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Contents

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Contents

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EDITORIAL

Fish oils in parenteral nutrition: Why could these be important for gastrointestinal oncology?

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Abstract

By the time a gastroenterology patient is moved to parenteral nutrition, he or she is usually in poor health. All parenteral nutrition formulae contain essential nutrients, avoiding components that could cause an adverse reaction. The lipid component is often provided by a soy extract, containing all the fatty acids considered to be essential in the diet. Several trials have considered parenteral nutrition formulas with added fish oils, high in the long chain omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Given the range of biological functions associated with such compounds, especially in reducing inflammatory symptoms, this move would appear rational. However, while data from such trials are often positive, there has been variability among results. Some of this variability could be caused by environmental contaminants in the fish, and/or oxidation of the lipids because of poor storage. The situation is complicated by a recent report that fish oils may counter the effects of platinum chemotherapy. However, this effect associated with a minor component, hexadeca-4,7,10,13-tetraenoic acid. It is suggested that pure DHA and EPA would be beneficial additions to parenteral nutrition, reducing the probability of carcinogenesis and enhancing rational disease management. However, the jury is still out on fish oils more generally.

Key words: Inflammatory bowel diseases; Colorectal cancer; Fish oils; Eicosapentanoic acid; Docosahexaenoic acid

Core tip: Parenteral nutrition formulae contain essential nutrients, in which the lipid component is often provided by a soy extract, containing essential fatty acids. Several trials have considered such formulas with added fish oils, high in the long chain omega-3 polyunsaturated fatty acids, eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA). Such compounds have a range of biological functions, especially in reducing

inflammatory symptoms. However, there has been variability among results of clinical trials, possibly caused by environmental contaminants in the fish, and/or lipid oxidation. It is suggested that pure DHA and EPA, but possibly not fish oils *per se*, would be beneficial.

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PARENTERAL NUTRITION REQUIREMENTS AND FORMULATION

Both enteral and parenteral nutrition become important in the care of hospitalised patients with Inflammatory bowel diseases and many other gastrointestinal (GI) disorders[1,2]. These formulas utilise essential nutrients, including lipids. However, there has been some controversy regarding optimal formulations, especially in regard to the nature of the most appropriate lipids[3]. Soybean has been the basis for the most commonly used formulations, since it is a well-recognised source of the essential omega-6 polyunsaturated fatty acid (PUFA), linoleic acid, and the omega-3 PUFA, alpha-linolenic acid. It also contains the saturated fatty acids, stearic acid and palmitic acid, as well as the monounsaturated fatty acid, oleic acid[2]. Where there seems to be some controversy is whether fish oil, which contains two long chain omega-3 PUFA, eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA), adds anything of importance. Many of the controversies raised are in relation to the need for this[4,5]. Unfortunately, however, currently available trials are underpowered to answer some of these controversies. Given the possibility that many of these GI disorders may progress to cancer[6], the questions raised are highly relevant to GI oncology.

LIPID FORMULAE AND RISK OF CANCER INITIATION IN NORMAL SUBJECTS

Shortened telomeres have been related to significantly increased risks of cancer[7]. Thus, there would be significant benefits in having a nutritional formula that increases the length of telomeres, or at least prevents or slows shortening. While there is no evidence that any known lipid formulas may be able to increase length, there are comparative data available for omega-3 (DHA-rich or EPA-rich) formulae, as compared with a formula containing only the omega-6 PUFA, linoleic acid. O'Callaghan *et al*[8] supplemented elderly adults for 6 mo with each of these formulas, and compared the groups in terms of telomere length at the beginning and end of that time. They found preliminary evidence that telomere shortening could be attenuated by either of the omega-3 PUFA-containing formulae, but not by the formula containing only the soy- derived linoleic acid.

LIPID FORMULAE AND PROGRESS OF GI SURGERY

It is difficult to compare all available studies on the effects of added fish oils to the clinical progress of GI surgery, since these are generally small, and not standard as regards to the formulae being compared in the presence or absence of fish oils[9].

Although addition of a fish oil to an olive oil-based parenteral nutrition formula for 5 d had no effects on measures of inflammation, it appeared that GI patients showed a lower risk of infection following surgery as compared with patients nourished by the olive oil formula alone[10].

While inflammation is necessary for responses to external challenges, there is no question but that excess inflammation is detrimental[2,11,12], and plays an important role in the progression of GI diseases towards a cancer phenotype[11]. A number of small studies had compared the effects of soybean oil in various combinations with medium chain triglycerides (MCT) and olive oil suggesting there may be benefits of these combinations, but larger and more systematic studies implied that this effect may not always hold[5,10]. However, the inclusion of fish oil in combination with one of these other oils was shown to have beneficial effects on immune status and inflammatory markers in patients following major GI surgery[2,13].

Wang *et al*[14] compared a fish oil-enriched emulsion to an MCT/long chain triacylglycerol mix in GI surgery patients for 5 d after surgery. Clinical outcomes were comparable across the groups and there were no significant differences in standard measures of inflammation such as C-reactive protein. However, the fish oil formula led to an increase in leukotrienes B5 and B6, along with significant decreases in the pro-inflammatory cytokines, interleukin 6, tumor necrosis factor-alpha and nuclear factor-kappa B. Interleukin 6 in particular has been strongly implicated in the development of colorectal cancer[15]. These effects all implied that inclusion of fish oil in the formula beneficially modulated inflammatory response, reducing the probability of post-surgery infection and subsequent adverse effects including CRC initiation.

LIPID FORMULAE IN COLORECTAL CANCER PATIENTS

In elderly patients after colorectal cancer surgery, Zhu *et al*[16] found that addition of fish oil to the soybean oil-based formula again reduced pro-inflammatory cytokines, reduced infectious complications and incidence of systemic inflammatory responses, and resulted in a shorter hospital stay. In a larger trial of similar lipid mixes, this time in colorectal cancer patients

of varying ages, de Miranda Torrinhas *et al*[17] again found improved post-operative immune responses. Thus, most of the published studies, albeit considering small numbers, suggest beneficial results from adding fish oils to the more standard parenteral nutrition formulas conventionally used.

LIPID FORMULAE IN LIVER DISEASE

A range of isolated case reports have appeared, showing significant changes in problems associated with non-alcoholic fatty liver disease, when fish oils are added to standard parenteral nutrition. For example, Crook *et al*[18] and also Venecourt-Jackson *et al*[19] reported on the successful treatment of parenteral nutrition-associated liver disease in individual adults using a fish oil-based formula. More generally, this area has been reviewed by several authors, including Bouzianas *et al*[20] and Premkumar *et al*[21]. Fish oil formulae have also benefited pediatric oncology patients who have developed liver disease[22], and promoted high rates of resolution of cholestasis[23].

The mechanisms of the fish oil-associated effects on liver disease are almost certainly associated with the EPA and DHA-associated shift towards anti-inflammatory proresolving lipid mediators[24,25].

POTENTIAL PROBLEMS WITH THE USE OF FISH OILS

Despite a generally positive climate, a significant warning has been raised following evidence that addition of fish oil during a cancer chemotherapy regime containing platinum compounds may lead to cancer drug resistance[26]. However, this effect was related to a fairly minor fish oil component, the omega-3 PUFA 16:4(n-3) (hexadeca-4,7,10,13-tetraenoic acid) that, when administered to mice, neutralized chemotherapeutic activity. Although such studies have not been done in humans to this date (and could not ethically be justified), Daenen *et al*[26] found that, when the recommended daily amount of 10 mL of fish oil was administered to healthy volunteers, rises in plasma 16:4 (n-3) levels were observed, reaching up to 20 times the baseline levels. Herring and mackerel contained high levels of 16:4 (n-3), whereas salmon and tuna had very much lower levels. The authors concluded that, until further data become available, it may be desirable to avoid fish oil and fish containing high levels of 16:4 (n-3) on the days surrounding chemotherapy[26].

We have previously pointed to apparently contradictory results of dietary supplementation with oily fish or with fish oils in the development and progression of inflammatory bowel diseases. The pattern which became apparent is that the nature of the results, *i.e.*, whether positive, neutral or negative, largely depended upon the source of the fish (whether polluted or not), or in the case of oils, the degree of purification and protection against oxidation[27]. These data are equally relevant to the case of colorectal cancer. That is, we believe that it may not only be somewhat desirable, but very important to add fish oils to parenteral nutrition therapy. However, it would also appear important that addition of the 16:4 omega-3 PUFA hexadeca-4,7,10,13-tetraenoic acid, or any possibility of formation of this product be avoided.

CONCLUSION

In summing up, there seems good evidence that the classic (usually) soy-based parenteral nutrition formulae may not provide adequate nutritional support, especially when used for patients with GI disorders. Furthermore, these formulae may themselves lead to complications, including liver disease. Fish oil-based formulae have given some extremely good results in most, but not all studies. Part of the reason for this could be environmental contaminants in the original fish source, or oxidation products because of poor storage. It would appear that a good case can be made for a strong EPA and/or DHA component, preferably as purified forms of these fatty acids, becoming an essential part of parenteral nutritional formulae. This would not only protect against the development of colorectal cancers, it would help to avoid the complications of current nutritional therapies in patients who already have the disease.

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REVIEW

Adenosquamous carcinoma of the pancreas: Molecular characterization of 23 patients along with a literature review

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Abstract

Adenosquamous carcinoma of the pancreas (ASCP) is a rare entity. Like adenocarcinoma of the pancreas, overall survival is poor. Characteristics of ASCP include central tumor necrosis, along with osteoclasts and hypercalcemia. Various theories exist as to why this histological subtype exists, as normal pancreas tissue has no benign squamous epithelium. Due to the rarity of this disease, limited molecular analysis has been performed, and those reports indicate unique molecular features of ASCP. In this paper, we characterize 23 patients diagnosed with ASCP through molecular profiling using immunohistochemistry staining, fluorescent *in situ* hybridization, chromogenic *in situ* hybridization, and gene sequencing, Additionally, we provide a comprehensive literature review of what is known to date of ASCP. Molecular characterization revealed overexpression in MRP1 (80%), MGMT (79%), TOP2A (75), RRM1 (42%), TOPO1 (42%), PTEN (45%), CMET (40%), and C-KIT (10%) among others. One hundred percent of samples tested were positive for *KRAS* mutations. This analysis shows heretofore unsuspected leads to be considered

for treatments of this rare type of exocrine pancreas cancer. Molecular profiling may be appropriate to provide maximum information regarding the patient's tumor. Further work should be pursued to better characterize this disease.

Key words: Adenosquamous carcinoma of the pancreas; Molecular profiling; Review

Core tip: This analysis of 23 adenosquamous carcinoma of the pancreas in light of the reviewed literature highlights the potential to identify novel treatments when using a personalized medicine approach to patient tumor characterization.

Borazanci E, Millis SZ, Korn R, Han H, Whatcott CJ, Gatalica Z, Barrett MT, Cridebring D, Von Hoff DD. Adenosquamous carcinoma of the pancreas: Molecular characterization of 23 patients along with a literature review. *World J Gastrointest Oncol* 2015; 7(9): 132-140 Available from: URL: http://www.wjgnet.com/1948-5204/full/v7/i9/132.htm DOI: http://dx.doi.org/10.4251/wjgo.v7.i9.132

INTRODUCTION

Pancreas cancer remains a deadly disease. In 2014 it is estimated that 46420 new cases will occur, along with 39590 deaths, making it the fourth leading cause of cancer deaths in the United States[1]. The most commonly diagnosed pancreas cancer histology is adenocarcinoma, with an incidence of 85% of pancreas malignancies[2]. As shown in Table 1, other pancreas cancer histological subtypes include mucinous cyst adenocarcinoma, adenosquamous, undifferentiated/anaplastic, papillary mucinous, acinar cell, spindle cell, and pancreatoblastoma[2-4].

Adenosquamous carcinoma of the pancreas (ASCP) is a rare entity. Its estimated incidence in the literature is between 0.38% to 10% of all exocrine pancreatic tumors (Table 2)[2,5-19]. ASCP has also been referred to as adenoacanthoma, mixed squamous and adenocarcinoma, and mucoepidermoid carcinoma[20]. The entity was first described in 1907 by Gotthold Herheimer, who referred it as cancroide[20]. Adenosquamous histology is seen in cancers of other organ systems such as lung, esophagus, colon, stomach, salivary glands, and the female reproductive system[20]. Compared to pancreatic adenocarcinoma, which has a poor 5-year overall survival, survival is worse in patients with ASCP[12-15].

The etiology of ASCP is unknown. Most literature reports of this disease have come from Asia. The largest known case study showed that 79% of 415 patients with ASCP were Caucasian[12]. It is unknown if risk factors for the development of pancreatic adenocarcinoma such as chronic pancreatitis, ABO blood group, alcohol use, tobacco use, germline mutations such as BRCA2, PALB2, ATM, and p53 are also risk factors for the development of ASCP[12,21].

In this review, we will discuss the current understanding of ASCP. We have profiled 23 patients with ASCP and will present our findings, along with other molecular analyses reported in the literature. We will also discuss potential treatment strategies specifically targeting ASCP.

Table 1 Frequency of malignant exocrine pancreatic neoplasms

Frequency of malignant exocrine pancreatic neoplasms	
Histological subtype	**Frequency**
Adenocarcinoma	85%
Mucinous cyst adenocarcinoma	2%
Adenosquamous	0.38%-10%
Undifferentiated/anaplastic carcinoma	< 1%
Intraductal papillary mucinous carcinoma	3%
Acinar cell carcinoma	< 1%
Rare subtypes	4%

Rare subtypes include signet ring cell carcinoma, giant cell tumor, cystadenocarcinoma, pancreatoblastoma, spindle cell carcinoma.

