



Observational Study

## Screening for hepatocellular carcinoma by Egyptian physicians

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### Abstract

**AIM:** To assess the practice of Egyptian physicians in screening patients for hepatocellular carcinoma (HCC).

**METHODS:** The study included 154 physicians from all over Egypt caring for patients at risk for HCC. The study was based on a questionnaire with 20 items. Each questionnaire consisted of two parts: (1) personal information regarding the physician (name, age, specialty and type of health care setting); and (2) professional experience in the care of patients at risk for HCC development (screening, knowledge about the cause and natural course of liver diseases and HCC risk).

**RESULTS:** Sixty-eight percent of doctors with an MD degree, 48% of doctors with a master degree or a diploma and 40% of doctors with a Bachelor of Medicine, Bachelor of Surgery certificate considered the hepatitis C virus (HCV) genotype as risk factor for HCC development ( $P < 0.05$ ). Ninety percent of physicians specialized in tropical medicine, internal medicine or gastroenterology and 67% of physicians in other specialties advise patients to undergo screening for HCV and hepatitis B virus infection as well as liver cirrhosis ( $P < 0.05$ ). Eighty-six percent of doctors in University Hospitals and 69% of Ministry of Health (MOH) doctors consider HCV infection as the leading cause of HCC in Egypt ( $P < 0.05$ ). Seventy-two percent of doctors with an MD degree, 55% of doctors with a master degree or a diploma, 56% of doctors with an MBBCH certificate, 74% of doctors in University Hospitals and 46% of MOH

hospital doctors consider abdominal ultrasonography as the most important investigation in HCC screening ( $P < 0.05$ ). Sixty-five percent of physicians in tropical medicine, internal medicine or gastroenterology and 37% of physicians in other specialties recommend as HCC screening interval of 3 mo ( $P < 0.05$ ). Seventy-one percent of doctors with an MD degree, 50% of doctors with a master degree or diploma and 60% of doctors with an MBBCH certificate follow the same recommendation.

**CONCLUSION:** In Egypt, physicians specialized in tropical medicine, internal medicine or gastroenterology with an MD degree and working in a University Hospital are best informed about HCC.

**Key words:** Hepatocellular carcinoma; Egyptian physicians; Screening; Hepatocellular carcinoma knowledge; Hepatocellular carcinoma management; Hepatocellular carcinoma diagnosis

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**Core tip:** We aim to assess the practice of Egyptian physicians in screening patients for hepatocellular carcinoma (HCC). We included 154 Egyptian physicians caring for patients at risk for HCC, personal information and professional experience of them were analysed. Physicians specialized in tropical medicine, internal medicine or gastroenterology with an MD degree and working in a University Hospital are best informed about HCC.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) considered being the sixth most prevalent cancer and the third most common cause of cancer leading to deaths worldwide<sup>[1]</sup>. Its annual incidence is increasing worldwide, ranging between 3% and 9% in patients with liver cirrhosis<sup>[2]</sup>. In Egypt, HCC was reported to develop in about 5% of patients with chronic liver disease<sup>[3]</sup>.

Worldwide, hepatitis B virus (HBV) is considered the major risk factor for the progression of liver cirrhosis to HCC<sup>[4]</sup>. The relative risk to develop an HCC is estimated to be 100-200-fold higher in HBV-infected patients as compared to non-infected individuals<sup>[5]</sup>. Integration of HBV DNA into the host genome is considered to be the initiating event for HBV-induced carcinogenesis<sup>[6]</sup>. In this context, the HBx protein may inactivate the *p53* tumor suppressor gene, resulting in HCC development<sup>[7]</sup>. While the prevalence of HBV infection in Egypt has been

decreasing during the last two decades<sup>[3]</sup>, the prevalence of hepatitis C virus (HCV) infection has increased to an estimated 14% in the general population<sup>[8]</sup> and was associated with a rising HCC incidence. HCV seems to primarily play an indirect role in HCC development by promoting fibrosis and cirrhosis. However, HCV may also play a direct role in hepatic carcinogenesis through viral gene products inducing liver cell proliferation<sup>[9]</sup>. In general, promotion of cirrhosis development seems to be the common pathway by which several risk factors exert their carcinogenic effect<sup>[9]</sup>.

Exposure to aflatoxin is an additional risk factor for HCC development through formation of DNA adducts in liver cells affecting the *p53* tumor suppressor gene<sup>[7]</sup>.

As a result, the major hepatological/gastroenterological professional societies worldwide, including the American Association for Study of Liver Disease (AASLD), recommend screening for HCC in high risk patients<sup>[10]</sup>. Alpha-fetoprotein (AFP) levels and imaging techniques such as ultrasonography are the most common screening modalities used by physicians to detect early HCC<sup>[11]</sup>. The majority of HCCs are diagnosed in advanced stages, which carries a poor prognosis<sup>[12]</sup>. Recent curative therapeutic regimens and liver transplantation for early stage HCC encourage physicians to screen high-risk patients<sup>[13]</sup>.

The aim of our study was to assess the practice of Egyptian physicians in screening patients for HCC.

## MATERIALS AND METHODS

The study included 154 physicians from different hospitals all over Egypt who care for patients at risk for HCC development. The study included physicians with the following 4 specialties: general practitioners/family medicine, tropical medicine, internal medicine and gastroenterology. The types of health care settings in which the physicians were employed were: primary health care, Ministry of Health (MOH) general hospitals, University hospitals and private hospitals/clinics.

### Questionnaire

We designed a 3-page questionnaire with 20 questions for Egyptian physicians to assess their practice in screening patients for HCCs. Each questionnaire consisted of two parts: (1) personal information regarding the physician (name, age, specialty and type of health care facility); and (2) professional experience with patients at risk for HCC development with respect to screening, knowledge about the cause and epidemiology of liver diseases, incl. HCC risk.

### Questionnaire distribution

The questionnaires were distributed to Egyptian physicians by personal contact at professional conferences and during seminars. The questionnaires were collected immediately after completion. Doctors were also contacted by e-mail with the questionnaire attached and asked to return the completed questionnaire by

**Table 1** Personal data of participating physicians

	<i>n</i> (154)	%
Age (yr)		
24-35	69	45
36-45	43	28
46-65	42	27
Sex		
Male	104	67.5
Female	50	32.5
Specialty		
GP	3	2
Tropical Medicine	78	50
Internal Medicine	48	31
Gastroenterology	4	3
Others	21	14
Highest qualification		
MBBCH	25	16
Msc	49	32
MD	69	45
Others	11	7
Clinical practice		
Primary Health Care	4	3
MOH	51	33
University Hospital	95	61
Private practice	4	3

MOH: Ministry of Health.

e-mail. It was also sent through the Gastrointestinal Club, a group in the Facebook facilitating scientific contacts.

