Evidence-Based Approach to Cholangiocarcinoma: A Systematic Review of the Current Literature

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Cholangiocarcinomas (CC) are relatively rare tumors, although their incidence is increasing worldwide.[1] Several advances in the diagnosis, therapy, and palliation for patients affected by CC have occurred during the last decades. The aim of this article is to provide a systematic review of the most recent literature on CC.

Evidence acquisition

We sought studies reporting at least one of the following aspects of CC: epidemiology, diagnosis, therapy, and palliation. Preference was given to randomized controlled trials (RCT) and prospective observational studies. For each of these topics we searched Medline, Ovid Medline In-Process, Cochrane Database of Systematic Reviews, Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, EMBASE, PubMed, National Library of Medicine Gateway by established systematic review methods (Jadad Scale for RCT controlled studies, Downs and Black checklist for observational studies.[2-4] We limited our search to English-language articles published from January 1990 to May 15, 2008. Our review did not include the management of gallbladder cancer. To identify all potential articles, we searched medical subject headings reported in (Table 1). Two authors (MA and MM) independently performed the selection of articles based on the content of titles and abstracts. When in doubt, each article was reviewed in its entirety. The decision to include articles in this review was reached by consensus.

Epidemiology

In the United States, the incidence of CC is approximately 5,000 new patients/year[5] accounting for almost 3% of all gastrointestinal tumors.[6]

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Intrahepatic CC

Estimated age-adjusted incidence of intrahepatic CC (ICC) in the United States has increased by 165% in 30 years (from 0.32 per 100,000 in 1975 to 1979 to 0.85 per 100,000 in 1995 to 1999),[7] accounting for 10% to 15% of all primary hepatic cancers.[8] Similarly, age-adjusted mortality rate increased from 0.07 per 100,000 in 1973 to 0.69 per 100,000 in 1997, with average age at presentation in the 7th decade of life and male-to-female ratio of 1.5.[9]

Extrahepatic CC

In the United States, age-adjusted incidence of extrahepatic CC (ECC) is 1.2 per 100,000 in men and 0.8 per 100,000 in women[10] and has decreased by 14% compared with two decades earlier. ECC usually present in the 7th decade of life.

Classification

Anatomic classification

ICC arise within the liver and ECC within the hepatoduodenal ligament. ECC are divided into hilar or distal tumors. Hilar CC (KCC) were first described by Klatskin in 1965 and 10 years later, Bismuth proposed a clinical classification of these tumors by anatomic location (Fig. 1).[11] Approximately 60 to 70% of CC are located in the hylum, 20 to 30% are ECC and 5 to 10% are ICC.

Pathologic classification

More than 90% of CC are well to moderately differentiated adenocarcinomas,[12] that present as solid masses or infiltrate surrounding tissues, grow intraductally, or have mixed characteristics.

Risk factors for CC

Only the minority of patients have known risk factors for CC (Table 2).[13]

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is the most important predisposing factor in Western countries.[14,15] Cumulative annual risk in PSC patients is 1.5% per year after the development of jaundice.[16] Predictive factors of CC in PSC patients are sudden progressive jaundice, unintentional

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Abbreviations and Acronyms

CC = cholangiocarcinoma
ECC = extrahepatic cholangiocarcinoma
ICC = intrahepatic cholangiocarcinoma
KCC = hilar cholangiocarcinoma
OCT = optical coherence tomography
PDT = photodynamic therapy
PSC = primary sclerosing cholangitis
RCT = randomized controlled trial
US = ultrasonography

weight loss, marked dilation of bile ducts proximal to biliary strictures, serum level of Ca 19-9 tumor marker >100 U/mL, and presence of cellular dysplasia on cytologic specimens.[17]

Parasitic infections

Liver flukes (Opisthorchis Viverrini and Clonorchis Sinensis) have been associated with an increased risk of CC in Southeast Asia,[18] where the adjusted prevalence for CC by age and gender is as high as 14%.[19]

Intrahepatic biliary stones (hepatolithiasis)

Oriental cholangiohepatitis has a prevalence of 20% in Southeast Asia[20] and ICC developed in almost 10% of affected patients.[21]

Congenital biliary cystic diseases

The incidence of CC is between 10% and 20% if the cyst is not excised by the age of 20 years.[22] The mechanism of malignant transformation is not completely understood,[23] because in some patients CC occur years after resection.[24]

Liver cirrhosis and viral infections

Risk of CC in cirrhotic patients is 10-fold higher than the general population (0.7% versus 10.7%).[25] Among patients with CC in the United States, the prevalence of hepatitis C virus infection was found to be four times higher

Table 1. Summary of the Terms Used Singly or in Combination for Evidence Acquisition

Primary MeSH terms	Secondary MeSH terms (epidemiology, diagnosis)	Secondary MeSH terms (treatment, palliation)
Cholangiocarcinoma(s)	Epidemiology	Hepatectomy
Adenocarcinoma(s)	Classification	Resection
Carcinoma(s)	Diagnosis	Therapeutic(s)
Bile duct neoplasm(s)	Differential diagnosis	Treatment outcome(s)
Biliary tract neoplasm(s)	Early diagnosis	Operation
Common bile duct	Risk factor(s)	Transplantation
Neoplasm(s) liver	Diagnostic Imaging	Biliary tract surgical
Neoplasm(s)	MRI	Procedures liver
Bile Duct(s)	Endosonography	Transplantation
Common bile duct	Ultrasonography	Organ transplantation
Intrahepatic bile duct(s)	Emission CT	Clinical trial
Extrahepatic bile duct(s)	Radionuclide imaging	Controlled clinical trial(s)
Biliary tract disease(s)	PET	Randomized controlled trial(s)
Bile duct disease(s)	X-ray CT	Clinical trial (phase I)
	Biopsy (needle)	Clinical trial (phase II)
	Biopsy (fine needle)	Clinical trial (phase III)
	Cytology	Clinical trial (phase IV)
	Cytodiagnosis	Drug therapy
	Tumor markers (biological)	Chemotherapy
	Antigen(s)	Adjuvant antineoplastic agent(s) combined
	Carcinoembryonic antigen	Modality therapy
	Ca 19-9 antigen	Antineoplastic combined chemotherapy protocols
	Ca 125 antigen	Neoadjuvant therapy
	ERCP	Radiotherapy adjuvant embolization
	In situ hybridization	Portal vein embolization
	Fluorescence in situ	Drainage
	Hybridization nucleic acid hybridization	Cholestasis
	Computed assisted image processing	Obstructive jaundice

MeSH, medical subject headings.