ABSTRACT

Cholangiocarcinoma is a rare and highly fatal neoplasm that arises from biliary epithelium, constitutes approximately 2% of all reported cancer, and accounts for about 3% of all gastrointestinal malignancies.

Up to date, there are many modalities to diagnosis and treatment with variety range of sensitivity and specificity, and also the advantage and disadvantage of its modality. As a physician, we should be able to assess and choose promptly which modality is best for our patient, even for palliative care.

Treatment modalities are surgery and non-surgery e.g. adjuvant chemotherapy, radiation, chemoradiation, radiotherapy, TACE, 5-FU chemoinfusion, intralesion PEI, photodynamic therapy, liver transplantation, and palliative therapy. The choice of treatment varies individually. Radical surgery remains the optimal therapy and offering a potential for cure. Overall prognosis in these patients is poor and survival is limited.

Keywords: Cholangiocarcinoma, diagnosis, management.

INTRODUCTION

Cholangiocarcinoma is an uncommon malignancy arising from the epithelial cells of the biliary tract. These tumors may arise anywhere along the intrahepatic or extrahepatic biliary tree. Patients with cholangiocarcinoma typically present at advanced stages, and cure rates are low, even with aggressive therapy. It has been estimated that there are 500 new cases annually in USA and the incidence is increasing with advance imaging technology. Patient with cholangiocarcinoma are predominantly male with age 50-70 years old. Diagnosis of cholangiocarcinoma should be based on good anamnesis and adequate examination because its variety of clinical manifestations whereas lack of effective therapy modality.3

The exact cause of cholangiocarcinoma is unknown, and most cases occur sporadically, but there are several well-defined risk factors. The most common of these is primary sclerosing cholangitis (PSC) and the clinical features of cholangiocarcinoma depends on the location of the tumor.
DEFINITION

Cholangiocarcinoma is a malignant biliary duct tumor, arising from abnormal growth of biliary duct which can be derived from intrahepatic and extrahepatic. More than 90% cases are adenocarcinoma and the rest are squamous cell tumor.4

CLASSIFICATION

Malignancy in biliary tract system can be divided into cancer of gall bladder, extrahepatic duct, and ampulla of Vateri, whereas intrahepatic tumor is classified as primary liver cancer and cholangiocarcinoma is a cancer of biliary duct. Perihilar tumor is the most common form and intrahepatic tumor accounts for the rare one.4 Cholangiocarcinoma can be classified according to its location and morphology. According to its location, it can be divided into 3 regions which are intrahepatic, hilar, and distal extrahepatic. According to its morphology, for non-hilar lesion can be divided into mass-like form, periductal or intraductal, and mixed type of mass-like and periductal, whereas extrahepatic lesion can form sclerotic, nodular, and papillary type.

Cancers arising in the perihilar region have been further classified according to their patterns of involvement of the hepatic ducts (Bismuth–Corlette classification), which divided into 4 types:

• Type I Tumors below the confluence of the left and right hepatic ducts.
• Type II Tumors reaching the confluence.
• Type III Tumors occluding the common hepatic duct and either the right or left hepatic duct.
• Type IV Tumors that are multicentric, or that involve the confluence and both the right or left hepatic duct.

This anatomy-morphology classification is used for treatment decision and epidemiological study.5

EPIDEMIOLOGY

Report from National Cancer Institute Surveillance, Epidemiology and End Results (SEER) 2006 in US shows there are 18,510 cases of primary liver cancer with 15% of cases are intrahepatic cholangiocarcinoma.6

For unclear reasons, the incidence of intrahepatic cholangiocarcinoma has been rising over the past two decades in Europe and North America, Asia, Japan, and Australia, while rates of extrahepatic cholangiocarcinoma are declining internationally, with man has five times higher rate than woman.7,8

ETIOLOGY

A number of risk factors for cholangiocarcinoma have been recognized, although a specific risk factor cannot be identified for many patients, some of them are:9

• Age > 65 year old.
• Primary Sclerosing Cholangitis (PSC), with or without ulcerative colitis.
• Chronic cholelithiasis intraductal.
• Adenoma of cystic duct and biliary papillomatosis.
• Caroli’s disease.
• Choledochus cyst.
• Toxigenic agent.
• Smoking and alcohol consumption. (related to PSC)
• In South East Asia:
  • Chronic infection of Opisthorchis. viverrini and Clonorchis.sinensis.
  • Chronic typhoid carrier.

DIAGNOSIS

Diagnosis should be based on good anamnesis, physical examination, laboratory, and imaging. Cholangiocarcinoma can be asymptomatic in the early stage and symptomatic if there’s biliary obstruction, usually with symptoms like
Figure 1. Cholangiocarcinoma classification. (A) By location. (B) By morphology. (C) Bismuth-Corlette classification.5

Figure 2. Cholangiography in Klatskin’s tumor
pruritus, abdominal pain, weight loss, fever, tea-colored urin, and pale feces.11

Laboratory test in patient with biliary obstruction will reveal increasing direct bilirubin (>10 mg/dl), alkali phosphatase (2-10x), and GGT can be within normal limit. In advance stage, there can be hypoalbuminemia and elevation of LDH.11 There is no specific tumor marker and there's no evidence that tumor marker level is related to progressivity of tumor. Generally, the sensitivity and specificity of the tumor marker is low but is useful if used as combination. CA 19-9, Carcinoembryonic antigen (CEA), and CA-125 was the most used tumor marker.