### Ethics and consent

The survey was approved by the Faculty's Ethics Committee. Further, permission was obtained from all department heads who had been assured that confidentiality would be maintained and ethical principles would be followed. Before distribution of the questionnaires, the aim of the survey was explained to the potential participants who were encouraged to participate without undue pressure.

### Statistical analysis

The data from questionnaires were entered into spread sheets of Microsoft Excel before being transferred to the Statistical Package for Social Sciences (SPSS) software (SPSS Inc., Chicago, IL, United States) version 16 for Windows 7 (Microsoft Corp., Redmond, WA) to be analyzed.

## RESULTS

The study included 154 physicians of different age groups, specializations and clinical settings. The aim of the study was to assess the physicians' attitude towards HCC screening, their knowledge regarding different aspects of HCC screening, including screening modalities, as well as awareness of published guidelines.

### Personal data of participating physicians

As shown in Table 1, 45% of the physicians were aged between 24-35, 28% between 36-45 and 27%

**Table 2** Relation of the physicians' age and knowledge of hepatocellular carcinoma epidemiology

	Age (yr)				<i>P</i> value
	< 45		≥ 45		
	<i>n</i>	%	<i>n</i>	%	
Recommended HCC surveillance					
Chronic hepatitis B, C and liver cirrhosis	94	84	39	93	0.15
Positive family history	36	32	18	43	0.215
Everyone	19	17	3	7	0.121
Reduction of deaths from HCC by screening					0.419
< 30%	25	22	12	29	
≥ 30%	87	78	30	71	
Risk factors for liver disease progression					
Age	49	44	14	33	0.242
Regular alcohol consumption	49	44	22	52	0.339
Gender	33	29	17	40	0.194
Obesity, DM	42	37	13	31	0.45
HCV genotype	54	48	32	76	0.002*
HBV-HCV co-infection	60	54	18	43	0.236
Leading cause of HCC in Egypt					0.11
HCV	93	83	30	71	
HBV	19	17	12	29	
Causes of death of HCC patients					0.096
Cancer	49	44	18	43	
Liver failure	34	30	19	45	
GI or variceal bleeding	29	25	5	12	

\**P* < 0.05 considered statistically significant. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

were between 46-65 years; 50% were specialized in tropical medicine, 31% in internal medicine, 3% in gastroenterology, 2% in general practice and 14% in other specialties (Table 1). Regarding their highest qualification 16% had Bachelor of Medicine, Bachelor of Surgery (MB BCh), 32% MSc, and 45% MD degree, and 7% another qualification (Table 1). Regarding their clinical setting 3% of the physicians worked in primary health care, 33% in MOH hospitals, 61% in University hospitals and 3% in private practice (Table 1).

### Knowledge of HCC epidemiology

**Relation with physicians' age:** Table 2 shows that 76% of doctors older than 45 years and 48% of doctors younger than 45 years think that the HCV genotype is a risk factor for progression of chronic hepatitis C to HCC (*P* < 0.05).

In both age groups there were otherwise no significant differences regarding the physicians' knowledge about HCC epidemiology, people who should undergo HCC surveillance or the number of deaths that can be prevented by adequate HCC screening.

**Relation with physicians' specialty:** There is significant difference between specialties with respect to patients who should be screened for HCC (Table 3): 90% of physicians in tropical medicine, internal medicine

**Table 3** Relation between physicians' specialty and knowledge of hepatocellular carcinoma epidemiology

	Specialty				P value
	Specialty A <sup>1</sup>		Specialty B <sup>2</sup>		
	n	%	n	%	
People who should undergo HCC surveillance					
Chronic hepatitis B, C and liver cirrhosis	117	90	16	67	0.006 <sup>a</sup>
Positive family history	51	39	3	12	0.112
Everyone	15	11	7	29	0.023 <sup>a</sup>
Reduction of deaths from HCC by screening					0.903
< 30%	31	24	6	25	
≥ 30%	99	76	18	75	
Risk factors for disease progression					
Age	54	41	9		0.712
Regular alcohol consumption	63	48	8	33	0.172
Gender	47	36	3	12	0.023 <sup>a</sup>
Obesity, DM	50	38	5	21	0.098
HCV genotype	74	57	12	50	0.53
Co-infection	69	53	9	37	0.161
Most common cause of HCC					0.711
HCV	105	81	18	75	
HBV	25	19	6	25	
Cause of death of HCC patients					0.217
Cancer	59	45	8	33	
Liver failure	41	32	12	50	
GI or variceal bleeding	30	23	4	17	

<sup>1</sup>Specialty A (Tropical medicine, Internal medicine, Gastroenterology);

<sup>2</sup>Specialty B (General practitioner, Radiology, General surgery). <sup>a</sup>*P* < 0.05 considered statistically significant. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

and gastroenterology consider patients with chronic HBV or HCV infection and/or liver cirrhosis at risk to develop an HCC as compared to 67% of physicians in other specialties, such as general physicians/family doctors, radiologists or general surgeons (*P* < 0.05). By comparison, 11% of physicians in tropical medicine, internal medicine and gastroenterology think that everyone should be screened for HCC as compared to 29% of general practitioners. With respect to gender, 36% of physicians in tropical medicine, internal medicine and gastroenterology consider gender as a risk factor for HCC development compared to 12% of general practitioners (*P* < 0.05).

There were no significant differences with respect to other aspects, such as the number of deaths that can be prevented by HCC screening or the fact that HCC are the leading cause of tumor deaths in Egypt.

