previous Belgian series of HCC where the main risk factor was abusive alcohol consumption in 77% of the cases (60). This higher prevalence of HCV infection in HCC does not mean that the risk of HCC is greater in viral cirrhosis than in alcoholic cirrhosis. In a cirrhotic population where alcohol is the main aetiologic factor, a greater prevalence of HCV infection in case of HCC may simply be explained by the longer survival of patients with cirrhosis of viral origin (61). The increasing impact of chronic hepatitis C on the emergence of HCC has also been noted in other european countries where alcohol classically remains the first cause of cirrhosis and HCC. In France, positivity of anti-HCV has been reported in up to 41% of patients with alcoholic cirrhosis and HCC (32). In a series of 72 UK patients with cirrhosis that developed HCC during follow-up, HCV RNA was detected in 44% but it only 23% of 76 matched cases of cirrhosis without HCC (62). In a Scottish (63) series as well as in an Austrian (64) series of HCC, HCV infection was the main risk factor accounting for 30% and 36.7% of the cases, respectively.

The clinical stage of the disease is preceded by a period of latency when the disease is already detectable

Primary liver cancer enters in its clinical phase at a size of about 10 cm. From this moment, the prognosis is dreadful with a median survival less than 4 months (22, 65,66). Before reaching the clinical phase, HCC has a relatively slow-growing pattern at least for the so-called

Table 3. — **Doubling time of small HCC at imaging techniques**

			Doubling time	
First author (ref.), year	N. HCC	Larger size	Median	Mean
Sheu (68), 1986	28	50 mm	117 days (Range : 29 – 398)	Arithmetic : 136 days Geometric : 110 days
Ebara (69), 1986	22	30 mm	NR	6.5 ± 5.7 months (Range : 1 – 19.5)
Okazaki (70), 1989	15	45 mm	NR	102 ± 77 days (Range : 41 – 305)
Barbara (71), 1992	59	50 mm	171.6 days (Range : 27 – 605)	204 ± 135 days
Kubota (72), 2003	49	30 mm	NR	93.5 days (34.8 – 496.4)

Abbreviations : NR : not reported.

encapsulated and expanding type that is frequent in European patients (67). In a series of 28 small (less than 5 cm) HCC, Sheu et al observed that none of them developed clinical symptoms in the follow-up period up to 860 days (68). The doubling time of small nodules of HCC has been assessed in several studies and ranged between 3 and 6 months placing HCC in the slow-growing group of tumours (Table 3). Considering that a HCC nodule may be discovered by US at a size of 1 cm and that the clinical phase will begin at a size of 10 cm, it has been proposed that the subclinical period would be of 9.6 months for HCC with the most rapid growth rate, 3.2 years for HCC with the median growth rate et 10.9 years for HCC with the slowest growth rate (68). Accordingly, ultrasonography performed every 3 months should detect all new nodules of HCC at a size under 30 mm (69).

Effective, safe and financially acceptable tools of early detection are available

Serum αFP and liver ultrasonography (US) are the usual tools of the surveillance for primary liver cancer in at-risk patients. It is now admitted that αFP is not an ideal tumoural marker for the early detection of small HCC. Indeed, for the detection of a small HCC not exceeding 3 cm in diameter, a slightly elevated level of aFP about 20 ng/ml has a sensitivity in a range 30-60%, a specificity in a range 70-90% and a low positive predictive value of about 20% (73,74). Conversely, a higher value about 200 ng/ml as a better specificity but a low sensitivity in a range 10-25% (73). However, even if αFP is not useful for the diagnosis of small HCC, it remains the most powerful predictive factor of further emergence of HCC and is interesting for determining the periodicity of screening in the surveillance program (Table 2). An interval screening not exceeding 3 months should be recommended when αFP is slightly elevated (39,53). Des-gamma-carboxyprothrombin, another tumour marker of HCC has been extensively studied but is also inadequate for the early detection of HCC. In patients with HCC less than 3 cm, Des-gamma-carboxyprothrombin is elevated in only 20% of the patients (75,76).