Table 2 Incidence of adenosquamous carcinoma of the pancreas

Pancreatic cancer specimens	No. (%) of ASCP	Ref.
15185	81 (0.05)	[2]
5075	46 (0.9)	[6]
264	10 (3.8)	[8]
391	13 (3.4)	[9]
80	8 (10)	[10]
202	6 (3)	[11]
3651	45 (1.2)	[12]
45693	415 (0.9)	[13]
237	7 (2.9)	[14]
406	14 (4)	[15]
1025	46 (4.5)	[16]
24604	95 (0.38)	[17]
635	20 (3.1)	[18]
8372	25 (0.3)	[19]
234	7 (2.9)	[20]

ASCP: Adenosquamous carcinoma of the pancreas.

PATHOLOGY

Normal pancreas tissue has no benign squamous epithelial components[9,15,22]. Various hypotheses have been proposed regarding the histogenesis of ASCP. One theory hypothesizes that squamous metaplasia occurs as a result of ductal inflammation due to chronic pancreatitis or obstruction by an adenomatous tumor, and this process leads to ASCP[5,23]. Another theory, termed the collision theory, suggests that two histologically distinct tumors arise independently in the pancreas and are joined together leading to ASCP[20,23,24]. Finally, the third theory, the differentiation theory, suggests that a primitive pancreatic stem cell

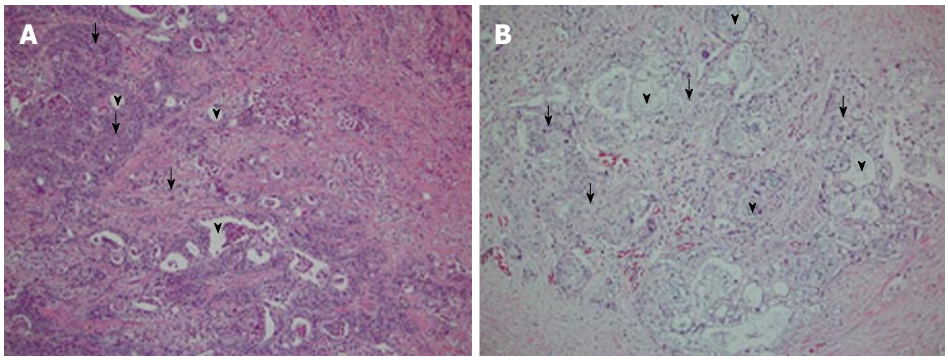

Figure 1 Typical pathology of adenosquamous carcinoma of the pancreas. H and E slides of two patient's tissues, showing the adeno *vs* squamous component (arrowheads = adeno; arrows = squamous component). A: Tissue from head of pancreas; B: Tissue from tail of pancreas; both are G2, moderately differentiated cancers.

differentiates into either squamous or adenocarcinoma or becomes a combination of both[14,22,23]. Despite different hypotheses, there has been no study to elucidate the mechanism of origination of ASCP.

The pathology of ASCP includes the typical squamous carcinoma pattern that is characterized by epithelium with whorls, keratohyalin, or pearls[14,16], as seen in Figure 1. Compared to nuclei of benign squamous cells, the nuclei of malignant squamous cells are hyperchromic and pleomorphic[15,22]. The squamous carcinoma component of ASCP appears to be more focal in the tumor. An interesting histological feature is the finding in several case series of ASCP that the squamous cell carcinoma component is located in the periphery of the tumor, while the adenocarcinoma component is in the center[9,22]. There is a transitional zone where the glandular structure blends into the squamous component[22]. There is an entity descriptive of pure squamous cell carcinoma of the pancreas, but this classification has been debated and is considered to be more secondary to metastasis to the pancreas from a non-pancreas primary carcinoma[15,25,26].

Tumor cell necrosis is frequently seen in patients with ASCP, along with high tumor grade[25,27]. Other unusual reported pathology has included the presence of clear cell and rhabdoid components[27,28]. One pathology case report noted the presence of both osteoclast and giant tumor cells which were scattered individually within the stroma[3]. The presence of osteoclasts is not unique to ASCP, as osteoclasts have been seen in adenosquamous carcinoma of other organs, including the esophagus, gallbladder, and kidney[3,13]. Acantholysis has also been noted[3]. The squamous component of the cancer has been shown to be more likely to demonstrate vascular invasion, but less likely to metastasize to the lymph nodes[16]. One study found that pancreatic adenosquamous carcinoma grows at twice the rate of pancreatic adenocarcinoma[29].

The current guideline to diagnose adenosquamous pancreatic cancer requires the presence of at least 30% of squamous component in the pancreas tumor tissue[18,20,30]. However, this classification system is being debated, due to both the subjective nature of estimating percentage composition and the sampling method of a patient's tumor at biopsy through fine needle aspiration (FNA) *vs* surgical resection. The clinical relevance of the degree of squamous cell differentiation in adenosquamous pancreas cancer is unknown[16,18]. The proportion of squamous differentiation in ASCP did not influence survival in one case series of 38 patients[22]. Some have proposed that presence of any squamous cell carcinoma component in a pancreatic tumor should classify the cancer as adenosquamous[16,26,31].

Prior immunohistochemistry (IHC) analysis on patients with adenosquamous carcinoma have shown the cancer to be positive for cytokeratin (CK) 5/6, CK 7, and p63 and negative for CK 20, p16, and p53[18,32]. IHC positivity for pancreatic adenocarcinoma includes CK7, CK20, mesothelin, cancer antigen 125 (CA-125), and lysozyme[18,33]. The KI-67 index for one patient with ASCP with approximately a 70%-80% squamous carcinoma component was 33%[32].

As in pancreatic adenocarcinoma, *KRAS* mutations have also been observed in ASCP[18,27,31,34]. A molecular study involving analysis for p53, Dpc4/SMAD4, p16, E-cadherin, EGFR protein expression levels, *KRAS* mutational analysis; *p16/CDKN2a* amplification, and HPV DNA detection was carried out on 8 patients with ASCP[27]. The *KRAS* mutations only screened for mutations in codons 12 and 13, which were present in 5/8 of the squamous component of the cancer samples. A homozygous deletion of the *p16* gene was present in 3/8 squamous components. Regarding protein expression in the same patient samples, DPC4 was lost in 5/8 samples, p53 was positive in 5/8 samples, p16 was universally lost, E-cadherin was either reduced or lost in 7/8 samples, and P63 and EGFR were positive in all 8 samples[27]. The lack of protein expression of p16 was particularly interesting since the gene was present in 5/8 patient samples, suggesting other causes of loss of protein expression, such as gene silencing like DNA methylation. There was no HPV DNA detectable in the eight patients tested[27]. HPV status was looked at another analysis of 7 patients, and none of these patients were positive[13]. The lack of positivity of HPV is noteworthy due to its influence in the development of

Table 3 Molecular profiling of patients with adenosquamous carcinoma of the pancreas: Immunohistochemistry analysis

IHC analysis percent positive expression (positive/number examined)																		
MRP1	BCRP	MGMT	TOP2A	TUBB3	PTEN	SPARC	TOPO1	RRM1	cMET	TLE3	TS	ERCC1	PGP	C-kit	PR	AR	ER	Her2
80 (8/10)	80 (4/5)	76 (16/21)	78 (14/18)	38 (3/8)	41 (9/22)	39 (9/23)	38 (8/21)	43 (9/21)	33 (4/12)	42 (5/12)	38 (8/21)	31 (4/13)	11 (2/18)	10 (1/10)	5 (1/21)	0 (0/21)	5 (1/21)	0 (0/22)

IHC: Immunohistochemistry.

Table 4 Molecular profiling of patients with adenosquamous carcinoma of the pancreas: Fluorescence *in situ* hybridization/ chromogenic *in situ* hybridization analysis

FISH/CISH percent positive expression (positive/number examined)				
cMET	EGFR	Her2	TOP2A	ALK
9 (1/11)	0 (0/6)	0 (0/12)	0 (0/2)	0 (0/1)

FISH: Fluorescence *in situ* hybridization; CISH: Chromogenic *in situ* hybridization.

other squamous histology cancers such as the cervix, head and neck, and anus[13].

We have conducted a molecular characterization using a commercially available assay[35]. Twenty-three patients with ASCP were identified and the results of the profiling are presented (Tables 3-5). The median age was 60 years old (range 41 to 86 years old), and 17/23 patients were male. Evaluation of protein expression by IHC analysis revealed the following: DNA topoisomerase2 (TOPO2A) overexpression was prevalent in 78% of the samples, which in some studies of other histologic types indicates sensitivity to agents such as doxorubicin or etoposide. Low expression of ribonucleotide reductase M1, which can indicate sensitivity to gemcitabine, was low in 57% of the patient samples. Low thymidylate synthase expression, found in 62% of patient samples, correlates to sensitivity in some tumor types to fluoropyrimidines such as 5-FU, capecitabine, and pemetrexed. Low expression of excision repair cross-complementation group 1, or ERCC1, is associated with sensitivity to platinum-based therapies in some tumor types and was found to be low in 69% of patient samples. Other positive findings included 10% (1 in 10) positivity of c-KIT, and TOPO1 overexpression in 38% of patient samples. These biomarkers are correlated to sensitivities to imatinib and topotecan/irinotecan, respectively, in some tumor types. The high expression of both MRP1 and BCRP1 at 80% highlights the difficulty of treating ASCP, as these proteins are involved in drug resistance to chemotherapy. FISH/CISH analysis revealed an 11% overexpression of c-MET, an oncoprotein that is increasingly targeted in new drug development. Also, one sample had a mutation in c-MET. Of note, mutation analysis revealed *KRAS* mutations in all sixteen patient samples tested, but none had *EGFR* mutations.

Very little genomic sequencing data is available in the literature on adenosquamous pancreatic cancers. However, a study published examining whole genomic sequencing in eleven patients with advanced cancer included one patient with ASCP[36]. This patient's sequencing included single nucleotide variations (SNV), whole genome sequencing (WGS), and whole transcriptome sequencing (WTS). Some of the variations found included the upregulation of two ligands, transforming growth factor (TGF)-β 1 and TGF-β 2 along with their accompanying receptor, TGF-β receptor type Ⅱ. These growth factors are involved in the epithelial to mesenchymal transition (EMT). Other members of a shared pathway, Lef-1, TCF8, and E2A, were also found to be upregulated. E-cadherin was found to be down-regulated, which is a hallmark of the EMT phenotype[33]. The EMT phenotype has been shown to play a crucial role in cancer cell metastasis along with resistance to chemotherapy and contributing to the formation of cancer stem cells[36]. This patient's tumor did have a mutation in KRAS at codon 12 along with a mutation in *PI3KCA*. The patient's sequencing was done during therapy and upon progression on gemcitabine and cisplatin. The patient was then enrolled on a phase I trial involving a combination PI3K and MEK inhibitor, and experienced a clinical benefit in the form of a dramatic decrease in his pain, along with tumor response[36].

Another genetic analysis done recently looked at 23 patients with ASCP through genomic sequencing and showed a mutation of the *UPF1* gene, which encodes a RNA helicase essential for the highly conserved RNA degradation pathway, nonsense-mediated RNA decay[37]. This mutation was not seen in the adjacent normal tissue of these patient samples. The pathways that UPF1 is implicated in are not all known but appear to be involved in the normal splicing of RNA, affecting such genes as *p53*[37].

IMAGING

While there is not a definitive characteristic appearance of ASCP on computed tomography (CT) imaging, they are usually not well circumscribed[38]. CT imaging of ASCP lesions commonly show the presence of central necrosis within the tumor mass[31,38,39], which is rarely seen in pancreatic ductal adenocarcinoma or in endocrine tumors of the pancreas[40,41]. Another common imaging finding is the propensity for vascular and nerve encasement[38].

A large series looking at ASCP through CT and magnetic resonance imaging showed the presence of frequent intra-tumor necrosis, increased enhancement, and exophytic growth[42]. It is theorized that this pheno-

Table 5 Molecular profiling of patients with adenosquamous carcinoma of the pancreas: Mutated gene analysis (either sanger or next generation sequencing)

Mutated genes percent positive (number found/examined)								
cMET	KRAS	TP53	BRAF	NRAS	SMAD4	cKIT	PIK3CA	EGFR
13 (1/13)	100 (16/16)	50 (4/8)	0 (0/9)	0 (0/9)	25 (2/8)	0 (0/9)	0 (0/11)	0 (0/10)

menon may reflect the presence of the squamous component causing rapid proliferation, as these characteristics are not seen as often in adenocarcinoma of the pancreas[43]. Other unique features noted in imaging evaluation with ASCP are the lack of pancreatic atrophy and mild duct dilatation, which are more common features of pancreatic adenocarcinoma[42]. Like adenocarcinoma of the pancreas, adenosquamous cancers of the pancreas may exhibit the double duct sign[38], which consists of simultaneous dilatation of the common bile and pancreatic ducts[44].

Gallium-67 is an older radioactive tracer that is taken up by some malignancies and infections and has been replaced by PET scans in relation to tumor staging[45]. Intense Gallium-67 uptake, which rarely is detected in pancreatic adenocarcinoma, has been observed in ASCP[45,46]. PET-CT imaging has been reported in a limited number of case reports. One case report noted a patient with localized ASCP to have a standardized uptake value (SUV) of 15.8, which was over 3 times higher than the SUV average for patients with pancreatic adenocarcinoma at their institution[47].