#### Relation with physicians' medical qualification:

Table 4 shows that there is a significant difference in awareness regarding HCC risk factors depending on the qualification of the doctors: 52% of doctors with MD degree, 17% of doctors with a master degree or diploma and 32% of doctors with MB BCh think that patients with a family history of HCC should be screened for HCC (*P* < 0.05). There is also a significant difference in knowledge about the risk factors for disease progression depending on the qualification of the doctors: 68% of doctors with MD degree, 48% of

**Table 4** Relation between physicians' qualification and knowledge of hepatocellular carcinoma epidemiology

	Highest qualification						P value
	MBBCH		Msc/diploma		MD		
	n	%	n	%	n	%	
People who should undergo HCC surveillance							
Chronic hepatitis B, C and liver cirrhosis	23	92	51	85	59	85	0.666
Positive family history	8	32	10	17	36	52	0.000 <sup>a</sup>
Everyone	4	16	8	13	10	14	0.948
Reduction of deaths from HCC by screening							0.581
< 30%	8	32	14	23	15	22	
≥ 30%	17	68	46	77	54	78	
Risk factors for progression of the disease							
Age	11	44	21	35	31	45	0.49
Regular alcohol consumption	10	40	26	43	35	51	0.562
Gender	4	16	13	22	33	48	0.001 <sup>a</sup>
Obesity, DM	8	32	19	32	28	41	0.525
HCV genotype	10	40	29	48	47	68	0.017 <sup>a</sup>
Co-infection	9	36	28	47	41	59	0.098
Leading cause of HCC							0.053
HCV	19	76	43	72	61	88	
HBV	6	24	17	28	8	12	
Cause of death of HCC patients							0.427
Cancer	12	48	25	42	30	43	
Liver failure	7	28	18	30	28	41	
GI or variceal bleeding	6	24	17	28	11	16	

<sup>a</sup>*P* < 0.05 considered statistically significant. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

doctors with a master degree or diploma and 40% of doctors with MB BCh think that the HCV genotype is a risk factor for progression of the disease; with respect to gender 48% of doctors with MD degree, 22% of doctors with a master degree or diploma and 16% of doctors with MB BCh are aware that gender is the risk factor for disease progression (*P* < 0.05).

There is no significant difference in awareness regarding other aspects, such as the number of deaths from HCC that can be prevented by appropriate screening or the most common cause of death of HCC patients in Egypt.

#### Relation with hospital setting:

Table 5 shows that there is a significant difference in knowledge about HCC risk groups between doctors in different hospital settings: 46% of doctors working in University hospitals and 17% of MOH doctors think that patients with family history of HCC should undergo surveillance (*P* < 0.05). There is also a significant difference in knowledge about the risk factors for disease progression depending on the hospital setting of the doctors: 39% of doctors working in University hospitals and 22% of MOH doctors are aware that gender is the risk factor for disease



**Table 5** Relation between hospital setting and knowledge of hepatocellular carcinoma epidemiology

	Type of hospital				<i>P</i> value
	University		MOH		
	<i>n</i>	%	<i>n</i>	%	
People who should undergo HCC surveillance					
Chronic hepatitis B, C and liver cirrhosis	79	83	54	91	0.141
Positive family history	44	46	10	17	0.000 <sup>a</sup>
Everyone	17	18	5	8	0.104
Reduction of deaths from HCC by screening					0.749
< 30%	22	23	15	25	
≥ 30%	73	77	44	75	
Risk factors for progression of the disease					
Age	43	45	20	34	0.163
Regular alcohol consumption	47	49	24	41	0.287
Gender	37	39	13	22	0.029 <sup>a</sup>
Obesity, DM	37	39	18	30	0.288
HCV genotype	55	58	31	52	0.516
HBV-HCV co-infection	50	53	28	47	0.532
Leading cause of HCC					0.011 <sup>a</sup>
HCV	82	86	41	70	
HBV	13	14	18	30	
Cause of death of HCC patients					0.493
Cancer	43	45	24	41	
Liver failure	34	36	19	32	
GI or variceal bleeding	18	19	16	27	

<sup>a</sup>P < 0.05 considered statistically significant. MOH: Ministry of Health; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

progression. With respect to the cause of HCC in Egypt, 86% of doctors working in University hospitals and 69% of MOH doctors know that HCV is the leading cause of HCC in Egypt.

There is no significant difference in knowledge with respect to other aspects, such as of the number of deaths that can be prevented by appropriate screening and the most common cause of death in HCC patients.

### Knowledge about screening modalities, educational resources and guidelines

**Relation with doctors' age:** Table 6 shows that there is significant difference in knowledge about the most important investigations for HCC screening, depending on the physicians' age: 58% of doctors < 45 years and 76% of doctors > 45 years of age think that ultrasound (US) is the most important investigation; 16% of doctors < 45 years and no doctor > 45 years think that computer tomography (CT) is the method of choice in HCC screening. Seventy-five percent of doctors < 45 years and 93% of doctors > 45 years think that treating HBV can reduce HCC incidence, while 25% of doctors < 45 years and 7% of doctors > 45 years do not think that treating of HBV can reduce HCC incidence ( $P < 0.05$ ).

There is no significant difference in other aspects of HCC screening such as screening intervals in high risk groups, knowledge about the existence of guidelines for the management of HCC, the prediction of increased

**Table 6** Relation between doctors' age and knowledge about screening modalities, educational resources and guidelines

	Age (yr)				P value
	< 45		≥ 45		
	n	%	n	%	
Most important HCC screening					0.037 <sup>a</sup>
Physical examination	2	2	1	3	
Alpha fetoprotein	27	24	9	21	
Ultrasound	65	58	32	76	
CT	18	16	0	0	
2 <sup>nd</sup> most important HCC screening					0.175
Physical examination	2	2	0	0	
Alpha fetoprotein	55	49	16	38	
Ultrasound	17	15	4	10	
CT	36	32	22	52	
Angiography	2	2	0	0	
3 <sup>rd</sup> most important HCC screening					0.585
Physical examination	3	3	2	5	
Alpha fetoprotein	21	19	13	31	
Ultrasound	14	12	3	7	
CT	55	49	18	43	
Angiography	8	7	3	7	
Laparoscopy	11	10	3	7	
Screening interval for high risk groups					0.212
3 mo	65	58	29	69	
6 mo or more	47	42	13	31	
HBV treatment reduces HCC incidence					0.014 <sup>a</sup>
Yes	84	75	39	93	
No	28	25	3	7	
Familiar with guidelines					0.205
Yes	62	55	28	67	
No	50	45	14	33	
HCV RNA/ALT level are HCC risk factors					0.08
Yes	57	51	28	67	
No	55	49	14	33	

<sup>a</sup>P < 0.05 considered statistically significant. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CT: Computer tomography.

HCC risk by elevated HCV RNA and ALT levels and the opinion regarding the second and third most important examinations in HCC screening.

