Recent Trends in Diagnosis and Treatment of Cholangiocarcinoma

An Essay Review
Submitted for the Partial Fulfillment of Master Degree in General Surgery

Submitted By

Mourad Mohammad Moataz Ali Abdul-Khaliq

(M.B., Ch.B. - Ain Shams University)

Under the Supervision of

Prof. Dr.

Hisham Abdel-Raouf Al-Akkad

Professor of General Surgery

Faculty of Medicine - Ain Shams University

Dr.

Mohamed Ibrahim Hassan

Lecturer of General Surgery

Faculty of Medicine - Ain Shams University

Ain-Shams University

2015

In the Name of Allāh, the Most Gracious, the Most Merciful

Acknowledgement

Praise is to ***Allah***, the one and the only, the most merciful, the most generous, for aiding me and allowing me to fulfill this quest; Peace and prayers are upon ***Mohammad,*** the prophet of mercy upon Mankind.

A cornerstone of acknowledgement, due gratitude and sincere apprecation to:

Prof. Dr. *Hisham A. Al-Akkad*

Professor of general surgery, Ain Shams University.

for his precious scientific supervision, kind assistance, patient guidance and great mentoring throughout this review.

'Sir, I can find no words of gratitude to express my debt and appreciation of your kind and precious support.'

I am very much indebted to:

Dr. *Mohamed Ibrahim Hassan*

Lecturer of general surgery, Ain Shams University.

who made this review possible throughout his elder-brotherly attitude, kind supervision, precious advices; and for his time, endless effort and support.

'Sir, no words of thankfulness can express my gratitude and appreciation of your generous help and kind support.'

*A rapid whisper of thankfulness, to my ever-supporting **wife** and **Parents**.*

Introduction:

The hallmarks of choosing this topic to be reviewed are the characters of that condition as being a sufficiently serious one, with a rather common existence on basis of classification of hepatic malignancies, meanwhile a modest delay in the diagnosis and initialization of treatment, will be reflected instantly in the prognosis of a given case.

Cholangiocarcinoma is difficult to be diagnosed in part because of its relative rarity, and because it is clinically silent until it becomes an advanced disease with obstructive symptoms **(Olnes & Erlich, 2004).**

Understanding of carcinogenesis and metastasis of cholangiocarcinoma at the molecular level will provide tools for better prevention, diagnosis and treatment. Cholangiocarcinoma is the term applied to the primary malignant neoplasm arising from the biliary tract (it was first described by Durand - Fardel in 1840), they are categorized according to its site into intra-hepatic, hilar and distal bile duct cancers, it is a slow growing tumor but highly metastatic with a poor prognosis **(Praviz and Pearce, 2004).**

The incidence of bile duct cancer in autopsy series ranges from 0.01% to 0.46% **(Praviz and Pearce, 2004).**

The intra-hepatic variety is the second most common primary hepatic malignancy after hepatocellular carcinoma **(Chari et al, 2009).**

Cholangiocarcinoma accounts for 3% of GI malignancies. Usually presents between ages 50-70 but can present earlier in patients with primary sclerosing cholangitis (PSC), ulcerative colitis and in patients with

choledochal cysts, slightly higher incidence in men. Recently, many advances have been made in understanding the causes and pathogenesis as well as in diagnosing and treating cases of cholangiocarcinoma & bile duct cancers **(Jones et al, 2000**).

Over the past few decades, remarkable advances in imaging technology have been made that allow more accurate diagnosis of biliary tract diseases and better planning of surgical procedures and other interventions aimed at managing these conditions. **(Taylor et al, 2006).**

Ultrasound or computed tomography scans usually detect dilated intrahepatic bile ducts. Transhepatic cholangiography or endoscopic retrograde cholangiopancreatography (ERCP) clearly detect the lesion and both are indicated in most cases, transhepatic cholangiography is of greater value. Recently, magnetic resonance imaging with cholangiography (MRCP) takes the upper hand as the most informative noninvasive modality for diagnosis of bile duct tumors **(Pitt et al, 2005).**

The clinical features of cholangiocarcinoma depend on the location of the tumor; Approximately 60%-70% of cholangiocarcinomas occur at the hepatic duct bifurcation, and the remainder occurs in the distal common bile duct (20%-30%) or within the liver (5%-15%).

Patients with extrahepatic tumors usually present with painless jaundice from biliary obstruction, Common complaints include pruritus (66%), abdominal pain (30%-50%), weight loss (30%-50%), and fever (up to 20%).Other symptoms related to the biliary obstruction include clay-colored stools and dark urine. Patients with intrahepatic

cholangiocarcinomas rarely present with jaundice; most often they present with dull right upper quadrant discomfort and weight loss.

Surgery is the only curative treatment for cholangiocarcinoma. However, there are several restrictions on which people are eligible for surgery. There are several large blood vessels which travel next to the common bile duct, namely the hepatic artery and portal vein. Generally, if these vessels are surrounded by tumor, surgery is not possible, though at some centers surgery will be attempted with reconstruction of the removed blood vessels. If the tumor has grown into the liver or metastasis form in the liver, surgery is generally not considered. If tumor has spread to the lymph nodes or to the abdominal cavity, surgery is also contraindicated **(Shinohara et al,2009).**

Operative techniques have been improved as a result of a better understanding of biliary and hepatic anatomy and physiology. Moreover, the continuing evolution of minimally invasive surgery has promoted the gradual adoption of laparoscopic approaches to these complex operations. Accordingly, biliary tract surgery, like many other areas of modern surgery, is constantly changing **(Bartlett et al, 2006).**