Figure 2 highlights several key imaging findings from patients we have treated with ASCP, including necrosis and mixed morphology. Of note is that in looking at one of our recent ASCP patients, the hypermetabolism that has been previously reported in patients with ASCP was not seen[47].

CLINICAL CHARACTERISTICS

The characteristics of patients with ASCP tend to favor more aggressive features with more node positive disease, more poorly differentiated disease, and more perineural invasion present compared to patients with pancreatic adenocarcinoma[16]. Patients with ASCP present with symptoms similar in nature to patients with pancreatic adenocarcinoma, with abdominal pain, weight loss, back pain, nausea, vomiting, anorexia, and jaundice being the most common presenting symptoms[19,20,38]. As with pancreatic adenocarcinoma, there appears to be an increased risk of deep vein thrombosis[25]. In larger case series, patients are typically male, white, present in their sixth decade of life, and the tumor is located in the head of the pancreas[12,13,20]. Serum lab abnormalities may include elevated bilirubin, elevated alkaline phosphatase, anemia, and elevated carbohydrate antigen 19-9 (CA 19-9)[19,20,25]. Occasionally, patients may also have elevated levels of carcinoembryonic antigen (CEA) or CA-125[38].

Long term survival overall is poor for ASCP. Survival, despite surgical resection, is slightly poorer for patients with ASCP than those with pancreatic adenocarcinoma. Those with ASCP have a 3-year survival rate of 14% with surgery, as opposed to 19% 3-year survival of resected pancreatic adenocarcinoma patients[29,48]. Like patients with pancreatic adenocarcinoma, patients with ASCP tend to present more commonly in advanced stage, with one large analysis through the California Cancer Registry database (CCR) indicating over 50% of ASCP patients presenting in advanced stage[11]. The mean tumor diameter in one series of resected ASCP patients was 46.3 mm *vs* 33.5 mm of adenocarcinoma pancreas patients (*P* value 0.0001)[11]. Comparisons between patients at single institutions and matching for stage have yielded an overall median survival of 6.51 mo *vs* 11.0 mo for ASCP *vs* adenocarcinoma[15]. In another large single institution analysis of patients with ASCP, the median survival of patients with resection was 10.9 mo, which was worse than those with pancreatic adenocarcinoma who underwent resection, which was 17.9 mo[16].

In an analysis of Surveillance, Epidemiology, and End Results (SEER) patients that identified 415 patients with ASCP, the mean age was found to be 66 years old and the tumor more likely to be in the head of the pancreas. Compared to patients with adenocarcinoma of the pancreas, patients with ASCP were more likely to be poorly differentiated (71.4% *vs* 45%), larger (5.7 cm *vs* 4.3 cm), and more likely to have positive lymph nodes (52.8% *vs* 47.1%)[12]. In patients with ASCP, overall 1 and 2-year survival was 21.2% and 10.8% compared to 24.7% and 10.9% in patients with pancreatic adenocarcinoma[12]. Patients with ASCP were found to have a median survival of 4 mo compared to 5 mo in patients with pancreatic adenocarcinoma[12]. Patients with ASCP who underwent resection had worse survival rates than those with adenocarcinoma pancreas cancer who underwent resection. One year and 2-year survival rates of 50.7% and 29% and median survival was 12 mo in patients with ASCP as opposed to 60.1% and 35.8% and median survival of 16 mo in those with adenocarcinoma of the pancreas[12]. After primary resection, recurrence may occur in a number of sites. Common sites of metastases include the liver, lung, retroperitoneum, and development of malignant ascites[16,38].

Several studies have examined various clinical features of survival in patients with ASCP. Lymph node status, tumor size, or resection in patients with ASCP does not impact survival when compared with

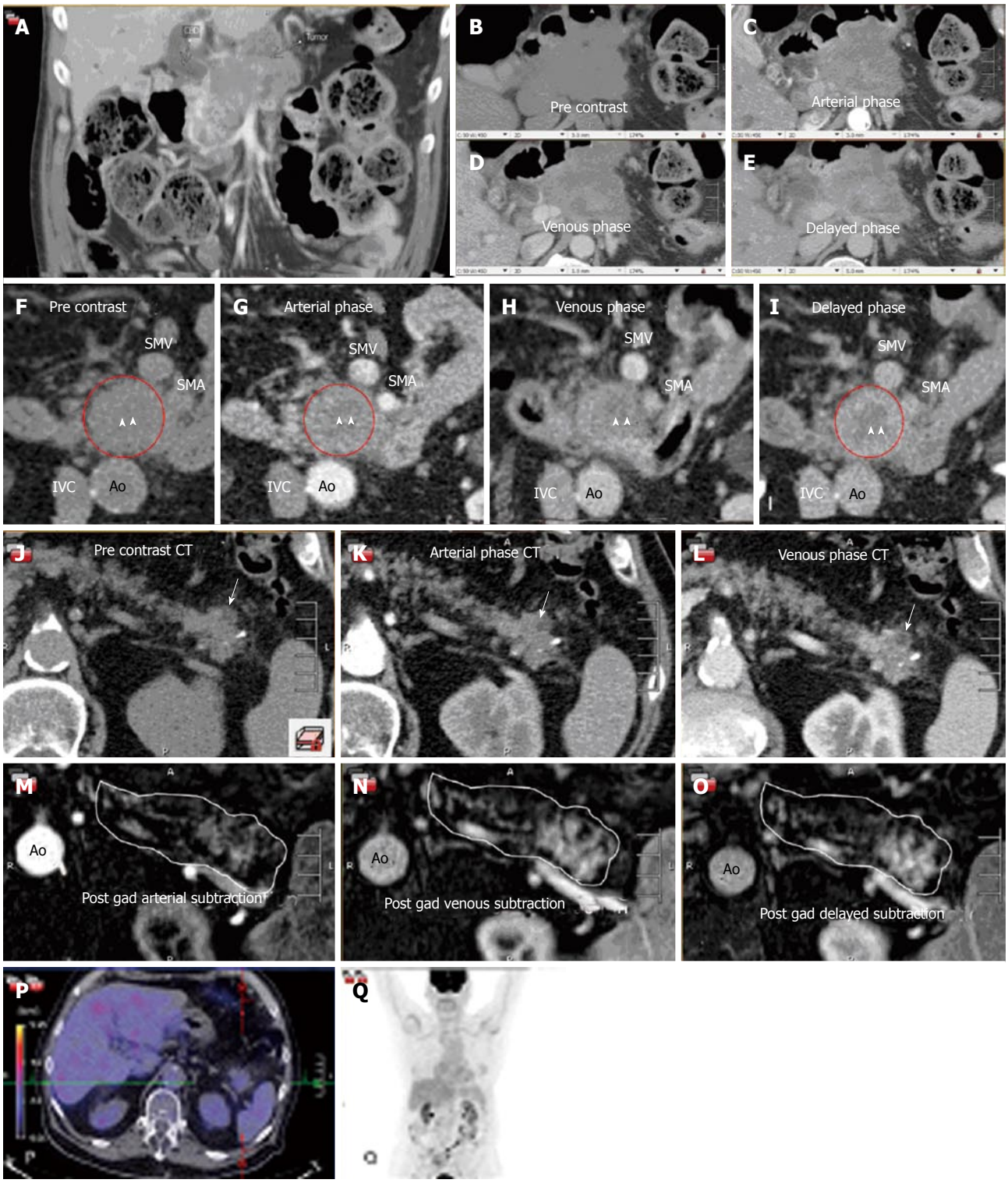

Figure 2 Collection of images from three separate patients with adenosquamous carcinoma of the pancreas. The typical complex enhancing mass and mixed morphology of necrosis and enhancing tissue is demonstrated in this figure. A-E are taken from a four phase contrast enhanced CT (pre-contrast, arterial, venous and delayed images). This type of scanning technique can be helpful to define the tumor and its invasion into surrounding structrures. A-E represent a coronal (A) and axial (B-E) images through a large, infiltrating, necrotic tumor with islands of slow enhancement (B-E). Note the islands of soft tissue enhancement increasing from arterial to delayed phase contrast enhanced CTs. These features are usually signs of very aggressive tumors. In another subject (F-I) there is again a central area of necrosis (arrowheads) surrounded by a ring of slowly enhancing tumor (red circle). Note the relative lack of surrounding soft tissue infiltration compared to the tumor on Panels A-E. Panels J-O are taken from a third subject and are an example of an atypical adenosquamous carcinoma involving the pancreas tail with a slowly enhancing, non-infiltrating lesion both on CT (J-L) and post gadolinium subtraction MRI (M-O). The white outline in Panels M-O outlines the contour of the pancreas with the enhancing lesion seen towards the tail of the pancreas. There is a small focus of necrosis present (arrow), a feature typical of adenosquamous carcinoma of the pancreas. The corresponding FDG PET/CT (P and Q) is unusual in that it shows that this mass is not hypermetabolic unlike most adenosquamous pancreas carcinomas. Ao: Aorta; IVC: Inferior vena caval; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein.

patients with adenocarcinoma of the pancreas[12,16]. Not surprisingly, risk factors for poorer survival of patients with ASCP are those with distant disease, advanced age, and patients unable to undergo surgical resection[12]. In one study, only 40% of patients with ASCP were resectable[12]. A single institution case series from the Mayo clinic showed that patients with an R1 resection still benefited in survival compared to those who did not undergo surgery[49]. Patients from that study that had either an R0 or R1 resection had a median survival of 14.4 and 8 mo respectively, compared to 4.8 mo who received no surgical treatment[49]. Location of the tumor matters, with poorer survival noted if the location was in the body or tail as opposed to the head of the pancreas[48]. This was based on a chart analysis of 39 patients with ASCP and may be accounted for by size of these tumors by location as the ones located in the head were smaller (4.7 ± 1.9 cm) as opposed to the body/tail lesions (7.3 ± 1.8 cm)[48]. The likely reason for poorer survival is that patients with head of pancreas lesions tend to present with obstructive symptoms, which are clinically evident when the lesion is smaller in comparison to body/tail lesions of the pancreas.

It is unclear why patients with ASCP have such a poor prognosis. Due to the small sample size, data to shed light on this disease has been limited. One case series from Voong *et al*[16] looking at patients diagnosed with ASCP and who had undergone surgery showed *via* univariate analysis that only patients who received adjunct chemoradiation had a clinical significant improvement in survival[16]. The patients who received adjunct chemoradiation had a median survival of 13.6 mo as opposed to 8.6 mo for those that did not[16]. Other factors such as age, tumor size, differentiation, margin, node status, type of surgery were not shown to affect survival in this case series[16].

Malignancy associated hypercalcemia, which is a rare phenomenon of exocrine pancreatic carcinoma, has been described in ASCP[50,51]. Of note is that malignancy associated hypercalcemia is more commonly associated with squamous cell carcinomas of the head, neck, lung, and esophagus. Case reports have also described patients with adenosquamous pancreatic cancer having elevated levels of calcium due to elevated levels of parathyroid hormone related protein[50,51]. In both reported cases, hypercalcemia persisted despite bisphosphonate treatment[50,51]. Curiously, hyperglycemia has not been reported with great frequency in ASCP despite being reported in up to 80% of patients with pancreatic adenocarcinoma[52].

MANAGEMENT

Diagnosis of patients with ASCP requires biopsy along with pathology review using criteria of ASCP with at least 30% of the tumor positive for squamous histology. Staging is done in a similar manner as pancreatic adenocarcinoma with guidelines set forth by the American Joint Committee on Cancer (AJCC)/ International Union Against Cancer (UICC). Unresectable disease is designated as Stage Ⅲ and metastatic disease is designated as stage Ⅳ. One issue with diagnosis includes the current standard approach of using endoscopic ultrasound for diagnosing pancreatic cancer and using FNA. In a retrospective review of patients at John Hopkins University and Emory University it was noted that in patients who eventually had a diagnosis of ASCP after surgical resection, two thirds of them (67%) were initially diagnosed as being pancreatic adenocarcinoma only. It is possible for pathologists to misclassify or ignore the squamous cell compartment in pancreatic FNA specimens, which not only leads to underreporting of ASCP but may also miss the diagnosis of malignancy altogether[15].

There are currently no guidelines for treating patients with ASCP. Literature reports often cite treatment regimens similar to adenocarcinoma[48]. Due to its relative infrequency in incidence there have been no published randomized clinical trials specifically targeting patients with ASCP. Treatments in years past have focused on resection of local adenosquamous pancreatic carcinoma using the same guidelines for pancreatic adenocarcinoma. These include pancreaticoduodenectomy (PD), pylorus-preserving PD, distal pancreatectomy, and total pancreatectomy[48]. These techniques are not modified for ASCP and surgical resection remains the best opportunity to achieve long lasting survival[48].

The role of neoadjuvant and adjuvant chemotherapy is unclear, mimicking some questions that continue to be explored in pancreatic adenocarcinoma[48]. Most case reports in the literature have used 5-fluorouracil based therapies for treatment around surgical procedures and have not examined the role of gemcitabine or more robust regimens such as FOLFIRINOX or nab-paclitaxel/ gemcitabine[49]. In a retrospective series of 62 patients identified with pancreatic adenosquamous carcinoma, 14 patients received platinum therapy in the adjuvant setting as opposed to 48 who did not[53]. The patients who received platinum therapy in the adjuvant setting had an overall median survival of 19.1 mo as opposed to 10.7 mo for those who did not (P = 0.011, hazard ratio of survival 0.48)[53].