**Relation with physicians' medical specialty:** Table 7 shows that there is a significant difference in opinion between different medical specialties with respect to the optimal screening interval in high risk groups ( $P < 0.05$ ): 65% of physicians in tropical medicine, internal medicine and gastroenterology think that the optimal screening interval is 3 mo while only 38% of physicians in other specialties think so; 35% of physicians in tropical medicine, internal medicine and gastroenterology think that the screening interval in high risk groups should be 6 mo or more; 62% of physicians in other specialties share this opinion.

There were no significant differences with respect to other aspects, such as the most important examination in HCC screening, the second and third most important

**Table 7** Relation between medical specialty and knowledge about screening modalities, educational resources and guideline

	Specialty A		Specialty B		P value
	n	%	n	%	
Most important screening for HCC					0.154
Physical examination	2	2	1	4	
Alpha fetoprotein	28	21	8	33	
Ultrasound	82	63	15	63	
CT	18	14	0	0	
2 <sup>nd</sup> most important screening for HCC					0.238
Physical examination	2	2	0	0	
Alpha fetoprotein	64	49	7	29	
Ultrasound	16	12	5	21	
CT	47	36	11	46	
Angiography	1	1	1	4	
3 <sup>rd</sup> most important screening for HCC					0.383
Physical examination	3	2	2	9	
Alpha fetoprotein	27	21	7	29	
Ultrasound	16	12	1	4	
CT	61	47	12	50	
Angiography	10	8	1	4	
Laparoscopy	13	10	1	4	
Screening interval for high risk group					0.010 <sup>a</sup>
Every 3 mo	85	65	9	38	
6 mo or more	45	35	15	62	
HBV treatment reduces HCC incidence					0.139
Yes	107	82	16	67	
No	23	18	8	33	
Guidelines in management of HCC					0.991
Yes	76	58	14	58	
No	54	42	10	42	
HCV RNA/ALT risk factors for HCC					0.147
Yes	75	58	10	42	
No	55	42	14	58	

<sup>a</sup> $P < 0.05$  considered statistically significant. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CT: Computer tomography.

examination in HCC screening, the reduction of the HCC incidence by treatment of HBV infection, the existence of guidelines for the management of HCC and the predictive value of elevated HCV RNA and ALT levels for HCC development.

#### Relation with physicians' highest qualification:

Table 8 shows that there is a significant difference of opinion between doctors with different qualifications with respect to the most important investigation in HCC screening ( $P < 0.05$ ): 73% of doctors with MD degree, 55% of doctors with a master degree and diploma and 56% of doctors with MBBCh think that US is the most important screening tool to detect HCC. There is also a significant difference in opinion with respect to the third most important investigation in screening for HCC ( $P < 0.05$ ) as well as with respect to the optimal screening interval ( $P < 0.05$ ): 60% of doctors with a MB BCh, 50% of doctors with a master degree and diploma and

**Table 8** Relation between highest qualification and knowledge about screening modalities, educational resources and guidelines

	Highest qualification						<i>P</i> value
	MBBCH		Msc/ diploma		MD		
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Most important screening for HCC							0.023 <sup>a</sup>
Physical examination	0	0	1	2	2	3	
Alpha fetoprotein	7	28	13	22	16	23	
Ultrasound	14	56	33	55	50	73	
CT	4	16	13	22	1	1	
2 <sup>nd</sup> most important examination in screening of HCC							0.585
Physical examination	1	4	1	2	0	0	
Alpha fetoprotein	12	48	26	43	33	48	
Ultrasound	2	8	11	18	8	12	
CT	9	36	22	37	27	39	
Angiography	1	4	0	0	1	1	
3 <sup>rd</sup> most important screening for HCC							0.004 <sup>a</sup>
Physical examination	1	4	3	5	1	1	
Alpha fetoprotein	3	12	14	23	17	25	
Ultrasound	6	24	2	3	9	13	
CT	12	48	25	42	36	52	
Angiography	1	4	4	7	6	9	
Laparoscopy	2	8	12	20	0	0	
Screening interval for high risk group							0.050 <sup>a</sup>
Every 3 mo	15	60	30	50	49	71	
6 mo or more	10	40	30	50	20	29	
HBV treatment reduces HCC incidence							0.441
Yes	20	80	45	75	58	84	
No	5	20	15	25	11	16	
Guidelines in management of HCC							0.000 <sup>a</sup>
Yes	13	52	20	33	57	83	
No	12	48	40	67	12	17	
HCV RNA/ALT risk factors for HCC							0.368
Yes	14	56	37	62	34	49	
No	11	44	23	38	35	51	

<sup>a</sup> $P < 0.05$  considered statistically significant. HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; CT: Computer tomography.

71% of doctors with MD degree think that the screening interval for high risk group should be 3 mo, while 40% of doctors with MB BCh, 50% of doctors with a master degree or diploma and 29% with MD degree think that the screening interval for high risk groups should be 6 mo. Fifty-two percent of doctors with MB BCh, 33% of doctors with a master degree or diploma and 83% of doctors with MD degree know guidelines for the management of HCC patients, while 48% of doctors with MB BCh, 67% of doctors with a master degree and diploma and 17% of doctors with MD used no guidelines for the management of HCC ( $P < 0.05$ ).

There were no significant differences with respect to other aspects, such as the reduction of HCC incidence by treatment of HBV infection and the predictive value of elevated HCV RNA and ALT levels for HCC

**Table 9** Relation between health care setting and knowledge about screening modalities, educational resources and guidelines

	Health care setting				<i>P</i> value
	University		MOH		
	<i>n</i>	%	<i>n</i>	%	
Most important screening for HCC					0.000 <sup>a</sup>
0.000 <sup>a</sup>	3	3	0	0	
Alpha fetoprotein	19	20	17	29	
Ultrasound	70	74	27	46	
CT	3	3	15	25	
2 <sup>nd</sup> most important screening for HCC					0.799
Physical examination	1	1	1	2	
Alpha fetoprotein	47	49	24	40	
Ultrasound	11	12	10	17	
CT	35	37	23	39	
Angiography	1	1	1	2	
3 <sup>rd</sup> most important screening for HCC					0.001 <sup>a</sup>
Physical examination	2	2	3	5	
Alpha fetoprotein	23	24	11	19	
Ultrasound	10	11	7	12	
CT	52	55	21	36	
Angiography	7	8	4	7	
Laparoscopy	1	1	13	22	
Screening interval for high risk group					0.173
Every 3 mo	62	65	32	54	
6 mo or more	33	35	27	46	
HBV treatment reduces HCC incidence					0.011 <sup>a</sup>
Yes	82	86	41	69	
No	13	14	18	31	
Guidelines in management of HCC					0.000 <sup>a</sup>
Yes	73	77	17	29	
No	22	23	42	71	
HCV RNA/ALT are risk factors for HCC					0.139
Yes	48	51	37	63	
No	47	49	22	37	

<sup>a</sup>P < 0.05 considered statistically significant. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MOH: Ministry of Health; CT: Computer tomography.

development.