Patients with cholangitis whose conditions fail to improve with conservative treatment usually require urgent decompression of the obstructed biliary system. Recent studies show that the long-term success rate of endoscopic stenting is comparable to that of surgery, with similar recurrence rates. Therefore, surgery should probably be reserved for those patients with complete ductal obstruction or those in whom endoscopic therapy has failed **(Furmanczyk et al, 2005).**

Surgical intervention is recommended for those patients who are otherwise healthy, whose disease appears to be localized, or in whom duodenal or gastric outlet obstruction is present, palliative surgery is directed towards relieving jaundice by creating a biliary-enteric anastomosis, and if a gastric or duodenal outlet obstruction is present or a likely possibility, a gastro-jejunostomy should be created at the same time. Although palliative surgery is effective in achieving its goal of circumventing the obstruction, no survival advantage has been described when compared with non-operative techniques **(Furmanczyk et al, 2005).**

We need to improve the diagnosis, so identifying tests that improve the yield of biopsy is very important. There is currently much work being performed with gene profiling in bile and identifying serum markers **(Alvaro et al, 2010).**

***

The aim of the study:

This study aims at *reviewing the different algorithms and protocols recently adopted in the diagnosis and treatment of cholangiocarcinoma*, in order to find an optimal plan for early diagnosis and for treatment of different patients having this disease.

***

Contents of the study:

List of Acronyms / Abbreviations

5′-NT	5′-Nucleo-Tidase
AFP	serum Alpha-FetoProtein
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	serum Alanine aminoTransferase
AST	serum Aspartate aminoTransferase
CA $^{19–9}$	Carbohydrate Antigen
CCA	CholangioCarcinoma (i=Intrahepatic, p=Perihilar, d=Distal)
CEA	CarcinoEmbryogenic Antigen
CEUS	Contrast-Enhanced UltraSound
CHA	Common Hepatic Artery
CHD	Common Hepatic Duct
CL	Caudate Lobectomy
CLC	Cholangiolocellular Carcinoma
CSC	Cancer Stem Cell
CT	Computed Tomography
CTC	CT Cholangiography
Cyfra	***Cy***tokeratin ***fra***gment (Cyfra 21-1 is a fragment of cytokeratin 19)
DIA	Digital Image Analysis
EASL–EORTC	European Association for the Study of the Liver - European Organisation for Research and Treatment of Cancer
EMT	Epithelial-Mesenchymal Transition
ENBD	Endoscopic NasoBiliary Drainage
ERC	Endoscopic Retrograde Cholangiography
ERCP	Endoscopic Retrograde Cholangio-Pacreatography
EUS	Endoscopic UltraSound
FCAT	Federative Committee on Anatomical Terminology
FDG	Fluoro-Deoxy-Glucose
FISH	Fluorescence In Situ Hybridization
FLR	Future Liver Remnant
FNA	Fine-Needle Aspiration
GGT	Gamma-Glutamyl Transpeptidase
HBcAb	Hepatitis B core Antibody
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCC	HepatoCellular Carcinoma
HCV (Ab)	Hepatitis C Virus (Antibody)
HIV	Human Immunodeficiency Virus
HPC	Hepatic Progenitor Cells
HPD	Hepato-Pancreatico-Duodenectomy
HR	Hepatic Resection
IDUS	IntraDuctal UltraSound
IFN - γ	Interferon – γ

IGF1	Insulin-like Growth Factor 1
IgG/ IgM	Immunoglobulin G/ Immunoglobulin M
IHPBA	International Hepato-Pancreato-Biliary Association
IL - 6 or 12	InterLeukin - 6 or 12
INR	International Normalized Ratio
IVC	Inferior Vena Cava
LGA	Left Gastric Artery
LHA	Left Hepatic Artery
LHV	Left Hepatic Vein
LTx	Liver Transplantation
Mcm	Minichromosome maintenance replication protein
MDCT	Multi-Detector Computed Tomography
MHV	Middle Hepatic Vein
MRCP	Magnetic Resonance Cholangio-Pancreatography
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
MUC5(A)/(C)	human Mucin 5, subtypes A and C
NHTMRI	National Hepatology and Tropical Medicine Research Institute (Cairo)
NLI	National Liver Institute (Menoufiya)
OCT	Optical Coherence Tomography
PBD	Preoperative Biliary Drainage
PBG's	Peri-Biliary Glands
PCB's	Polychlorinated Biphenyls
PD	Pancreatico-Duodenectomy
PDT	PhotoDynamic Therapy
PET	Positron Emission Tomography
PPPD	Pylorus-Preserving Pancreatico-Duodenectomy
PSC	Primary Sclerosing Cholangitis
PT	Prothrombin Time
PTBD	Percutaneous Transhepatic Biliary Drainage
PTT	Partial Thromboblastin Time
PVE	Portal Vein Embolization
RFA	Radio-Frequency Ablation
RHA	Right Hepatic Artery
RHV	Right Hepatic Vein
SMA	Superior Mesenteric Artery
TACE / TACI	Trans-Arterial Chemo-Embolization / Trans-Arterial Chemo-Infusion
TARE	Trans-Arterial Radio-Embolization
TGF	Tumor Growth Factor
THC	Trans-Hepatic Cholangiography
TNF - α	Tumor Necrosis Factor – α
TNM	Tumor - Node (L.N.) - Metastases staging system
UICC	Union for International Cancer Control
VEGF	Vascular Endothelial Growth Factor

● *List of Figures* ●

● *List of Tables* ●

Review of the literature