The role of radiation therapy as an adjunct to resection of ASCP is also unclear[48,54,55]. Two retrospective studies examined adjuvant radiation therapy, but did not show a benefit in overall survival for those that received adjuvant therapy *vs* those who did not. In a previously published literature review of 30 patients who received radiation therapy either intra and/or postoperatively, the 2-year survival rate was 20% and median survival 13 mo[48]. In the patients who did not receive radiation therapy their 2-year survival rate was 9% and median survival period was 6 mo. Despite the differences in survival between the 2 groups, they did not reach statistical significance[48].

CONCLUSION

ASCP is an aggressive variation of carcinoma of the pancreas. Overall it carries a poor prognosis. A study to assess the percentage component of squamous carcinoma in ASCP and associating this with differences in clinical outcome is certainly warranted, but may be difficult to carry out due to the scarcity of this disease and the subjective evaluation needed by pathologists to determine percent squamous in a pancreas carcinoma specimen. Obtaining the proper amount of tissue makes diagnosis difficult and is akin to diagnosing patients with lymphoma by way of FNA: there may be diagnostic inaccuracies depending upon where the sample is biopsied. This role of subjective evaluation also makes interpreting retrospective analysis difficult, such as examining databases like SEER.

There is a need to better characterize the disease beyond traditional pathology analysis. Doing further work characterizing this disease on a molecular level may further elucidate the requirements for classifying pancreatic carcinomas as adenosquamous or adeno. Our work in molecular characterization, while small in sample size, points to the use of novel therapeutic combinations in patients with ASCP, such as epirubicin/cisplatin/5-FU, which may be tested in small clinical trials. Targeting novel pathways such as those affecting the epithelial to mesenchymal change pathway, using agents that target APC, WNT, B-catenin, along with those targeting chromatin remodeling may be worth trying against this disease. Using cell lines derived from ASCP patients and studying them in growth assays and xenograft models may yield clues regarding their response to newer anti-cancer agents in development[54,55]. Understanding the key genetic drivers for this disease may lead to better treatment outcomes since it is clear traditional treatments for pancreatic adenocarcinoma do not translate well to ASCP.

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Proton therapy for pancreatic cancer

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Abstract

Radiotherapy is commonly offered to patients with pancreatic malignancies although its ultimate utility is compromised since the pancreas is surrounded by exquisitely radiosensitive normal tissues, such as the duodenum, stomach, jejunum, liver, and kidneys. Proton radiotherapy can be used to create dose distributions that conform to tumor targets with significant normal tissue sparing. Because of this, protons appear to represent a superior modality for radiotherapy delivery to patients with unresectable tumors and those receiving postoperative radiotherapy. A particularly exciting opportunity for protons also exists for patients with resectable and marginally resectable disease. In this paper, we review the current literature on proton therapy for pancreatic cancer and discuss scenarios wherein the improvement in the therapeutic index with protons may have the potential to change the management paradigm for this malignancy.

Key words: Proton therapy; Pancreatic cancer; Review

Core tip: Radiotherapy is commonly offered to patients with pancreatic malignancies although its ultimate utility is compromised since the pancreas is surrounded by exquisitely radiosensitive normal tissues, such as the duodenum, stomach, jejunum, liver, and kidneys. Proton radiotherapy can be used to create dose distributions that conform to tumor targets with significant normal tissue sparing. Because of this, protons appear to represent a superior modality for radiotherapy delivery to patients with unresectable tumors and those receiving postoperative radiotherapy. A particularly exciting opportunity for protons also exists for patients with resectable and marginally resectable disease.

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INTRODUCTION

Radiotherapy is commonly offered to patients with pancreatic malignancies although its ultimate utility

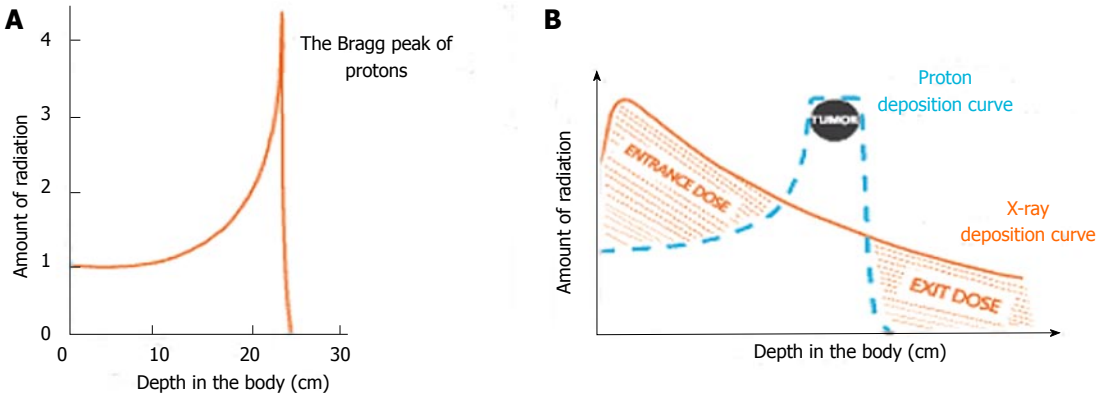

Figure 1 Charged particles like protons travel a finite distance into tissue, as determined by their energy, and then release that energy in a tightly defined region called "Bragg peak" (A). By delivering a range of energies toward the tumor target, a summation of these Bragg peaks allow for the creation of a "spread-out Bragg peak", which conforms to the depth and position of the tumor target (B). Image borrowed from the University of Florida Health Proton Therapy Institute.

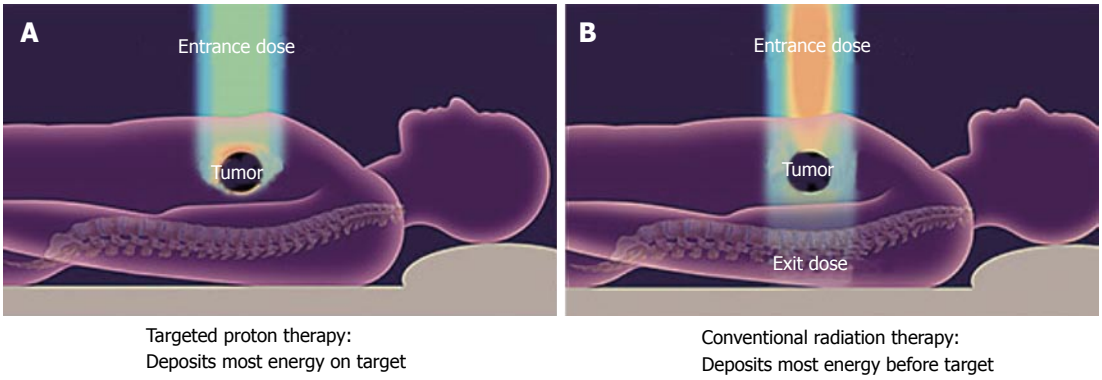

Figure 2 With X-rays, the tumor dose is significantly less than the entry dose and exit dose is delivered beyond the tumor target. With conventional radiotherapy (A) using X-rays (photons), the highest dose is near the point of beam entry into the patient. The tumor dose is significantly less than the entry dose. Also, an exit dose is delivered beyond the tumor target. With protons (B) and other particle therapies, such as carbon ions, the entry dose is low. The highest dose is at the depth of the tumor target and there is no exit dose beyond the target. Image borrowed from the University of Florida Health Proton Therapy Institute.

is compromised since the pancreas is surrounded by exquisitely radiosensitive normal tissues, such as the duodenum, stomach, jejunum, liver, and kidneys. Proton radiotherapy can be used to create dose distributions that conform to tumor targets with significant normal-tissue sparing. Because of this, protons appear to represent a superior modality for radiotherapy delivery to patients with unresectable tumors and those receiving postoperative radiotherapy. A particularly exciting opportunity for protons also exists for patients with resectable and marginally resectable disease. While many surgeons are hesitant to perform major pancreatic operations on patients who have received preoperative X-ray-based radiotherapy, it is possible that the normal tissue-sparing characteristics of protons will allow for more wide-spread adoption of preoperative radiotherapy in the setting of resectable potentially curable disease.

PHYSICS OF PARTICLE THERAPY

Charged particles such as protons travel a finite distance into tissue, determined by their energy, and then release most of that energy in a tightly defined region called the "Bragg peak". By delivering a range of energies directed toward the tumor target, a summation of these Bragg peaks allow for the creation of a "spread-out Bragg peak", which conforms to the depth and position of the tumor target (Figure 1). This process stands in contrast to X-rays for which the highest dose is near the point of beam entry into the patient. With X-rays, the tumor dose is significantly less than the entry dose and exit dose is delivered beyond the tumor target (Figure 2).

With X-ray-based therapies such as intensity-modulated radiotherapy (IMRT), the conformality of the dose distribution around a tumor target is achieved by delivering multiple treatment beams from multiple angles which intersect to create a central high-dose volume. This necessarily results in radiation exposure to virtually the entire cylinder of the abdomen. With protons, because the radiation dose deposition can be modulated along the beam path, fewer beam angles are required to create a conformal dose distribution. As a result, radiation exposure to large volumes of normal tissues is either minimized or eliminated (Figure 3)[1].

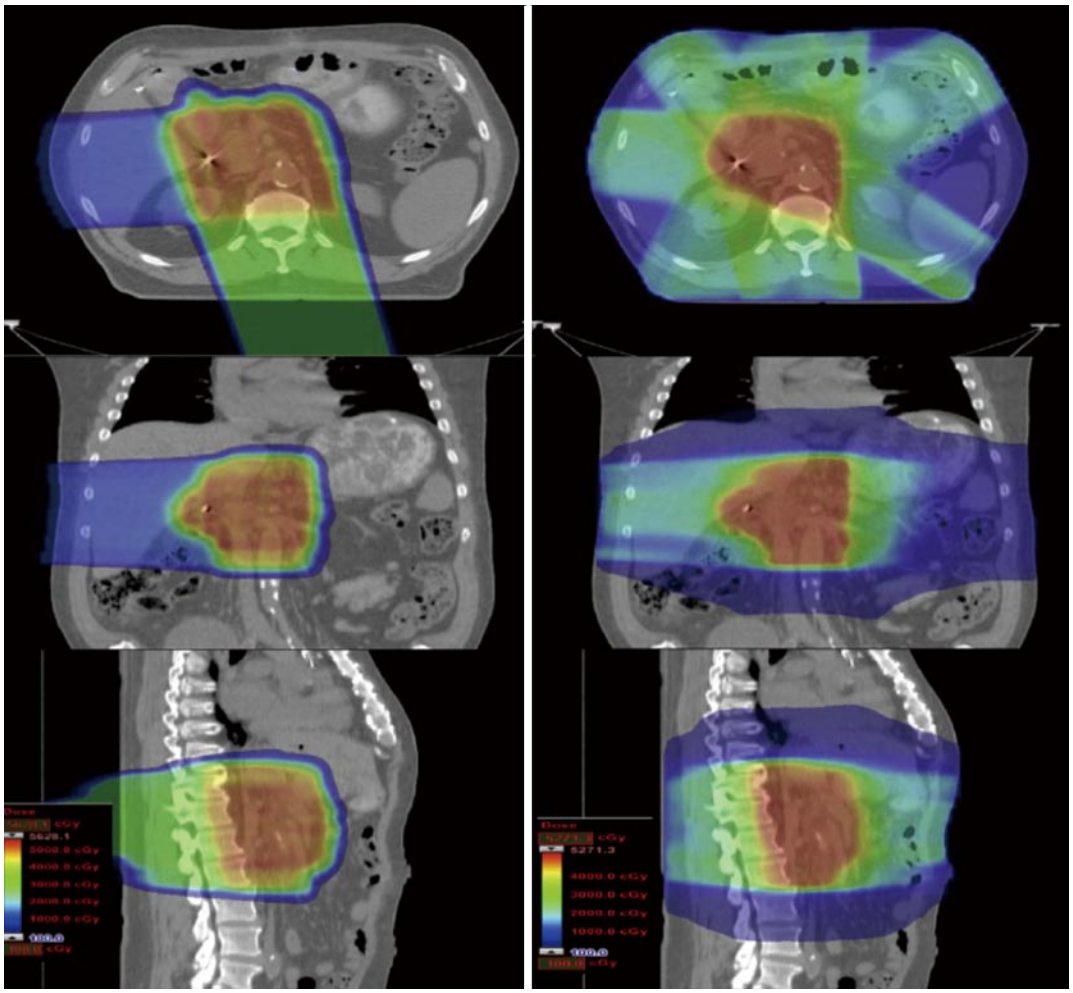

Figure 3 A passively scattered proton plan is shown on the left and an intensity-modulated X-ray therapy plan is shown on the right for a typical patient receiving postoperative radiotherapy for pancreatic cancer. To achieve a conformal dose distribution, the intensity-modulated X-ray therapy plan delivers beams from multiple angles and necessarily irradiates the entire cylinder of the abdomen. With protons, however, because the dose distribution can be modulated along the beam path, significant sparing of sensitive gastrointestinal structures (small bowel and stomach) can be achieved. In the proton plan, 75% of the dose is delivered *via* a posterior field that irradiates the tumor bed but does not exit into the small bowel. The remaining dose is delivered through a right lateral field that also irradiates the tumor bed but does not exit into the stomach.