**Relation with hospital setting:** Table 9 shows that there is a difference in opinion between doctors in different hospital settings with respect to the most important investigation in screening for HCCs ( $P < 0.05$ ): 74% of doctors working in University Hospitals and 46% of MOH doctors think that US is the most important investigation in screening of HCC; by comparison, only 3% of doctors working in University hospitals and 25% of MOH doctors consider CT as the most important investigation in screening for HCC ( $P < 0.05$ ); 55% of doctors working in University hospitals and 36% of MOH doctors think that CT is the third most important investigation in screening for HCC. Eighty-six percent of doctors working in University hospitals and 69% of MOH doctors think that treatment of chronic HBV infection can reduce HCC incidence while 14% of University doctors and 31% of MOH doctors do not think so ( $P < 0.05$ ). Further, 77% of doctors working in University

**Table 10** Relation between physicians' age and hepatocellular carcinoma screening

	Age (yr)				<i>P</i> value
	< 45		≥ 45		
	<i>n</i>	%	<i>n</i>	%	
HCC surveillance					0.013
Yes	20	18	15	35	
No	92	82	27	65	
Screening of patients with HCV cirrhosis and SVR					0.661
Yes	94	4	34	81	
No	18	16	8	19	
Screening of patients with hemochromatosis					0.11
Yes	73	65	33	79	
No	39	35	9	21	
No. of incidental HCCs/month					0.087
0	34	30	7	17	
1 or more	78	0	35	83	
No. of HCCs/month					0.193
0	33	29	8	19	
1 or more	79	71	0.000 <sup>a</sup>	81	

<sup>a</sup>P < 0.05 considered statistically significant. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; SVR: Sustained virological response.

hospitals and 29% of MOH doctors use guidelines for the management of HCC, while 23% of doctors working in University hospitals and 71% of MOH doctors do not ( $P < 0.05$ ).

There is no significant difference with respect to other aspects, such as the 3<sup>rd</sup> most important examination in HCC screening, the screening interval for high risk group and the predictive value of elevated HCV RNA and ALT for the individual HCC risk.

### Physicians' practice and attitude towards HCC

**Relation with physicians' age:** Table 10 shows that there is a significant difference of opinion regarding HCC surveillance with respect to the physicians' age ( $P < 0.05$ ): 18% of doctors < 45 years and 35% of doctors > 45 years screen of liver cancer while 82% of doctors < 45 years and 65% of doctors > 45 years do not.

There is no significant difference in opinion regarding other aspects, such as the clinical care of patients with HCV cirrhosis who responded to antiviral therapy or hemochromatosis as well as with respect to number of HCC discovered accidentally per month and the number of HCC patients that physicians care for.

**Relation with physicians' medical specialty:** Table 11 shows that there is a significant difference in the care for patients with hemochromatosis depending on the physicians' medical specialty ( $P < 0.05$ ): 72% of physicians in tropical medicine, internal medicine and gastroenterology and 50% in other specialties screen patients of hemochromatosis for HCCs while 28% of physicians in tropical medicine, internal medicine and gastroenterology and 50% of general practitioners do not.

**Table 11** Hepatocellular carcinoma screening depending on medical specialty

	Specialty				<i>P</i> value
	Specialty A <sup>1</sup>		Specialty B <sup>2</sup>		
	<i>n</i>	%	<i>n</i>	%	
HCC surveillance					0.193
Yes	32	25	3	13	
No	98	75	21	87	
Screening of patients with HCV cirrhosis and SVR					0.79
Yes	109	84	19	79	
No	21	16	5	21	
Screening of patients with hemochromatosis					0.030 <sup>a</sup>
Yes	94	72.3	12	50	
No	36	27.7	12	50	
No. of incidental HCCs/month					0.418
0	33	25	8	33	
1 or more	97	75	16	67	
No. of HCCs/month					0.759
0	34	26	7	29	
1 or more	96	74	17	71	

<sup>a</sup> $P < 0.05$  considered statistically significant. <sup>1</sup>Specialty A (Tropical medicine, Internal medicine, Gastroenterology); <sup>2</sup>Specialty B (General practitioner, Radiology, General surgery). HCC: Hepatocellular carcinoma; SVR: Sustained virological response; HCV: Hepatitis C virus.

There is no significant difference with respect to other aspects, such as HCC screening of patients with HCV cirrhosis with sustained virological response (SVR), the number of HCC cases discovered accidentally per month and the number of HCC patients the physicians care for.

#### Relation with physicians' highest qualification:

Table 12 shows that there is a significant difference with respect to HCC surveillance depending on the highest medical qualification ( $P < 0.05$ ): 20% of doctors with MB BCh and 17% of doctors with a master degree or diploma and 25% of doctors with MD degree screen all patients for HCC while 80% of MB BCh doctors, 83% of Msc doctors and 75% of doctors with MD degree do not. Similarly, 60% of MB BCh doctors, 58% of Msc/diploma doctors and 81% of doctors with MD degree screen patients of hemochromatosis for HCCs ( $P < 0.05$ ), while 40% of MB BCh doctors, 42% of Msc/diploma doctors and 19% of doctors with MD degree do not. There is also a significant difference in the accidental HCC detection per month between the doctors with different medical highest qualification ( $P < 0.05$ ): 44% of MB BCh doctors, 40% of Msc/diploma doctors and 9% of doctors with a MD degree detect less than one HCC per month while 56% of MB BCh doctors, 60% of Msc/diploma doctors and 91% of doctors with a MD degree detect one or more than one HCC per month. Further, there is significant difference with respect to the number of HCC patients cared for by the physician depending on his/her highest medical qualification ( $P < 0.05$ ): 36% of MB BCh doctors, 48% of doctors with Msc/diploma and 4% of doctors with MD degree do not have any HCC patient while 64% of MB BCh doctors,

**Table 12** Hepatocellular carcinoma screening depending on highest medical qualification

	Highest qualification						<i>P</i> value
	MBBCH		MSc/ diploma		MD		
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
HCC surveillance							0.0423
Yes	5	20	10	17	17	25	
No	20	80	50	83	52	75	
Screening of patients with HCV cirrhosis and SVR							0.638
Yes	20	80	52	87	56	81	
No	5	20	8	13	13	19	
Screening of patients with hemochromatosis							0.012 <sup>a</sup>
Yes	15	60	35	58	56	81	
No	10	40	25	42	13	19	
No. of incidental HCCs/month							0.000 <sup>a</sup>
0	11	44	24	40	6	9	
1 or more	14	56	36	60	63	91	
No. of HCC patients							0.000 <sup>a</sup>
0	9	36	29	48	3	4	
1 or more	16	64	31	52	66	96	

<sup>a</sup> $P < 0.05$  considered statistically significant. HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; SVR: Sustained virological response.