Liver US is the most appropriate tool for surveillance of cirrhosis and early detection of small HCC. It is effective in this particular field, it is a non-invasive non-expensive imaging technique and it is convenient for the patient. Liver US may detect hepatic nodules at a threshold of about 1 cm diameter and, in experienced hands, should detect the vast majority of HCC nodules at a size less than 3 cm in diameter (77). Indeed, it is crucial to detect HCC at a size not exceeding 3 cm given the diminution of possible curative treatment by percutaneous ablation (percutaneous ethanol or acetic acid injection and radiofrequency ablation) above this size (78-80). The Table 4 summarises the results of surveillance programs by liver US (and αFP) in term of detection of small HCC less than 3 cm and 5 cm. The detection rate of tumours less or equal to 3 cm ranged from 22.5% to 76.4% (Table 4). The lowest rates of detection were reported when the screening periodicity was 12 months instead of 3-6 months (Table 4). Nevertheless, a large discrepancy (range 37% - 76.4%) may be observed in programs with the common 6-month interval. The most recent study (51) reported a low detection rate of 42% for unifocal lesions $\leq$ 5 cm. Such a poor performance does not mean that liver US is not effective for the surveillance for HCC but suggests that US was performed by multiple and inexperienced operators. The importance of the quality of the US examinations performed by the same, experienced operator has been pointed out by investigators who reported good results (44,52).

Liver US cannot distinguish accurately between macroregenerative nodules and small HCC (50,83). Sonographically detected nodules require further evaluation by helical CT or MRI and in some cases, by percutaneous image-guided biopsy (83). The European Guidelines for the non-invasive diagnosis of HCC in patients with cirrhosis include either 1/ two coincident imaging techniques showing a focal lesion > 2 cm with arterial hypervascularization or 2/ one imaging technique showing a focal lesion > 2 cm with arterial hypervascularization with αFP level above 400 ng/ml (84). The place of percutaneous liver biopsy of focal lesions has been extensively reviewed recently (85). In the setting of the surveillance for HCC on cirrhosis, it has been

Table 4. — **Effectiveness of US liver for early detection of HCC ≤ 3 cm and ≤ 5 cm in prospective serie of surveillance in cirrhosis**

			Detection of an unifocal lesion (%)	
First author (ref.), *country / year*	N. cirrhosis / N. HCC	Surv. interval	≤ 3 cm	≤ 5 cm
Oka (35), *Japan / 1990*	140 / 40	αFP / 2 M US / 3 M	70%	82.5%
Colombo (36), *Italy / 1991*	417 / 29*	12 M	31%	NR
Imberti (37), *Italy / 1993*	200 / 38	3 – 6 M	37%	48%
Cottone (41), *Italy / 1994*	147 / 30	6 M	53%	87%
Pateron (42), *France / 1994*	118 / 14	6 M	42%	64%
Zoli (44), *Italy / 1996*	164 / 34	6 M	73%	82%
Solmi (45), *Italy / 1996*	254** / 24 (+ 106 hep. chr.)	6 M	75%	75%
Bolondi (49), *Italy / 2001*	313 / 61	6 M	52.4%	80.4%
Trevisani (81), *Italy / 2002*	NR / 215	6 M	42.3%	54.4%
	NR / 155	12 M	22.5%	49.6%
Caturelli (50), *Italy / 2002*	1599 / 269	4 M	NR	94%
Marrero (82), *US / 2002*	NR / 53	6 – 12 M	38%	73%
Velazquez (51), *Spain / 2003*	463 / 38	3 – 6 M	NR	42%
Henrion (52), *Belgium / 2003*	293 / 17	6 M	76.4%	94.1%

* In the study, 30 HCC were discovered at the initial screening and 29 during the follow-up.
** This study included patients with cirrhosis and chronic hepatitis ; twenty-three of 24 detected HCC were in patients with cirrhosis.

Abbreviations : NR : not reported ; Surv. : Survival.