CONTROVERSIES REGARDING THE ROLE OF RADIOTHERAPY FOR PANCREATIC CANCER

While radiotherapy has historically been offered to patients with unresectable disease or postoperatively to patients with resected disease, several recent studies have questioned its value, suggesting that its toxicity outweighs its potential benefit. The ESPAC-1 trial, using a complicated randomization scheme[2,3], concluded that postoperative radiotherapy was associated with a nominal, but statistically insignificant, survival decrement as irradiated patients demonstrated a 15.5-mo median survival *vs* 16.1 mo for patients receiving chemotherapy alone. While valid criticisms of the ESPAC-1 study have been published[4], chemotherapy alone, without radiotherapy, has been adopted as a standard postoperative approach for resected patients in many centers. For patients with unresectable disease, the recent report of the LAP 07 study (of patients with locally advanced pancreatic cancer) showing a 16.4-mo median overall survival for patients receiving chemotherapy alone *vs* 15.2 mo for the chemoradiation arm[5] has led to further doubts about the utility of radiotherapy in this group of patients. Finally, while some institutions have advocated preoperative X-ray-based radiotherapy for patients with marginally resectable or resectable disease, many surgeons are reluctant to operate on previously irradiated patients, citing concerns about radiotherapy toxicities complicating what is already a complicated operation.

CAN PROTONS IMPROVE THE THERAPEUTIC RATIO?

Considering the above concerns regarding the toxicity-efficacy tradeoffs for X-ray-based radiotherapy, numerous dosimetric and clinical studies have explored the possibility that protons might offer an improved

therapeutic index for pancreatic cancer patients receiving radiotherapy.

Dosimetric studies

Hsiung-Stripp *et al*[6] demonstrated the ability of 130-180 MeV protons to effectively treat unresectable pancreatic cancers. Compared with similarly effective X-ray plans, proton plans significantly reduced doses to the spinal cord (P = 0.003), left kidney (P = 0.025), right kidney (P = 0.057), and liver (P = 0.061). The authors argued that this reduction in normal tissue exposure might allow for radiotherapy dose escalation.

Kozak *et al*[7] demonstrated the dosimetric feasibility of hypo-fractionated proton therapy for neoadjuvant pancreatic cancer treatment using anatomical data from 9 patients. Compared with IMRT, protons offered a significant reduction of dose to the liver, kidneys and small bowel-particularly in the low-dose regions.

Bouchard *et al*[8] compared 3-dimensional (3D) conformal photon radiotherapy with IMRT and protons in the delivery of 72 Gy (RBE) to unresectable tumors. The authors concluded that protons were superior to photons for tumors with anteriorly located small bowel.

Nichols *et al*[9] compared passively scattered protons with intensity-modulated X-ray therapy for 8 patients in the postoperative setting. Patients were treated with a planning target volume dose of 50.4 Gy (RBE). Proton plans offered significantly reduced normal tissue exposure over the IMRT plans with respect to median small bowel V20Gy (RBE) (P = 0.0157), median gastric V20Gy (RBE) (P = 0.0313), and median right kidney V18Gy (RBE) (P = 0.0156). The authors argued that, by reducing small bowel and gastric exposure, protons have the potential to reduce acute and late toxicities of postoperative chemoradiation.

Lee *et al*[10] explored the feasibility of using proton therapy in the neoadjuvant setting to cover a planning target volume including gross disease and regional lymph nodes. Utilizing a field arrangement heavily weighted to a posterior field, the investigators demonstrated the feasibility of expanding the target volume to cover nodal targets without significantly increasing critical normal tissue exposure. The authors argued that treating a similar increase in target volume would be substantially more difficult with X-rays due to normal tissue exposure issues.

Ding *et al*[11] compared passively scattered and modulated scanning proton therapy to a number of X-ray-based strategies including 3D conformal radiation therapy (3DCRT), 5-field IMRT, and 2-arc volumetric modulated radiation therapy. Proton plans demonstrated lower doses to the kidneys, stomach, liver, and bowel.

Thompson *et al*[12] compared proton and IMRT plans in 13 patients with unresectable cancer of the pancreatic head. Both the double-scattered and pencil-beam plans decreased gastric, duodenal, and small bowel dose in the low-dose regions compared to IMRT; however, protons were associated with increased dose in the mid- to high-dose regions.

Clinical studies

Three groups (Massachusetts General Hospital in Boston, Hyogo Ion Beam Center in Japan, and University of Florida) have published preliminary clinical data on the treatment of pancreatic cancer patients with protons.

The group from Massachusetts General Hospital completed a phase 1 study of preoperative short-course chemoradiation confirming the safety of a preoperative dose of 25 Gy (RBE) in 5 fractions over 1 wk with concomitant oral capecitabine at 825 mg/m² twice a day, Monday through Friday, for 10 d followed by surgery. No dose-limiting toxicities were observed. Grade 3 toxicity was noted in 4 of 15 patients. Eleven patients underwent resection. Mean postsurgical length of stay was 6 d with no unexpected 30-d postoperative complications[13]. Of note, a corresponding study of hypofractionated preoperative X-ray-based radiotherapy using the same dose with X-rays was closed early due to toxicities that included intraoperative fibrosis and increased operating room time[14]. A phase Ⅱ trial of proton therapy using the above dose regimen enrolled 50 patients, of whom 47 were eligible for analysis and 37 underwent pancreaticoduodenectomy. Of this cohort, 81% had positive nodes. Local regional failures occurred in 6 of 37 resected patients and distant metastases in 35 of 48. With a median follow-up of 38 mo, the median progression-free survival for the entire group was 10 mo and overall survival was 17 mo. The grade 3 toxicity rate was 4.1%.

Investigators at the Hyogo Ion Beam Center in Japan published the results of an aggressive phase I/II study of chemoradiation for patients with locally advanced pancreatic cancer. All patients received gemcitabine at 800 mg/m² weekly for 3 wk concurrent with proton therapy. Most of the patients received a dose of 67.5 Gy (RBE) in 25 fractions. The initial report suggested tolerability of this regimen[15]; however, a subsequent publication in the gastroenterology literature reported a high rate of upper gastrointestinal complications[16]. Post-treatment endoscopic examinations in 45 of 91 patients revealed radiation-induced ulcers in the stomach and duodenum. While the authors of the second publication suggested that proton therapy for inoperable pancreatic cancer was associated with a high rate of gastric and duodenal ulceration, a subsequent criticism of this study[17] pointed out that the severe toxicity exhibited was more likely due to the extremely aggressive radiotherapy dose offered with full-dose gemcitabine rather than any toxicity unique to proton therapy.

Researchers at the University of Florida published a preliminary report on the outcomes of 22 patients treated with proton therapy and concomitant capecitabine (1000 mg by mouth twice a day) for resected (n = 5), marginally resectable (n = 5), and unresectable/inoperable (n = 12) biopsy-proven pancreatic and ampullary adenocarcinoma[18]. Proton doses ranged from 50.4 Gy (RBE) to 59.4 Gy (RBE). No patient demonstrated any grade 3 toxicity during treatment

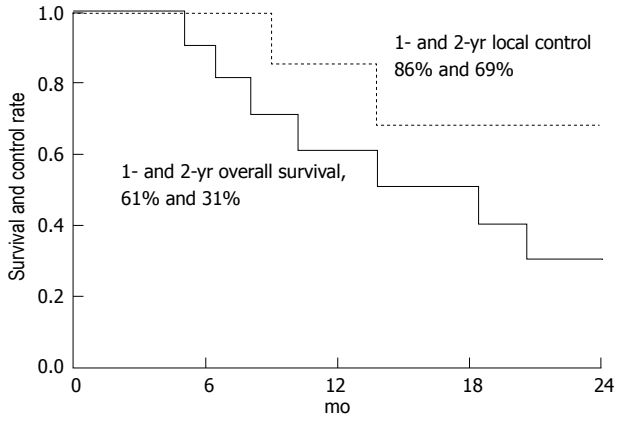

Figure 4 Overall survival and freedom from local progression at 2 years for 11 patients accrued to a phase II clinical trial for unresectable pancreatic cancer. Image borrowed from Ref. [19].

or during follow-up. Three patients experienced grade 2 gastrointestinal toxicity; all 3 of these patients were treated early in the series with fields that included anterior and left lateral components. When field design was modified to deliver the majority of the dose through the posterior field with a lightly weighted right-lateral field, grade 2 gastrointestinal toxicity was eliminated. The median weight loss during treatment was 1.3 kg. Chemotherapy was well-tolerated with a median of 99% of the prescribed doses delivered.

A subsequent publication by the same group reported the outcomes of a phase II clinical trial for patients with unresectable pancreatic cancer[19]. A total of 11 patients were reported. All patients received 59.4 Gy (RBE) at 1.8 Gy (RBE) per fraction over 7 wk with concomitant oral capecitabine at 1000 mg by mouth twice a day on radiation treatment days only. The median follow-up for surviving patients was 23 mo. The 2-year overall survival rate was 31%, the median survival rate was 18.4 mo, and the 2-year freedom from local progression rate was 69% (Figure 4). No patient experienced grade 2 or higher gastrointestinal toxicity. Four patients had an adequate radiographic response to radiation therapy to justify surgical exploration.

RATIONALE FOR PREOPERATIVE RADIOTHERAPY

Of the approximately 49000 cases of pancreatic cancer diagnosed annually in the United States, only 20% of these patients can be considered resectable or "curable"[20]. Unfortunately, the "cure" rate for these patients is only approximately 20%[21]. While many of these patients fail exclusively with distant metastatic disease, a substantial number experience local recurrence after surgery. Published data suggest that the local failure rate after surgery, even with negative margins, is in the range of 50%-80% if these patients do not receive radiotherapy[22,23]. Postoperative radiation therapy, however, has intrinsic limitations in this disease site. For example, postoperative convalescence generally necessitates a 10- to 12-wk window between surgery and initiation of postoperative radiation therapy. In reality, many patients are unable to receive postoperative radiation therapy within a clinically meaningful time frame. Additionally, the dose of postoperative radiation therapy is limited by the fact that a large volume of transposed small bowel is located in the radiotherapy field, making it unlikely that doses above 50 Gy can be safely delivered to these patients - a dose that is unlikely to control anything larger than the smallest microscopic adenocarcinoma deposits. In fact, published studies on patients receiving postoperative radiation therapy after surgery indicate local-regional failure rates ranging from 25%-36%[24,25]. Additionally, published data from respected high-volume centers suggest that patients undergoing extirpative surgery in the modern era for pancreas cancer have a high rate of margin and lymph node positivity. The series published by investigators at Johns Hopkins Medicine (Baltimore, MD) on 905 patients undergoing pancreaticoduodenectomy between 1995 and 2005 indicated a 41% margin positivity rate and a 79% node positivity rate[26]. The series from Memorial Sloan-Kettering Cancer Center (New York, NY) on 625 resections between 2000 and 2009 indicated a 16% margin positivity rate and a 70% node positivity rate[27]. Based on these data it is reasonable to believe that even "resectable" patients would be likely to benefit from preoperative radiotherapy - perhaps even with fields that could cover regional lymph nodes.

PLANNED PREOPERATIVE PROTON THERAPY FOR RESECTABLE OR MARGINALLY RESECTABLE DISEASE

It is possible that proton therapy in the postoperative setting will offer reduced toxicity compared to X-ray-based therapy and thereby improve local control and offer a positive impact on survival. While the results of proton therapy for patients with unresectable pancreatic cancer are encouraging, it is unlikely that this therapy, without meaningful improvements in systemic therapy, can be viewed as a potentially curative intervention.

It may be argued, however, that the best use of particle therapy would be in the preoperative setting for patients with resectable or marginally resectable disease. Preoperative radiotherapy is well-established in the treatment of other gastrointestinal disease sites (such as the esophagus and rectum) and improves local disease control and survival. It is reasonable to infer that a similar benefit could be achieved in the setting of pancreatic malignancy. As stated earlier, the main resistance to the use of preoperative radiotherapy involves concerns about radiotherapy toxicity and its potential to complicate what is already a complicated operation. If proton therapy can be delivered with negligible toxicity so that it does not compromise the

performance of extirpative surgery, proton therapy would represent more than a "kinder/gentler" form of radiotherapy; proton therapy would have the potential to alter the management paradigm for this group of potentially curable patients.

CLINICAL DATA SUPPORTING THE FEASIBILITY OF PREOPERATIVE PARTICLE THERAPY

In addition to the data published by Massachusetts General Hospital regarding the feasibility of surgery after preoperative hypofractionated proton therapy, a report from the University of Florida analyzed the outcomes of 5 patients with initially unresectable disease who unexpectedly achieved enough of a tumor response to justify surgical resection after high-dose conventionally fractionated proton therapy[28]. All patients received 59.4 Gy (RBE) in 33 fractions with concomitant oral capecitabine. Three patients subsequently underwent a laparoscopic standard pancreaticoduodenectomy, 1 underwent open pylorus-sparing pancreaticoduodenectomy, and 1 underwent an open distal pancreatectomy with irreversible electroporation after biopsies of the pancreatic head were negative. Duration of surgery, blood loss, intensive care unit stay, total hospital stay, and readmissions were consistent with historical benchmarks. None of the operating surgeons described fibrosis, anastomotic leaks, or perception that the proton therapy complicated the operation. The fact that surgery could be performed without significant complications after high-dose radiotherapy for patients who are initially unresectable suggests that lower doses of preoperative proton therapy in the range of 50 Gy (RBE) or even higher should not complicate surgery for patients with resectable or borderline resectable disease.

CONCLUSION

Dosimetric studies and early clinical outcomes suggest that particle therapy improves the therapeutic index for pancreatic cancer patients receiving radiotherapy. By reducing or eliminating the gastrointestinal toxicity historically associated with X-ray-based radiotherapy, proton therapy should address the concerns of clinicians who are hesitant to employ radiotherapy in the postoperative setting (based on the ESPAC-1 data) and those who are reluctant to offer radiotherapy to patients with unresectable disease (based on the LAP-07 data).