52% of doctors with Msc/diploma and 96% of doctors with MD degree care for one or more HCC patients.

**Relation with hospital setting:** Table 13 shows a significant difference in the number of accidentally discovered HCC per month between the physicians' hospital setting ( $P < 0.05$ ): 10% of doctors working in University Hospitals and 54% of MOH doctors do not discover any HCC per month while 90% of doctors working in University hospitals and 46% of MOH doctors discover one or more cases per month. There is also a significant difference with respect to the number of HCC patients that doctors care for depending on the physicians' hospital setting ( $P < 0.05$ ): 9% of doctors working in University hospitals and 54% of MOH doctors do not care for any HCC patient while 91% of doctors working in University hospitals and 46% of MOH doctors see one or more HCC patient in their practice.

## DISCUSSION

### Knowledge of HCC epidemiology

The results from the questionnaire show that the majority of doctors think that individuals at risk requiring screening for HCC are patients with chronic hepatitis B or C and patients with liver cirrhosis, consistent with the Practice Guidelines from the American Association of the Study of Liver Diseases (AASLD) from 2005 and from the European Association for the Study of the Liver (EASL) from 2001 which recommended HCC surveillance for patients at high risk of developing HCC<sup>[8]</sup>. Patients at high risk are those with liver cirrhosis and those with chronic HBV infection irrespective of



**Table 13 Hepatocellular carcinoma C screening depending on health care setting**

	Health care setting				<i>P</i> value
	University hospital		MOH		
	<i>n</i>	%	<i>n</i>	%	
HCC surveillance					0.178
Yes	25	26	10	17	
No	70	74	49	83	
Screening of patients with HCV cirrhosis and SVR					0.386
Yes	77	81	51	86	
No	18	19	8	14	
Screening of patients with hemochromatosis					0.196
Yes	69	73	37	63	
No	26	27	22	37	
No. of incidental HCCs/month					0.000 <sup>a</sup>
0	10	10	31	53	
1 or more	85	90	28	47	
No. of HCCs/month					0.000 <sup>a</sup>
0	9	10	32	54	
1 or more	86	90	27	46	

<sup>a</sup>P < 0.05 considered statistically significant. HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; SVR: Sustained virological response; MOH: Ministry of Health.

cirrhosis<sup>[14,15]</sup>.

The Cairo Liver Center evaluated in a retrospective study between 2003 and 2008 the effect of surveillance on the early detection of HCC in patients with liver cirrhosis. This cohort was compared to non-screened cirrhosis patients who presented with first symptoms or incidentally. The study clearly showed that surveillance doubled the chance of HCC detection at an early Barcelona Liver Cancer Center (BCLC) stage with a chance for successful loco-regional ablation or liver transplantation. Therefore, the implementation of HCC surveillance in Egypt is recommended<sup>[16]</sup>.

Chronic hepatitis B infection accounts for about 50% of all HCC cases worldwide. At the same time, in approx. Forty percent of patients with chronic HBV infection HCCs develops in a non-cirrhotic liver. Therefore, HCC screening is recommended in all patients of chronic HBV infection<sup>[17]</sup>. In Egypt, the increasing HCC incidence is due to the high prevalence of HCV infection<sup>[10]</sup>, estimated to be around 14% in the general population<sup>[8]</sup>.

The questionnaire results show that most of doctors agree that more than 30% of deaths can be prevented by HCC screening, consistent with results from a multiple-choice survey study in the United States<sup>[18]</sup>, based on the AASLD Practice Guidelines. The questionnaire asked for an estimate of the proportion of deaths from HCC that can currently be prevented by suitable screening. Most gastroenterologists stated that appropriate screening and surveillance could prevent 20%-50% of deaths<sup>[18]</sup>.

In the United States there was no significant difference of opinion based on the physicians' age, specialty, highest qualification or hospital setting. The question-

naire results indicated that most doctors' know that co-infection, gender, HCV genotype and obesity are risk factors for progression of the liver disease to HCC. This is in line with the data of Crockett *et al.*<sup>[19]</sup> demonstrating that HBV-HCV co-infection is a predictive factor for HCC development. The contribution of the gender to the progression to HCC has also been shown by Buch *et al.*<sup>[20]</sup>, demonstrating that the natural history of HCC is different between men and women.

Our results show that the majority of doctors consider chronic HCV infection as the leading cause of HCC in Egypt, reflecting the high prevalence of HCV infection in the general population of around 14%<sup>[8]</sup> that is responsible for to the increasing incidence of HCCs in Egypt<sup>[10]</sup>.

Our results further show that doctors consider cancer as the main cause of death in HCC patients, followed by decompensated liver cirrhosis and its complications such as bleeding from varices in other HCC patients. This is consistent with the findings of Couto *et al.*<sup>[21]</sup>, demonstrating that 57% of patients with unresectable HCC died from cancer progression while 43% died from complications of liver cirrhosis, including sepsis, GI bleeding and renal failure.

#### **Knowledge of screening modalities, educational resources and guidelines**

Our questionnaire revealed that 74% of University doctors and 46% of MOH doctors consider US as the most important HCC screening test, consistent with many studies in the United States. This is based on its adequate sensitivity, specificity, its low cost, non-invasive character and wide availability. The effectiveness of US screening for HCCs in the United States depended on the screening frequency, the experience of the examiner and the nature of the patients' liver disease. The sensitivity of US for HCC detection was variable and ranged between 35% and 84%, depending on the expertise of the operator as well as on the US equipment<sup>[22]</sup>.