In radiology, USG and CT-scan can be used before performing cholangiography. USG is the first modality for suspicion of biliary obstruction to evaluate any distended of intrahepatic biliary duct.11

MRI gives information about hepatobiliary anatomy and local extention from tumor, liver parenchym abnormality, and liver metastases. MRCP shows the extention of biliary duct involvment and MRA shows involvement of vascular hilar.11

Cholangiography is the important modality for diagnostic and evaluation of resection accessiblity. It can be divided into 3 modalities which are MRCP, ERCP, and Percutaneous Transhepatic Cholangiography (PTC).11

Others modality are Endoscopic Ultrasound (EUS) dan Positron Emission Tomography (PET). EUS reveals clear imaging of distal extrahepatic biliary tract, gall bladder, regional lymph nodes, and vascular system. PET with [18F]-2-deoxy-D-glucose will show high glucose metabolism in cholangiocarcinoma cell as hot spots.11

**TREATMENT**

The goal of treatment is to cure the cancer and relieve the obstruction. Type of treatment is depending on its tumor location and must be evaluated individually.

Surgery is the mainstay of treatment if possible and if no metastases was found. Distal cholangiocarcinoma has high resectability, accounts for 91%, whereas intrahepatic is 60%, and perihilar is 56%.16 Adjuvant chemotherapy or radiation or chemoradiation can be performed following operation to reduce recurrency rate but its effectiveness is still not clear. Cholangiocarcinoma is relatively chemosensitive, mostly with 5-fluorouracil (5-FU). Combination chemotherapy with gemcitabine and cisplatin shows partial response as 30–50% of cases and improves quality of life.17

Radiotherapy doesn't increase survival rate or quality of life in resectable perihilar cholangiocarcinoma. Local radiation can be implemented as intraoperatively or intraluminal brachitherapy.18

TACE, 5-FU chemoinfusion into hepatic artery or biliary duct, and PEI intralesion are still under investigation.19 Photodynamic therapy can eliminate the obstruction but not many facilities can not perform this treatment.20-21 Liver transplantation is still contradictive because of high recurrency and average survival rate is about 3 years.22-23 Majority of cases, transplantation is done for cholangiocarcinoma with PSC.24-26

Palliative therapy with stent insertion, PTBD, or bypass can decrease biliary duct obstruction in unresectable case. Endoscopic approach is preferable for long term palliative care because related to similar survival rate with low risk morbidity. Adjuvant chemo/radiotherapy has not been proved for its efficacy.27 Palliative therapy can be done by using drug eluting stent, but the effectiveness is still in ongoing trial.28 Endoscopically, plastic or metal stent can be used but metal stent has high patency rate for long term (8-12 month vs 4.8 month).29
Figure 3. Management algorithm for cholangiocarcinoma

1. Histological diagnosis
2. Exclude primary from other site
3. Staging investigations

Resectable
- Surgery
- Consider novel treatment: in setting of clinical trials, for example,
  - Chemo/radio/brachy-therapy (adjuvant)
  - Gene therapy
  - Ablation therapy

Non-resectable
- Palliative treatment, for example,
  1. Metal stent
  2. Symptom relief; pruritus, pain
  3. Nutrition
  4. Palliative care team
II.7. PROGNOSTIC

Prognosis depends on the stadium, tumor location, and successfulness of the treatment. Predictor factor for poor prognosis factors are lymphadenopathy, vascular invasion, and p53 gene mutation. Best result are with distal CBD tumors completely excised (cure rate 40%), incomplete resection plus radiation gives a median survival of 30 months, stenting plus chemo/radiation gives a median survival of 17-27 months, with surgery and chemo/radiation is about 24 to 36 months, with chemo/radiation alone is about 12 to 18 months, those stented alone live only a few months. Five years survival rate of cholangiocarcinoma with surgical treatment is 9%-18% for proximal lesion and 20%-30% for distal lesion.

CONCLUSION

1. Cholangiocarcinoma is biliary duct neoplasm that arises from biliary epithelium, accounts for about 3% of all gastrointestinal malignancies and more than 90% of cases are adenocarcinoma.

2. Diagnosis of cholangiocarcinoma based on anamnesis, physical examination, laboratory examination, and radiology including USG, CT-scan, EUS, PET, and cholangiography (MRCP, ERCP, PTC).

3. Treatment modalities depends on the tumor location, can be surgical and/or non-surgical e.g. adjuvant chemotherapy, radiation, chemoradiation, radiotherapy, TACE, 5-FU chemoinfusion, intralesion PEI, photodynamic therapy, liver transplantation, and palliative therapy (stent, PTBD, bypass surgery).

4. Prognosis depends on the stadium, tumor location, treatment modality, and successfulness of the treatment.