Arguably, the most exciting potential role for particle therapy is in the neoadjuvant treatment of patients with resectable and marginally resectable disease. These patients are well recognized to suffer a high risk of local and regional failure after surgery - a risk that is only marginally reduced with postoperative X-ray-based radiotherapy. Based on the treatment of other gastrointestinal disease sites (such as the esophagus and rectum) it is reasonable to believe that preoperative radiotherapy would have a greater impact on securing local and regional control than chemotherapy or postoperative radiotherapy. Recognizing that the primary barrier to the adoption of preoperative radiotherapy in this setting is the concern of operating surgeons that the gastrointestinal toxicity of radiotherapy will complicate the procedure, it is possible that the favorable toxicity profile associated with proton therapy will make the oncologically rational intervention (preoperative radiation therapy) technically feasible. If this is the case, proton therapy would indeed result in a change in the management paradigm for patients with resectable and potentially curable pancreatic cancer.

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MINIREVIEWS

Intrahepatic therapy for liver-dominant metastatic colorectal cancer

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Abstract

In patients with metastatic colorectal cancer, the liver is the most common site of metastatic disease. In patients with liver-dominant disease, consideration needs to be given to locoregional treatments such as hepatic arterial infusion chemotherapy, transarterial chemoembolisation and selective internal radiation therapy because hepatic metastases are a major cause of liver failure especially in chemorefractory disease. In this review we provide insights on the published literature for locoregional treatment of liver metastases in metastatic colorectal cancer.

Key words: Colorectal cancer; Liver metastases; Intrahepatic treatment; Chemoembolization; Radioembolisation

Core tip: Thanks to the increased chemotherapeutic options in patients with metastatic colorectal cancer (mCRC), the overall survival has significantly improved the last decade. Liver failure is a common cause of death in mCRC with liver metastases. Therefore in these patients locoregional treatment is a valuable treatment option in order to increase survival. In this review we provide insights on the published literature.

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INTRODUCTION

Although the incidence and the mortality of colorectal cancer (CRC) have decreased over the years in some countries, it still remains one of the most prevalent and the third leading cause of cancer death worldwide[1]. Even with improved screening, the incidence of synchronous and metachronous disease remains high. Approximately half of patients with CRC will develop liver metastases[2]. When mCRC is treated with a combination of chemotherapy (5-FU, oxaliplatin, irinotecan) and targeted agents such as the anti-epidermal growth factor receptor and anti-vascular growth factor

monoclonal antibodies, median overall survivals now extend beyond 24 mo in the clinical trial setting[3]. Hepatic metastases are a major cause of liver failure especially once all chemotherapeutic and/or surgical options have been exhausted. Although surgical resection of liver metastases for curative intent is the treatment of choice, most patients present with unresectable liver-predominant metastatic CRC (mCRC). In these cases, consideration needs to be given to the (often favorable) efficacy and safety of locoregional treatments such as hepatic arterial infusion (HAI) chemotherapy, transarterial chemoembolization (TACE) and selective internal radiation therapy (SIRT), either alone or in combination with systemic chemotherapy.

In this review, we provide further insights on the published literature for the locoregional treatment of liver metastases in patients with mCRC.

HEPATIC INTRA-ARTERIAL CHEMOTHERAPY

There is a compelling argument for HAI chemotherapy in patients with liver-predominant mCRC because of the preferential perfusion of liver metastases (compared with the normal parenchyma) by the hepatic arterial network whereas non tumor liver parenchyma is preferentially perfused by the portal vein. In addition, local intra-arterial treatment circumvents the first-pass effects of the liver, exposing the liver metastases to high concentrations of chemotherapy while at the same time reducing the incidence of unwanted systemic side effects.

The femoral artery is the most common access route. The catheter tip is placed into the hepatic artery at the junction of the gastro-duodenal artery to enable bilobar hepatic infusion. To avoid gastric or duodenal lesions, selective distal embolization is performed of the side branches of the hepatic artery leading to the adjacent organs. Catheter displacement or occlusion remains the most frequently reported complication of HAI chemotherapy use[4].

In the United States, fluorodeoxyuridine (FUDR), a 5-FU derivative, is the most commonly used chemotherapy agent in patients treated with HAI chemotherapy FUDR has the advantage of being rapidly metabolized, with a 94%-99% extraction rate within the liver *via* first-pass metabolism, so enabling high intrahepatic concentrations when given by HAI, but the downside of this HAI chemotherapy is hepato-biliary toxicity which may lead to biliary sclerosis. However, when combined with dexamethasone (Dex), the toxicity of HAI FUDR toxicity is reduced[5]. In Europe, 5-FU is more frequently used which has only a 50% extraction rate in the liver, but systemic blood concentrations of 5-FU are higher than FUDR, making it a more effective against extra-hepatic (micro)metastases. 5-FU is also less hepatotoxic compared with FUDR. Oxaliplatin and irinotecan, the other chemotherapeutic agents active in CRC are also now more commonly used for HAI; although the available data are scant[6-8].

Although its rationale is appealing, the benefit of HAI chemotherapy is unclear because of the lack of large randomized trials. Chemotherapy can be used either as neo-adjuvant therapy for isolated, potentially resectable CRC liver metastases or as adjuvant therapy after complete resection in patients at high-risk of recurrence. In the neo-adjuvant setting, the aim of chemotherapy is to render unresectable liver metastases resectable. It is recognized that classical chemotherapy schedules in combination with monoclonal antibodies can achieve response rates up to 80%[9] but the optimal HAI chemotherapy regimen has yet to be established. In the absence of large phase Ⅲ trials, evidence for the reported improvements in resectability with HAIC in CRC-related inoperable liver metastases is based solely on small phase Ⅱ studies[6,7,10]. In the adjuvant setting after curative hepatectomy, phase Ⅱ studies also provide evidence for lower recurrence rates when HAI chemotherapy is combined with systemic chemotherapy[11,12]; thereby providing proof-of concept but evidence from large phase Ⅲ trials are still needed.

In inoperable liver-only mCRC, HAI chemotherapy might also be used to achieve locoregional control. A study conducted by the Medical Research Council and the European Organization for the Research and Treatment of Cancer, randomly assigned 290 patients with unresectable CRC liver metastases to either HIA with 5-FU and leucovorin (LV) or systemic 5-FU/LV. The study observed no difference between the treatment arms for overall survival (OS) (14.7 mo *vs* 14.8 mo), progression-free survival (PFS) or toxicity[13]. There was, however, a high frequency of catheter-related thrombosis in the HAI chemotherapy arm (36%) resulting a lower proportion of patients receiving the intended six or more chemotherapy cycles compared with systemic chemotherapy (38% *vs* 75%)[13]. Some patients in this trial crossed-over to intravenous chemotherapy, but were still analyzed as HAI in an intention-to-treat manner, thereby making it difficult to draw any definitive conclusions from this trial. In contrast, another study lead by the Cancer and Leukemia Group B (CALGB) randomly assigned 135 patients with inoperable CRC liver metastases CRC liver metastases to either HAI-FUDR/LV/Dex or systemic 5-FU/LV and observed a significant benefit in favor of HAI for both median OS (24.4 mo *vs* 20 mo, $P = 0.0034$) and response rate (47% *vs* 24%; $P = 0.12$)[14]. There was no significant difference in time to progression (TTP) (5.3 mo *vs* 6.8 mo), but the time to hepatic progression was longer in the HAI group (9.8 mo *vs* 7.3 mo), and time to extra-hepatic progression was longer in the systemic group (14.8 mo *vs* 7.7 mo)[14].

More recent studies have also evaluated oxaliplatin and irinotecan for HAI. In a French phase Ⅱ study, 26 patients with inoperable, liver-only mCRC were treated with a combination of HAI-oxaliplatin plus systemic

5FU/LV[6]. Twenty-one patients had been pretreated with one line of 5-FU-based therapy, none had previously received oxaliplatin. The median OS was 27 mo, and response rate reported was 64%, which were comparable to regimens with HAI-FUDR and systemic 5FU-LV. In a second study of HAI-FUDR plus systemic 5FU/LV, the same research group investigated patients who had received more than one line of systemic chemotherapy: either FOLFIRI or FOLFOX or both (percentage of 86%, 77% and 96% respectively). The median OS was 16 mo, response rate 62% (18% down-staged for resection) and median PFS 7 mo. Although the results of these studies are initially promising, the advantage of this approach still needs to be confirmed in a phase Ⅲ study *vs* systemic chemotherapy alone.

TRANSARTERIAL (CHEMO)EMBOLIZATION

TACE, the combination of the injection of a drug and embolic material, has mostly been used in hypervascular tumors such as hepatocellular carcinoma. The use of drug-eluting beads (DEB) enables the controlled release of drug after the beads are trapped in the tumoral circulation. Modern angiographic techniques make it possible to selectively deliver the material to the tumor resulting in minimal release of cytoxic agent(s) into the surrounding tissues.

In mCRC, different chemotherapeutic agents can be used to load the drug eluting beads. A prospective single-center study evaluated 463 patients with chemorefractory, unresectable CRC liver metastases who were treated with TACE at 4-wk intervals[15]. Three TACE regimens were used, either: mitomycin C alone, mitomycin C with gemcitabine, or mitomycin C with irinotecan. Embolization was performed with lipiodol and starch microspheres. A total of 2441 TACE procedures were performed (mean of 5.3 sessions per patient). The median OS in this chemorefractory population was 14 mo, with no significant difference between the different chemotherapy protocols. Disease control was 62.9% [14.7% partial response (PR), 48.3% stable disease (SD)][15]. Another German study also evaluated retrospectively the same chemotherapy schedules in 564 patients in either the neoadjuvant or palliative setting[16]. Like the previous study, no significant differences in OS were observed between the chemotherapy regimens and response rates were also in the same range (16.7% PR, 48.2% SD). Finally disease control rates of 43% were found in another retrospective analysis of 121 patients in the chemorefractory setting with TACE with cisplatin, doxorubicine and mitomycin C[17].

To date, the published experience with chemoembolization using DEB-irinotecan (DEBIRI) has mostly been performed in liver-predominant CRC. DEBIRI was evaluated in a phase Ⅱ study in 82 chemorefractory liver-predominant CRC patients, resulting in very high response rates of 78% at 3 mo post-treatment and a mean PFS of 8 mo[18]. In another study response rates with DEBIRI were 66% and 75% at 6 and 12 mo, respectively and PFS was 11 mo[19]. In both these studies of DEBIRI, the most common adverse event was post-embolization syndrome reported as abdominal pain, nausea and vomiting[18,19]. Usually symptoms were mild and transient; rarely has there been any reports of liver toxicity associated with liver abscess, liver failure or pancreatitis and only when more extensive embolization was performed.

Pharmacokinetic studies evaluating DEBIRI show that plasma levels of irinotecan and its active agent SN-38 were almost undetectable 24 h after administration[20]. Only one small randomized phase Ⅲ study has been performed comparing DEBIRI with systemic chemotherapy (FOLFIRI)[21] in 74 patients with unresectable mCRC without extrahepatic disease, who were refractory to at least two lines of chemotherapy. A survival advantage with DEBIRI was suggested (median OS of 22 mo *vs* 15 mo with FOLFIRI; $P = 0.031$). The DEBIRI group also had a significantly higher objective response rate (69% *vs* 20%)[21].

In conclusion, several studies suggest that TACE can achieve disease stabilization in 40%-60% of patients, but whether this leads to a prolongation of OS relative to systemic chemotherapy is uncertain, since almost no randomized-controlled trials have been performed. Therefore larger randomized trials are needed for comparison with standard intravenous chemotherapy.

SELECTIVE INTERNAL RADIATION THERAPY

Selective internal radiation therapy (SIRT) (or radioembolization) is a form of intra-arterial brachytherapy using resin-based microspheres impregnated with ^{90}Yttrium (^{90}Y) as the radiation source. SIRT using ^{90}Y resin microspheres was approved by the FDA in 2002. ^{90}Y-resin microspheres are delivered into the tumor-feeding arteries of the hepatic arterial circulation and embed permanently in the pre-capillary arterioles of liver tumors where they deliver very high doses of localized radiation (and so minimizing the damage to the healthy liver parenchyma). In general, SIRT is safe and well tolerated with fewer side effects and milder post-embolization syndrome than with observed TACE. However, SIRT is more complex to administer and therefore its use is often restricted to specialized centers. Specific complications are rare, and include gastroduodenal ulceration, pancreatitis, cholecystitis, abscess formation and radiation-induced liver or lung disease.

Approval was based on one randomized controlled trial in which 74 patients with liver isolated CRC metastases were assigned to either HAI-FUDR alone or HAI-FUDR in conjunction with a single administration of SIRT[22]. The study found that compared with HAI, the combination of SIRT and FUDR-HAI led to a significantly better complete response rates (44% *vs* 18%) and

prolonged the median time to progression (16 mo *vs* 10 mo).

Radioembolization has also been compared to intravenous chemotherapy in two prospective randomized-controlled trials[23,24]. The first RCT was a small phase Ⅱ study conducted by Van Hazel *et al*[23] in 21 patients with previously untreated liver-predominant mCRC. Systemic 5-FU/LV preceded by a single SIRT procedure significantly prolonged median OS (29.4 mo *vs* 12.8 mo) as well as time to progression (TTP) (18.6 mo *vs* 3.6 mo) compared with 5FU/LV alone. More recently, a phase Ⅲ study assigned 44 patients with chemotherapy refractory liver-limited metastatic CRC to treatment with 5-FU monotherapy or SIRT during the first cycle of chemotherapy followed by 5-FU monotherapy, until hepatic progression[24]. Cross-over to SIRT was permitted after progression in the 5-FU monotherapy arm. Once again the combination of SIRT and systemic chemotherapy significantly improved TTP (4.5 mo *vs* 2.1 mo), but without any difference in OS between the two arms (10.0 mo *vs* 7.3 mo) primarily due to the cross-over of some patients from 5-FU monotherapy to the SIRT arm following progression studies in which SIRT is added to more modern systemic chemotherapy such as FOLFOX and bevacizumab (SIRFLOX and FOXFIRE study) are now ongoing with initial results from SIRFLOX likely to be presented in 2015.