AFP alone as screening test is no longer considered adequate for HCC screening and surveillance by AASLD and EASL guidelines due to the high rate of false-positive and false-negative results in patients with chronic liver disease. Nevertheless, AFP alone may be used if US is not available<sup>[8]</sup>.

Asked about the second and third choice of screening tests, some doctors favor AFP while others favor CT as the second choice for HCC screening. While CT is an attractive imaging modality for HCC screening because it can detect lesions in cirrhotic livers, allows lesion characterization and contributes to clinical staging, it is expensive and its use as screening test is difficult, especially in countries with limited resources and high HCC prevalence, such as Egypt.

Cost-effectiveness studies of HCC screening revealed that screening European patients with Child-Pugh class A cirrhosis using serum AFP and US every 6 mo costs about 74000 U\$ for each HCC detected, while CT alone

every 6 mo costs about 101000U\$<sup>[23]</sup>.

With respect to the screening interval in high risk patients our study showed that most doctors consider 3 mo as optimal while some consider 6 or more months as adequate. The 6 mo screening interval for high risk groups has been adopted by many organizations, such as the AASLD, the EASL, the APASL (Asian Pacific Association for the Study of the Liver) and the NCCN (National Comprehensive Cancer Network). The recommendation of the screening interval of 3 mo is based on the estimate that the tumors > 1 cm in diameter may double every 2 mo<sup>[24]</sup>.

With respect to the physicians' age, our study revealed that 93% of doctors older than 45 years and 75% of doctor younger than 45 years think that treatment of HBV infection can reduce the HCC incidence in Egypt, similar to the study of Lok *et al*<sup>[25]</sup>.

It is known that HBV infection is oncogenic, resulting in HCC development also in non-cirrhotic livers. The relative HCC risk of HBV carriers is estimated to be 100-200-fold higher than that of non-carriers<sup>[5]</sup>.

Our questionnaire results show in addition that 93% of doctors' older than 45 years and 75% of doctors younger than 45 years use guidelines in the management of HCC patients while 17% of doctors older 45 and 25% of doctors younger than 45 years do not. The significant difference in the use of guidelines by physicians of different age may be due to the following reasons: most of the older doctors hold a higher medical degree than younger physicians. Further, older doctors had more opportunities to attend medical conferences to update their knowledge. Further, some of them are professors teaching their students the most advanced medical knowledge. The questionnaire results further show that about 71% of doctors in MOH do not know about guidelines for the management of HCC. This may be due to the limited interest of managers and division heads in these hospitals to adapt existing protocols or guidelines appropriate for Egypt as well as the Egyptian government considering other endemic diseases of higher priority with respect to guidelines and screening programs.

### **Physicians' practice and knowledge about HCC**

The questionnaire results clearly show that the majority of doctors do not implement or recommend HCC surveillance according to international guidelines. This may be due to limited information about the benefits and importance of screening programs that allow detecting HCCs at an early, potentially curable stage, resulting in improved patient survival. It also may be due to the unawareness of the Egyptian Ministry of Health and government about the importance of HCC screening among high risk groups which overall may save money, last but not least money that must be spent for the palliative care for HCC patients.

Screening for HCC in Egypt depends on the specialty and qualification of physicians' with general practitioners

and family doctors having the lowest rate of practical implementation of HCC screening compared to other doctors. This may be due to the lack of facilities for HCC screening in primary care settings and the limited knowledge of these doctors about the importance of HCC screening among high risk group and about epidemiology of HCCs, being the second most frequent cause of cancer death in Egypt after bladder cancer.

The questionnaire results demonstrate that most doctors screen patients with liver cirrhosis due to chronic HCV infection who responded to antiviral treatment, consistent with a study showing that these patients should still undergo surveillance<sup>[26]</sup>. A more recent study by Singal *et al*<sup>[27]</sup> showed that patients with cirrhosis and a SVR had a relative risk for HCC of 0.35 compared to non-responders, resulting in HCC development in 5% of patients with a SVR, warranting regular post-treatment surveillance.

Finally, the answers to the questionnaire show that about 70% of doctors identified one or more HCCs per month. Further, 94% of doctors feel that the HCC incidence in Egypt is increasing while 3% are not sure. In fact, in Egypt the HCC incidence (10-120 cases per 100000 population and year), has nearly doubled from 4.0% in 1993 to 7.2% in 2002 among patients with chronic liver disease<sup>[16]</sup>.

In Egypt, physicians specialized in tropical medicine, internal medicine or gastroenterology, older than 45 years, having MD degree and working in University hospitals are better informed about the HCC epidemiology, the appropriate screening modalities, educational resources and practice guidelines than physicians with other specialties.

## **COMMENTS**

### **Background**

In Egypt, hepatocellular carcinoma (HCC) was reported to develop in about 5% of patients with chronic liver disease. The major hepatological/gastroenterological professional societies worldwide, including the American Association for Study of Liver Disease, recommend screening for HCC in high risk patients. The majority of HCCs are diagnosed in advanced stages, which carries a poor prognosis. Recent curative therapeutic regimens and liver transplantation for early stage HCC encourage physicians to screen high-risk patients. The aim of this study was to assess the practice of Egyptian physicians in screening patients for HCC.

### **Research frontiers**

Screening of HCC is important for early detection and treatment. The study is observational questioner study among Egyptian physicians to assess their knowledge in HCC screening, diagnosis, treatment, and recent guidelines.

### **Innovations and breakthroughs**

The difference to other related or similar studies is that their study conducted among Egyptian physician.

### **Applications**

The study shows the deficient HCC knowledge among Egyptian physicians. It also conclude that physicians with MD degree and those who work in university hospitals having better knowledge than other. Distribution of recent guidelines among physicians is recommended to improve their knowledge.

**Peer-review**

The manuscript is an interesting and very important study of Egyptian physicians' awareness and screening for HCC.