Table 5. — **Macroregenerative nodules (ordinary and dysplastic) identified on cirrhotic livers harvested at autopsy or during liver transplantation**

			Macroregenerative nodules	
First author (ref.), *year*	Definition of MRN	N livers/% of livers	N	Size (mm)
Terada (89), *1993*	> 8 mm	209 / 36.5%	123 O MRN : 85 D MRN : 38	O MRN : mean 10.1 (range : 8 – 20) D MRN : mean 12.6 (range : 8 – 22)
Hytiroglou (90), *1995*	> 10 mm	155 / 28%	100	Mean : 12 > 15 mm : < 10%
Le Bail (91), *1995*	> 6 mm cirrh. micro > 8 mm cirrh. micro/macro > 10 mm cirrh. macro	41 / 24%	35 O MRN : 17 D MRN : 18	None > 15 mm
Earls (92), *1996*	Different in size and color from adjacent parenchyma	28 / 21%	27	8 – 22 mm (> 15 mm : 3)
Bhattacharya (93), *1997*	> 10 mm and different aspect from adjacent parenchyma	45 / 33%	48	< 5 mm : 27 5 – 10 mm : 13 > 10 mm : 18

Abbreviations : MRN : macroregenerative nodules ; O MRN : ordinary MRN ; D MRN : dysplastic MRN.

recommended to perform a biopsy when the lesion measures ≥ 1 cm < 2 cm or where the imaging techniques may not establish with accuracy the diagnosis for lesions above 2 cm (85). It is interesting to point out that in 3 studies including at a whole 773 patients, the accuracy of the non-invasive preoperative evaluation of focal lesions of the liver (clinical evaluation, tumoural markers, imaging techniques) was confirmed after surgery in 98% of the cases (86-88).

Several histological studies of cirrhotic livers harvested at autopsy (89) or at the time of liver transplantation (90-93) have shown the presence of macroregenerative nodules in a large proportion of them (range 21-36%) (Table 5). These macroregenerative nodules have a well-established potential of malignancy development (94, 95). Moreover, several studies have shown that cirrhotic liver could contain very small HCC not detected by the conventional imaging techniques (96,97). Subsequently some investigators have proposed to use more performant imaging techniques such as Helical CT or MRI for the surveillance of cirrhotic patients (83). However, it is important to stress that the vast majority of benign macroregenerative nodules (more than 90%) did not exceed a diameter above 15 mm (Table 5) and that the majority of nodules of a size about 10 mm were not HCC (98). Hitherto, the aim of the surveillance for HCC on cirrhosis is not to find always smaller HCC necessitating additional procedures for confirmation, but to discover evident HCC nodules less than 3 cm allowing a curative treatment (99). A cancer surveillance program is a burden for the patients and must remain simple and convenient to diminish the risk of non-observance. As

Table 6. — **Therapeutic eligibility and prognosis between HCC detected through surveillance programs and incidentally diagnosed HCC**

	Surveillance HCC			Incidental HCC		
First author (ref.), *Country / Year*	N. HCC / % ≤ 3 cm	Curative TR*.	Med. survival (months)	N. HCC / % ≤ 3 cm	Curative TR.	Med. survival (months)
Yuen (108), *Hong Kong / 2000*	142 / 40.1%	26.8% (surgery)	22	164 / 4.9%	7.9%	5
Gianini (109), *Italy / 2000*	34 / NR	67.6%	24	27 / NR	40.7%	6
Bolondi (49), *Italy / 2001*	61 / 52.4%	49%	30	104 / NR	31.7%	15
Trevisani (81), *Italy / 2002*	αFP + US / 6 M 215 / 42.3%	} 41.5%	36	451 / 15.7%	27.1%	14
	αFP + US / 12 M 155 / 22.5%		35			
Marrero (82), *US / 2002*	53 / 38%	57%	19	52 / 18%	19%	5
Henrion (52), *Belgium / 2003*	17 / 76.4%	82%	32	40 / 25%** (**≤ 5 cm)	35%	10

* Curative treatments included surgical resection, percutaneous ethanol injection, liver transplantation but not chemoembolization.

Abbreviations : NR : not reported.

pointed out by Wolf and Becker (100) : *"false positive results will lead to considerable discomfort, inconvenience, cost, risk and anxiety without benefit to the patients"*.