To date most of the published studies with SIRT are in chemorefractory liver predominant mCRC. A systematic review of twenty studies comprising 979 patients treated with ^{90}Y-resin microspheres revealed a median time to intrahepatic progression of 9 mo and OS of 12 mo[25]. Although this review has several shortcomings such as: the inclusion of multiple observational studies, studies with small sample sizes and the heterogeneity of patients, it still demonstrated that SIRT was safe and an effective treatment for unresectable, chemorefractory mCRC.

CONCLUSION

The management of chemorefractory liver metastases from mCRC is a major challenge and effective treatment options are urgently needed. Both HAI chemotherapy as well as TACE and SIRT appear to be effective in this setting when used in centers with expertise in the technical aspects of these local treatments. However, adequately powered prospective phase Ⅲ studies are still needed. Landmark studies such as SIRFLOX and FOXFIRE with SIRT are expected to help better define the role of these treatments earlier in the course of liver-predominant mCRC.

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Hereditary diffuse gastric cancer: What the clinician should know

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Abstract

Hereditary diffuse gastric cancer (HDGC) is an inherited autosomal dominant syndrome with a penetrance of up to 80% affecting diverse geographic populations. While it has been shown to be caused mainly by germline alterations in the E-cadherin gene (*CDH1*), problematically, the genetic diagnosis remains unknown in up to 60% of patients. Given the important knowledge gaps regarding the syndrome, asymptomatic carriers of *CDH1* mutations are advised for a prophylactic total gastrectomy. Intensive annual endoscopic surveillance is the alternative for carriers who decline gastrectomy. As HDGCs have a prolonged indolent phase, this provides a window of opportunity for surveillance and treatment. Recent findings of other gene defects in *CTNNA1* and *MAP3K6*, as well as further characterization of *CDH1* mutations and their pathogenicity will change the way HDGC patients are counselled for screening, surveillance and treatment. This review will bring the reader up to date with these changes and discuss future directions for research; namely more accurate risk stratification and surveillance methods to improve clinical care of HDGC patients.

Key words: Hereditary diffuse gastric cancer; *CDH1*; *CTNNA1*; *MAP3K6*; Gastrectomy

Core tip: While the incidence of hereditary diffuse gastric cancer remains low, it is an important clinical entity to recognize due to its high pathogenicity and penetrance. The International Gastric Cancer Linkage Consortium has outlined *CDH1* testing criteria and developed clinical utility gene cards to help clinicians manage such patients. Significant progress has been made in recent years and in future, testing of other genes is likely for *CDH1*-negative families. The mainstay of treatment for asymptomatic carriers of *CDH1* pathogenic mutations remains prophylactic total gastrectomy. Future research should focus on better risk stratification and surveillance methods.

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INTRODUCTION

Gastric cancer (GC) is currently the fourth most common cancer and the second leading cause of cancer associated death worldwide[1]. Based on the Lauren classification, at least two main histological types of GC have been identified: intestinal and diffuse[2]. Both histological types have different clinical features and molecular mechanisms[3-8]. Hereditary GCs account for only 1%-3% of GC cases[9], but are important for clinicians to identify as potentially curative interventions are available. One well-characterized syndrome is Hereditary diffuse gastric cancer (HDGC), which was attributed to germline mutations of the E-cadherin gene (*CDH1*) in 1998[10]. The International Gastric Cancer Linkage Consortium (IGCLC) has since established the latest set of clinical criteria in 2010 (listed in Table 1) to guide genetic screening[11].

Only about 40% of probands meeting the 2010 criteria carry *CDH1* germline alterations (often point or small frameshift mutations)[9,12]. Of the remaining 60%, a small percentage is due to *CDH1* deletions not detected by conventional DNA sequencing. More intriguingly, mutations in other genes like *CTNNA1*[13], *MAP3K6*[14], *INSR*, *FBXO24* and *DOT1L*[15] are starting to be identified. However, pathogenicity and penetrance of many newer mutations remain unanswered, creating management dilemmas. These non-*CDH1* mutations published thus far have been summarized in Table 2. Most studies are small and will require validation in consortium-led efforts for us to better understand the longitudinal impact.

CLINICAL HISTORY

Presentation

Similar to other gastric carcinomas, patients with HDGC are often asymptomatic in the early stages and tend to present late with symptoms such as weight loss, abdominal pain, nausea, anorexia, dysphagia, melaena and early satiety. The median age at diagnosis is 38 years, with the range varying greatly from 14-82 years[10,16].

Majority of HDGCs are inherited in an autosomal dominant pattern. It exhibits high penetrance and invasive disease often manifests before age 40. Therefore, one should have a high clinical suspicion when a family history reveals two or more cases of gastric cancer in first or second degree relatives, especially with one case diagnosed before age 50. The lifetime cumulative risk for diffuse GC reaches > 80% in men and women by age 80 years[11].

Other features seen in HDGC familes

There is an association of HDGC with lobular breast cancer (LBC) and it can be the presentating pathology[17]. Data based on 11 HDGC families, estimated the cumulative risk for LBC for female *CDH1* mutation carriers to be 39% (95%CI: 12%-84%) by 80 years of age[18]. Thus, personal or family history of multiple LBCs at a young age should also prompt CDH1 screening even if there is no HDGC. There have also been case reports of colorectal, prostate and ovarian carcinomas in HDGC families although these are rare and of uncertain significance[19-22]. Interestingly, cleft-lip, with or without cleft-palate malformations have been reported in several HDGC families, some of whom have specific *CDH1* splice site mutations[23,24].

Table 1 Clinical criteria for *CDH1* genetic testing (adapted from Fitzgerald *et al*[11])

⩾ 2 diffuse GC cases in 1st or 2nd degree relatives with one < 50 yr of age
⩾ 3 diffuse GC cases in 1st or 2nd degree relatives independent of age
Diffuse GC < 40 yr of age, without a family history
Personal or family history of diffuse GC and lobular breast cancer with one < 50 yr of age

GC: Gastric cancer.

Other relevant hereditary cancer syndromes

It should be remembered that GC can develop in the setting of other hereditary cancer syndromes aside from HDGC. One example would be Lynch syndrome which more often presents with intestinal-type gastric cancers and also has a high lifetime risk of colorectal and endometrial cancer. Other examples include Familial adenomatous polyposis, Li-Fraumeni syndrome, Peutz-Jegher's syndrome (PJS) and Juvenile Polyposis Syndrome (JPS) (Table 3). The lifetime risk of GC in these syndromes varies considerably but is generally lower than that in HDGC.

PATHOPHYSIOLOGY

Genetic susceptibility

E-cadherin is a cell adhesion protein that is required for development, cell differentiation and maintenance of epithelial architecture[6]. Since the E-cadherin gene *CDH1* was identified as a genetic basis for HDGC in 1998, more than 120 *CDH1* germline mutations have been published[25]. The most common germline alterations are small frameshifts, splice-site and nonsense mutations[9]. Of note, only two *de novo* mutations have been reported to date[26,27].

However, newer HDGC-susceptibility genes have been identified (Table 2). In 2012, an alpha-E-catenin (*CTNNA1)* germline truncating mutation was been found in a large Dutch HDGC pedigree[14] although the evidence presented was not definitive given a number of carriers remained cancer-free and other studies have failed to replicate findings[28]. At time of writing, *MAP3K6*[15], *INSR*, *FBXO24* and *DOT1L*[16] have also identified as candidate genes although they remain reports from single families. The insulin receptor (*INSR)* gene mutation is of special interest given insulin signaling has been reported to affect tumour cell invasion capability by modulating E-cadherin

Table 2 Summary of non-*CDH1* germline mutations in hereditary diffuse gastric cancer

Gene	Mutation	Location	Mutation type	Ethnicity	Ref.	Study type	Frequency	Remarks
CTNNA1	c.76delGA	Chr 5: 138117693	Nonsense	No data	[13]	Family study	1/1 family	Results in a framshift after Arg27 (p.Arg27Thr.fs*17)
MAP3K6	c.598G>T	Chr 1: 27690792	Missense	Canada	[14]	Family study and case series	1/1 family 1/115 cases	Likely pathogenic
MAP3K6	c.620T>G	Chr 1: 27690770	Missense	No data	[14]		No data	
MAP3K6	c.2837C>T	Chr 1: 27684750	Silent	No data	[14]		No data	Single nucleotide variant also in Canadian family, likely pathogenic
MAP3K6	c.2872C>A	Chr 1: 27684715	Missense	No data	[14]		No data	
MAP3K6	c.2544delC	Chr 1: 27685238 - 27685239	Nonsense	Portugese	[14]		1/115 cases	
INSR	c.3937 G>A	Chr 19: 7117279	Missense	Finland	[15]	Family study	1/1 family	
FBXO24	c.242G>C	Chr 7: 100187900	Missense	Finland	[15]		1/1 family	
DOT1L	c.3437C>T	Chr 19: 2223326	Missense	Finland	[15]		1/1 family	

Table 3 Comparison of hereditary cancer syndromes

Condition	Genetic pathology	Lifetime risk of gastric cancer	Histological subtype	Other clinical features
Hereditary diffuse gastric cancer	*CDH1* germline and other gene mutations	80%	Diffuse	Association with lobular breast cancer and cleft-lip malformations
Lynch syndrome	Mutations in mismatch repair genes	4.8% in *MLH1* carrier 9% in *MLH2* carrier[58]	Mainly intestinal-type	Lifetime risk of colon cancer 31%-38%, endometrial cancer 34% and ovarian cancer 20%[59]
Familial adenomatous polyposis	*APC* germline mutations	Population risk[60]	No data	Malignant extraintestinal tumours rare < 3% (thyroid, pancreas, medulloblastoma)[61]
Li-Fraumeni syndrome	*TP53* mutations	[1]4.9%[62]	No predominant subtype	Associated with wide range of early-onset cancers. Includes haematological and solid organ cancers: sarcomas, breast, brain, adrenal and lung cancers
Peutz-Jegher's syndrome	*STK11* mutations	29%[63]	No data	Characteristic mucocutaneous pigmentation commonly around mouth and nose High cumulative lifetime risk of any cancer (85%), most commonly colorectal (50%)[58]
Juvenile polyposis syndrome	*SMAD4* or *BMPR1A* mutations	[1]21%[64]	No data	Also at increased

[1]Frequency based on cross-sectional sample rather than lifetime risk from cohort study.

glycosylation[29] and is known to play a role in a variety of cancers[30]. There has also been a reported possibility of an association of early onset gastric cancer with *IL12RB1* mutation carriers[31] although this is mainly of the intestinal-type.

Somatic events

Guilford *et al*[10] has suggested HDGC develops from multiple foci of signet ring cell carcinomas (SRCC) in mutation carriers before 30 years of age. These SRCC, which have been termed "early HDGC"[32], develop after loss of the second *CDH1* allele *via* a 2nd-hit mechanism[33-36]. The same patient may present with distinct 2nd hit mechanisms in different lesions. Promoter methylation is the most common 2nd-hit mechanism in primary HDGC tumours although loss of heterozygosity was found to be the most prevalent in lymph node metastases[37].

Interestingly, other studies are starting to look at oncogenic pathways involved in metastatic progression in HDGC and have found one such candidate driver in a transforming growth factor beta receptor 2 loss-of-function mutation[38].

MANAGEMENT

Diagnosis

The identification of germline mutations in families fulfilling the criteria for HDGC relies on information from pathology reports from at least one proband. A report by Hebbard *et al*[39] on 23 patients who underwent prophylactic total gastrectomy showed 21 of them had evidence of diffuse/signet-ring carcinoma on final standardized pathological evaluation which was not picked up by preoperative endoscopic screening. Thus, for adequate pathological sampling, IGCLC recommends targeting any endoscopically visible lesions as well as random sampling of six biopsies for each of the following anatomical zones: antrum, transitional zone, body, fundus, cardia. This would give a minimum of 30 biopsies[11].

Treatment

Probands often present with advanced stage GC and

treatment consists of palliative chemotherapy (often taxanes, platinum agents or irinotecan), targeted radiotherapy and bypass surgery. While research looks into E-cadherin pathway regulators to increase chemosensitivity to epidermal growth factor receptor inhibitors and cytotoxics[40-42], there are currently no specific targeted therapies for diffuse GCs although there is an ongoing Phase I clinical trial studying everolimus in combination with chemotherapy[43].

As personalized therapy becomes increasingly prominent in cancer care, management of patients with HDGC should involve a multidisciplinary team of geneticists, surgeons and pathologists to address the following aspects of care: (1) genetic counselling and screening for both *CDH1* positive and negative patients. This should include a three-generation family pedigree, analysis of *CDH1*/other candidate gene mutation and translation into lifetime risks of diffuse GC and LBC[11]; and (2) discussion of prophylactic gastrectomy *vs* surveillance.

Guidelines for the clinical management of *CDH1* mutation carriers have been reviewed by the IGCLC (2010) and are outlined in clinical utility cards for HDGC[44]. Figure 1 summarises the management algorithm.