**REFERENCES**

- 1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]
- 2 **Velázquez RF**, Rodríguez M, Navascués CA, Linares A, Pérez R, Sotorrios NG, Martínez I, Rodrigo L. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology* 2003; **37**: 520-527 [PMID: 12601348 DOI: 10.1053/jhep.2003.50093]
- 3 **Rahman El-Zayadi A**, Abaza H, Shawky S, Mohamed MK, Selim OE, Badran HM. Prevalence and epidemiological features of hepatocellular carcinoma in Egypt-a single center experience. *Hepatol Res* 2001; **19**: 170-179 [PMID: 11164741 DOI: 10.1016/S1386-6346(00)00105-4]
- 4 **Ohata K**, Hamasaki K, Toriyama K, Ishikawa H, Nakao K, Eguchi K. High viral load is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis B virus infection. *J Gastroenterol Hepatol* 2004; **19**: 670-675 [PMID: 15151623 DOI: 10.1111/j.1440-1746.2004.03360.x]
- 5 **Xiong J**, Yao YC, Zi XY, Li JX, Wang XM, Ye XT, Zhao SM, Yan YB, Yu HY, Hu YP. Expression of hepatitis B virus X protein in transgenic mice. *World J Gastroenterol* 2003; **9**: 112-116 [PMID: 12508363]
- 6 **Feitelson M**. Hepatitis B virus infection and primary hepatocellular carcinoma. *Clin Microbiol Rev* 1992; **5**: 275-301 [PMID: 1323384 DOI: 10.1128/CMR.5.3.275]
- 7 **Szabó E**, Páska C, Kaposi Novák P, Schaff Z, Kiss A. Similarities and differences in hepatitis B and C virus induced hepatocarcinogenesis. *Pathol Oncol Res* 2004; **10**: 5-11 [PMID: 15029254]
- 8 **Bruix J**, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208-1236 [PMID: 16250051 DOI: 10.1002/hep.20933]
- 9 **Merican I**, Guan R, Amarapuka D, Alexander MJ, Chutaputti A, Chien RN, Hasnain SS, Leung N, Lesmana L, Phiet PH, Sjalfoellah Noer HM, Sollano J, Sun HS, Xu DZ. Chronic hepatitis B virus infection in Asian countries. *J Gastroenterol Hepatol* 2000; **15**: 1356-1361 [PMID: 11197043 DOI: 10.1046/j.1440-1746.2000.0150121356.x]
- 10 **El-Serag HB**. Hepatocellular carcinoma: an epidemiologic view. *J Clin Gastroenterol* 2002; **35**: S72-S78 [PMID: 12394209]
- 11 **Kuo YH**, Lu SN, Chen CL, Cheng YF, Lin CY, Hung CH, Chen CH, Changchien CS, Hsu HC, Hu TH, Lee CM, Wang JH. Hepatocellular carcinoma surveillance and appropriate treatment options improve survival for patients with liver cirrhosis. *Eur J Cancer* 2010; **46**: 744-751 [PMID: 20060710]
- 12 **Cabibbo G**, Maida M, Genco C, Parisi P, Peralta M, Antonucci M, Brancatelli G, Cammà C, Craxi A, Di Marco V. Natural history of untreatable hepatocellular carcinoma: A retrospective cohort study. *World J Hepatol* 2012; **4**: 256-261 [PMID: 23060970 DOI: 10.4254/wjh.v4.i9.256]
- 13 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127 [PMID: 21992124 DOI: 10.1056/NEJMra1001683]
- 14 **Zhang BH**, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004; **130**: 417-422 [PMID: 15042359]
- 15 **Bruix J**, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]
- 16 **el-Zayadi AR**, Badran HM, Barakat EM, Attia Mel-D, Shawky S, Mohamed MK, Selim O, Saeid A. Hepatocellular carcinoma in Egypt: a single center study over a decade. *World J Gastroenterol* 2005; **11**: 5193-5198 [PMID: 16127751 DOI: 10.3748/wjg.v11.i33.5193]
- 17 **Arguedas MR**, Chen VK, Eloubeidi MA, Fallon MB. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. *Am J Gastroenterol* 2003; **98**: 679-690 [PMID: 12650806]
- 18 **Sharma P**, Saini SD, Kuhn LB, Rubenstein JH, Pardi DS, Marrero JA, Schoenfeld PS. Knowledge of hepatocellular carcinoma screening guidelines and clinical practices among gastroenterologists. *Dig Dis Sci* 2011; **56**: 569-577 [PMID: 20978844 DOI: 10.1007/s10620-010-1453-5]
- 19 **Crockett SD**, Keffe EB. Natural history and treatment of hepatitis B virus and hepatitis C virus coinfection. *Ann Clin Microbiol Antimicrob* 2005; **4**: 13 [PMID: 16159399 DOI: 10.1186/1476-0711-4-13]
- 20 **Buch SC**, Kondragunta V, Branch RA, Carr BI. Gender-based outcomes differences in unresectable hepatocellular carcinoma. *Hepatol Int* 2008; **2**: 95-101 [PMID: 19669284 DOI: 10.1007/s12072-007-9041-2]
- 21 **Couto OF**, Dvorchik I, Carr BI. Causes of death in patients with unresectable hepatocellular carcinoma. *Dig Dis Sci* 2007; **52**: 3285-3289 [PMID: 17436087]
- 22 **Peterson MS**, Baron RL. Radiologic diagnosis of hepatocellular carcinoma. *Clin Liver Dis* 2001; **5**: 123-144 [PMID: 11218911]
- 23 **Saab S**, Ly D, Nieto J, Kanwal F, Lu D, Raman S, Amado R, Nuesse B, Durazo F, Han S, Farmer DG, Ghobrial RM, Yersiz H, Chen P, Schwegel K, Goldstein LI, Tong M, Busuttil RW. Hepatocellular carcinoma screening in patients waiting for liver transplantation: a decision analytic model. *Liver Transpl* 2003; **9**: 672-681 [PMID: 12827551 DOI: 10.1053/jlts.2003.50120]
- 24 **Murakami T**, Mochizuki K, Nakamura H. Imaging evaluation of the cirrhotic liver. *Semin Liver Dis* 2001; **21**: 213-224 [PMID: 11436573 DOI: 10.1055/s-2001-15497]
- 25 **Lok AS**, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]
- 26 **Sun CA**, Wu DM, Lin CC, Lu SN, You SL, Wang LY, Wu MH, Chen CJ. Incidence and cofactors of hepatitis C virus-related hepatocellular carcinoma: a prospective study of 12,008 men in Taiwan. *Am J Epidemiol* 2003; **157**: 674-682 [PMID: 12697571 DOI: 10.1093/aje/kwg041]
- 27 **Singal AK**, Singh A, Jagannathan S, Guturu P, Mummadi R, Kuo YF, Sood GK. Antiviral therapy reduces risk of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. *Clin Gastroenterol Hepatol* 2010; **8**: 192-199 [PMID: 19879972]

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