Curative treatment exist at an early stage resulting in survival improvement

Studies focusing on the early detection of HCC in large Asian or Alaskan populations of HBsAg carriers have demonstrated their efficacy in terms of tumour resectability and survival prolongation (101,102). Nevertheless, the majority of these patients had no underlying cirrhosis and therefore for them, large surgical resection yielded good prognosis. The problem is different in patients with cirrhosis who suffer from two diseases : the primary liver cancer and the cirrhosis. In these patients, the efficiency of the surveillance for a benefit in survival has not been fully demonstrated and remains hotly debated (103). Several surveillance studies were disappointing showing a low rate (around 10-20%) of resectability for small HCC identified during surveillance due to poor liver function, comorbid medical conditions or technical reasons such as a tumour deeply located or close to vital structures (36,42,44). Moreover, in some of these studies, when a HCC was detected, survival was not different between untreated and surgically treated patients (36,104). Trends in HCC survival in Europe (105) and in the United States (106) have shown a small improvement comparing the late seventies and early nineties with a 1-year survival improving from 8% to 18% (105) and 14 to 23% (106) respectively, but this could be attributed to the "lead-time bias" i.e an artifactual survival period corresponding to the interval from the point of detection by screening to the usual point of detection in the absence of screening (106).

Nevertheless, a growing body of evidences strongly suggests that surveillance of patients with cirrhosis for the early detection of HCC could be effective in term of survival prolongation at least in well selected cases. First, these studies reporting no survival benefit from surveillance program proposed surgical resection as the only curative treatment for HCC. Since, percutaneous ablation therapy by ethanol injections, acetic acid injection or radiofrequency, and orthotopic liver transplantation were added to the range of curative possibilities for small HCC provoking a regain of enthusiasm for HCC surveillance (107). Second, some recent studies demonstrated a benefit in terms of therapeutic eligibility and prognosis for HCC detected during surveillance program by comparison with HCC incidentally detected during the same period (Table 6). Third, the main evidence came from recent therapeutic studies showing that the 3-year survival of small HCC less than 5 cm in Child'A class cirrhosis exceeded 60% and even 70% after surgical resection (110) percutaneous ethanol injection (111,112) or liver transplantation (113). Albeit the natural history of the small HCC remains ill-defined, these results showed a substantial improvement in survival compared with the spontaneous course of small HCC. In a study of 30 untreated small HCC (less than 3 cm) with underlying cirrhosis (Child'A : 40.7%), Ebara et al reported a 1-year survival of 92.6% but a 3-years survival of only 12.9% (114). The high 1-year survival contrasting with the low 3-year survival suggested that tumour progression rather than poor liver function was the main death factor. Similarly, in a study of 391 patients with cirrhosis of Child'A class (n = 260) or Child'B class (n = 131) with unifocal HCC nodule ⩽ 5 cm, Livraghi et al showed that the 3-year survival was : 1/ 26% in Child'A, and 13% in Child'B for the not treatment group (n = 116), 2/ 79% in Child'A, and 40% in Child'B for the surgery group (n = 120), 3/ 71% in Child'A, and 41% in Child'B for the percutaneous ethanol injection group (n = 175) (115).

Recommendations

1. In Belgium, surveillance for HCC addresses almost exclusively to patients with cirrhosis regardless of the aetiology, to patients with chronic hepatitis C with extensive fibrosis of F3 stage in the METAVIR classification and to HBsAg carriers. In these at-risk patients, surveillance should be reserved to those manifesting their willingness to attend the surveillance program and exhibiting a life expectancy of at least 5 years. Alcoholic patients unable to stop drinking and patients with poor liver function (Child's C cirrhosis) or severe comorbid medical conditions should not be included.

2. The pivotal tool for surveillance is liver ultrasonography. Alfa-foetoprotein is useless for the diagnosis of small HCC but is of great interest for determining the interval between screenings. Ideally, the ultrasonography should be performed by the same, experienced operator. When a nodule is detected, its tumoural nature should be confirmed by helical computed tomography or magnetic resonance imaging in order to assess the arterial vascularization of the lesion. When the tumoural nature of the lesion remains doubtful, a image-guided percutaneous biopsy may be performed. Another possibility is to perform another ultrasonography 2 or 3 months later and consider the nodule as a HCC when it is rapidly growing.

3. The schedule of the surveillance program could be as follows

- For patients with cirrhosis, liver US should be performed every 6 months or every 3 months when α-FP is above 20 ng/ml.
- For patients with chronic hepatitis C and F3 fibrosis, and for patients with chronic hepatitis B, the surveillance interval should be 6 months.
- For inactive HBs carrier, the surveillance interval should be 12 months or 6 months in case of familial history of HCC.

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