CDH1 missense mutation carriers

It is suggested that these individuals go on to have their mutations assessed for pathogenicity *via* functional *in-vitro* testing (aggregation and invasion assays) and *in-silico* models that have been developed[45]. These techniques have found a significant number of pathogenic missense variants and should be carried out by molecular diagnostic laboratories with appropriate expertise.

CDH1-negative individuals

Mutation screening in the research setting of HDGC families without *CDH1* mutations can be considered. Approaches needed would include high density single-nucleotide polymorphism (SNP) genotyping, non-parametric and parametric linkage analysis, whole exome sequencing as well as aforementioned pathogenicity assessments[14,15].

Surveillance

There is currently no reliable screening test for early diagnosis of diffuse GCs in mutation carriers. While IGCLC guidelines suggest annual endoscopic surveillance in specific settings, it should be known that direct visualization with endoscopy tends to detect lesions late in the disease process[46] and multiple random endoscopic samples often returns false negatives[39]. Other screening methods like chromoendoscopy and positron emission tomography have not been deemed to be consistently effective[47,48].

Prophylactic gastrectomy

Due to the lack of reliably sensitive surveillance methods, prophylactic total gastrectomy should be considered in the early 20s and is usually advised before age 40 for those carrying *CDH1* mutations. Some authors suggest consideration of gastrectomies in *CDH1* mutation carriers at an age 5 years younger than the youngest family member who developed gastric cancer[49].

There are currently no recommendations with regards to prophylactic gastrectomy in *CDH1*-negative individuals. Prospective studies evaluating prophylactic gastrectomy in HDGC have offered the surgery only to *CDH1* positive individuals[50], while a systematic retrospective review of 28 articles on prophylactic gastrectomy found a small sample of 11 *CDH1*-negative individuals who had undergone the gastrectomy before *CDH1* testing all had negative histopathology results for cancer[51].

Patients may refuse or decide to postpone the procedure due to young age, fertility concerns or fear of surgical complications. Fortunately, there have been reports of successful pregnancies post-prophylactic gastrectomy[52] and the youngest known carrier to date to undergo gastrectomy was 16 years of age[53].

ONGOING CHALLENGES

Risk stratification for CDH1-negative individuals

A significant proportion of HDGC families are likely to be *CDH1* negative. Further study to identify other genetic causes is needed before their risk and therefore management measures such as prophylactic gastrectomy can be assessed. As more cases of HDGC are identified, two lines of study are especially valuable. First, pathogenicity and penetrance of new germline mutations need to be documented to improve genetic counselling and decision-making. This is especially so for missense mutations. Second, prophylactic gastrectomy specimens provide material to identify molecular mechanisms that may predict progression from SRCC lesions to HDGC. In particular, elucidating epigenetic mechanisms, such as analysis of hypermethylation of cell cycle or DNA repair genes[54-57], may provide useful insights into possible environmental or pharmaceutical chemoprevention strategies.

Surveillance methods

Better surveillance methods could reduce morbidity by picking up target lesions earlier such that they are amenable to endoscopic therapies. While detection of diffuse GCs has proven difficult and surveillance frequency remains challenging, one paradigm to guide further research would be to assume that microfoci of SRCC will be present in all adult mutation carriers. Thus, rather than trying to detect all microfoci, the aim of surveillance should be geared towards detecting "high risk" SRCC. While this will require further elucidation of mechanisms of carcinogensis, it is plausible to imagine current surveillance methods, combined with genetic data, as a reliable alternative to prophylactic total

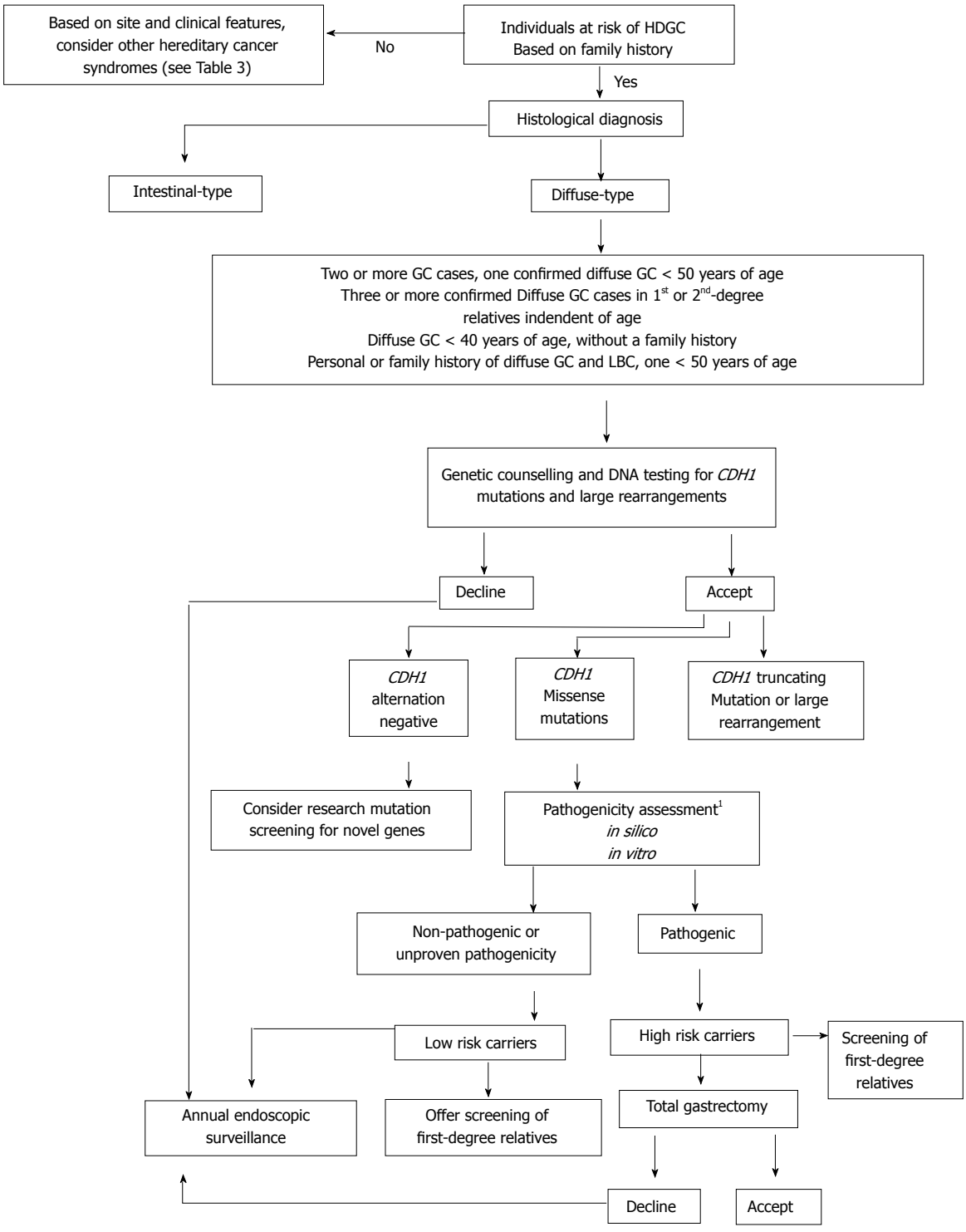

Figure 1 Clinical management of individuals suspected to have hereditary diffuse gastric cancer. Adapted from Pinheiro *et al*[9]. [1]Analyses recommended include: mutation frequency in healthy control population, co-segregation of mutation within pedigree, recurrence of mutation in independent families, in-silico predictions and *in vitro* functional assays[45,65-68].

gastrectomy.

CONCLUSION

While the incidence of HDGC remains low, it is an important clinical entity to recognize because of its high pathogenicity and penetrance. The IGCLC 2010 has outlined *CDH1* testing criteria and developed clinical utility gene cards to help clinicians manage such patients. Significant progress has been made in recent years and in future, testing of other genes is likely for *CDH1*-negative families. The mainstay of treatment for asymptomatic carriers of *CDH1* pathogenic mutations remains prophylactic total gastrectomy. However, it is hoped future research will lead to better risk stratification and surveillance methods to improve clinical

care for patients in terms of screening, prevention and treatment.

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ORIGINAL ARTICLE

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

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[1]. Its annual incidence is increasing worldwide, ranging between 3% and 9% in patients with liver cirrhosis[2]. In Egypt, HCC was reported to develop in about 5% of patients with chronic liver disease[3].

Worldwide, hepatitis B virus (HBV) is considered the major risk factor for the progression of liver cirrhosis to HCC[4]. 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[5]. Integration of HBV DNA into the host genome is considered to be the initiating event for HBV-induced carcinogenesis[6]. In this context, the HBx protein may inactivate the *p53* tumor suppressor gene, resulting in HCC development[7]. While the prevalence of HBV infection in Egypt has been decreasing during the last two decades[3], the prevalence of hepatitis C virus (HCV) infection has increased to an estimated 14% in the general population[8] 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[9]. In general, promotion of cirrhosis development seems to be the common pathway by which several risk factors exert their carcinogenic effect[9].

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[7].

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[10]. Alpha-fetoprotein (AFP) levels and imaging techniques such as ultrasonography are the most common screening modalities used by physicians to detect early HCC[11]. The majority of HCCs are diagnosed in advanced stages, which carries a poor prognosis[12]. Recent curative therapeutic regimens and liver transplantation for early stage HCC encourage physicians to screen high-risk patients[13].

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 allover 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

	n (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% 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).

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

	Age (yr)				*P* value
	< 45		⩾ 45		
	n	%	*n*	%	
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	787	30	71	
Risk factors for liver disease progression					
Age	49	448	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[a]
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	302	19	45	
GI or variceal bleeding	29	25	5	12	

[a]$P < 0.05$ considered statistically significant. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

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[1]		Specialty B[2]		
	n	%	*n*	%	
People who should undergo HCC surveillance					
Chronic hepatitis B, C and liver cirrhosis	117	90	16	67	0.006[a]
Positive family history	51	39	3	12	0.112
Everyone	15	11	7	29	0.023[a]
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[a]
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	

[1]Specialty A (Tropical medicine, Internal medicine, Gastroenterology); [2]Specialty B (General practitioner, Radiology, General surgery). [a]$P < 0.05$ considered statistically significant. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

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[a]
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[a]
Obesity, DM	8	32	19	32	28	41	0.525
HCV genotype	10	40	29	48	47	68	0.017[a]
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	

[a]$P < 0.05$ 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 practioners. 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 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				*P* value
	University		MOH		
	n	%	*n*	%	
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[a]
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[a]
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[a]
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	

[a]*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[a]
Physical examination	2	2	1	3	
Alpha fetoprotein	27	24	9	21	
Ultrasound	65	58	32	76	
CT	18	16	0	0	
2nd 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	
3rd 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[a]
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	

[a]*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	
2nd 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	
3rd 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[a]
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	

[a]*P* < 0.05 considered statistically significant. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CT: Computer tomography.

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

	Highest qualification						*P* value
	MBBCH		Msc/ diploma		MD		
	n	%	*n*	%	*n*	%	
Most important screening for HCC							0.023[a]
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	
2nd 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	
3rd most important screening for HCC							0.004[a]
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[a]
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[a]
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	

[a]*P* < 0.05 considered statistically significant. HCC: Hepatocellular carcinoma; 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 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				*P* value
	University		MOH		
	n	%	*n*	%	
Most important screening for HCC					0.000[a]
0.000[a]	3	3	0	0	
Alpha fetoprotein	19	20	17	29	
Ultrasound	70	74	27	46	
CT	3	3	15	25	
2nd 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	
3rd most important screening for HCC					0.001[a]
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[a]
Yes	82	86	41	69	
No	13	14	18	31	
Guidelines in management of HCC					0.000[a]
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	

[a]*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 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 ($P < 0.05$).

Table 10 Relation between physicians' age and hepatocellular carcinoma screening

	Age (yr)				*P* value
	< 45		⩾ 45		
	n	%	*n*	%	
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[a]	81	

[a]*P* < 0.05 considered statistically significant. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; SVR: Sustained virological response.

There is no significant difference with respect to other aspects, such as the 3rd 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				*P* value
	Specialty A[1]		Specialty B[2]		
	n	%	*n*	%	
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[a]
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	

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

Table 12 Hepatocellular carcinoma screening depending on highest medical qualification

	Highest qualification						*P* value
	MBBCH		Msc/ diploma		MD		
	n	%	*n*	%	*n*	%	
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[a]
Yes	15	60	35	58	56	81	
No	10	40	25	42	13	19	
No. of incidental HCCs/month							0.000[a]
0	11	44	24	40	6	9	
1 or more	14	56	36	60	63	91	
No. of HCC patients							0.000[a]
0	9	36	29	48	3	4	
1 or more	16	64	31	52	66	96	

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

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, 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[8]. 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				*P* value
	University hospital		MOH		
	n	%	*n*	%	
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[a]
0	10	10	31	53	
1 or more	85	90	28	47	
No. of HCCs/month					0.000[a]
0	9	10	32	54	
1 or more	86	90	27	46	

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

cirrhosis[14,15].

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[16].

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[17]. In Egypt, the increasing HCC incidence is due to the high prevalence of HCV infection[10], estimated to be around 14% in the general population[8].

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[18], 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[18].

In the United States there was no significant difference of opinion based on the physicians' age, specialty, highest qualification or hospital setting. The questionnaire 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*[19] 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*[20], 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%[8] that is responsible for to the increasing incidence of HCCs in Egypt[10].

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*[21], 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[22].

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[8].

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$[23].

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[24].

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*[25].

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[5].

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 my 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[26]. A more recent study by Singal *et al*[27] 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[16].

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.

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