PLACE OF SURGERY IN OPISTHORCHIASIS ASSOCIATED CHOLANGIOCARCINOMA

Vajarabhongsa Bhudhisawasdi

Department of Surgery, Faculty of Medicine, Khon Kaen University,
Khon Kaen 40002, Thailand

The northeastern part of Thailand, commonly called "Esan", is an endemic area of *Opisthorchis viverrini* (Upatham *et al,* 1984). This area is also well-known among surgeons and pathologists for the strong relationship between cholan-giocarcinoma and opisthorchiasis. In Bangkok nearly all of cases of cholangiocarcinoma occur in workers from Esan who migrated to Bangkok and all had liver flukes in their biliary tracts. The largest autopsy case report, from Siriraj Hospital (Koompirochana *et al,* 1978), also shows this relation.

Opisthorchiasis by itself cannot produce cholangiocarcinoma. This is indirectly proved in experimental animals (Bhamarapravati *et al,* 1978; Thamavit *et al,* 1978; Flavell and Lucas, 1983; Thamavit *et al,* 1987). But opisthorchiasis and nitrosamine compounds induce cholangiocarcinoma.

"Plarah" (a kind of fermented fish), the popular and regular food of native people of Esan, is very rich in nitrosamine compounds. Recently, provincial-based cancer registration (Vatanasapt *et al,* 1988) and hospital-based study (Green *et al,* 1990), have clearly convinced us that cholangiocarcinoma has a very high incidence rate in Northeast Thailand and is one of the biggest health problems of Thailand, it seems that opisthorchiasis acts as a strong promoter of cholangiocarcinoma.

As a general surgeon who has worked in the middle part of Northeast Thailand since 1976 and has a special interest in cholangiocarcinoma, I present my experience and impressions about *Opisthorchis viverrini*-associated cholangiocarcinoma (OV-CCA).

Surgical patholgy

OV-CCA in Northeast Thailand has its own definition as an adenocarcinoma arising from epithelia of the biliary trees. This includes both intra- and extra-hepatic portions. (Those arising from gall bladder and ampulla of vater are excluded).

OV-CCA is a mucin-producing adenocarcinoma. Mucin can be seen by special staining, both intra - and extra-cellular. This type of tumor usually spreads through the lymphatic system to the cystic nodes, the common bile duct nodes, the celiac nodes and then to the left supraclavicular nodes. Left lobe tumors may spread directly to the celiac nodes.

There are two types of OV-CCA:

Peripheral type: The tumor originates in the cholangiole or small peripheral bile ducts. Its cut surface is greyish-white and shiny from its mucinous content. It may be multiple or single and be confined to one lobe or both lobes of the liver. It tends to have umbilication on its surface and has a tendency to have central necrosis. Some tumors produce humoral substances that cause pyrexia or induce deep vein thrombosis.

The tumor has a tendency to adhere to the surrounding structure so that direct invasion to the diaphragm, the rib cage, the gall bladder, the colon and the stomach is not uncommon. From the diaphragm and the ribs, the tumor may disseminate via the lymphatic system to the paravertebral lymphatic chain and the parasternal lymph chain or via the vertebral venous plexus to the vertebrae, the skull, the pelvis and the brain. It may have hematogenous spreading to distant structures such as the skin in remote areas and the long bones. Transcelomic spread is usually present in late stages.

Central type: The carcinoma arises from the large bile ducts, both intra and extra-hepatic. The most common site is the hilar region (The confluence of the right and left hepatic ducts at the porta hepatis) (Table 1). This

lesion may be confused with the peripheral type lesion that invades the porta hepatis.

Table 1

The site of central type cholangiocarcinoma (based on 125 obstructive jaundice cases from OV-CCA).

Site	No. of cases	%
Hilar	54	43.2
Cystic duct junction	16	12.8
Distal common bile duct	25	20.0
Skip lesion	12	9.6
Diffused lesion	18	14.4

The unique feature of this type is skip lesions, that is two distant lesions separated by a normal duct. In operations the second lesion at the hilar or intrahepatic duct is often missed if careful bile duct exploration is not carried out.

The tumors have a tendency to invade surrounding structures at earlier stages than peripheral types. The tendency to spread submucosally and invade of the hepatic artery or the portal vein in the hepatoduodenal ligament makes complete removal of the tumor unlikely.

Lymphatic spreading to cystic lymph nodes and the common bile duct nodes is common but transcelomic spread often occurs in later stages than in the peripheral type.

The combination of the peripheral and central types is usual. In 125 cases of obstructive jaundice, only 73 cases (58.4%) were the pure central type and another 52 cases were the combination of various forms of central and peripheral types (Fig 1).

The gross appearance of central type cholangiocarcinoma has three forms: nodular, infiltrative and polypoid masses (Weinbren and Mutum, 1983). The last one tends to have a better prognosis because tumor invasion to surrounding structures is less.

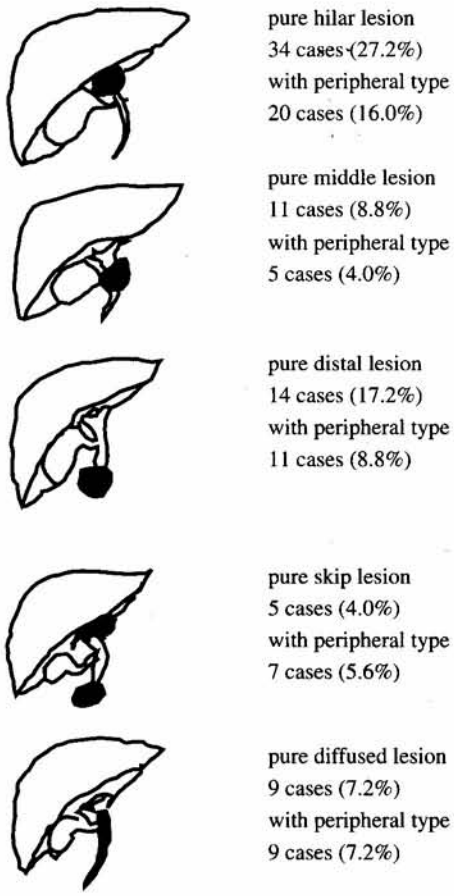

Fig 1 - Combinations of various types of cholangiocarcinoma in 125 obstructive jaundice cases.

Gall bladder pathology in OV-CCA is always determined by the site of obstruction, the presence of cystic duct obstruction and secondary infection. These factors cause the following features of gall bladder:

1. Collapsed and empty gall bladder because the site of obstruction is above the cystic duct junction.

2. Hydrops or mucocele of the gall bladder due to cystic duct obstruction either from tumor at the cystic duct junction or secondary deposits from hilar or distal lesions.

3. Distal bile duct obstruction with patent cystic duct causes distended gall bladders, often full of green bile.

4. Acute acalculous cholecystitis, gangrenous gall bladder and empyema of gall bladder are secondary to cystic duct obstruction and secondary infection.

It is not uncommon that the gall bladder may be invaded by the nearby tumor or distended by blood from bleeding ductal tumors (Table 2).

In OV-CCA, not only the presence of dead or viable flukes or their eggs in the bile but the characteristic appearance of chronic OV-infected livers ("superficial bile lake dilatation") is always observed, especially in obstructive jaundice cases (Ninety-seven of 125 cases (77.6%) had this appearance).

Table 2

Gall bladder pathology observed in 125 obstructive jaundice cases from cholangiocarcinoma.

Gall bladder pathology	No. of cases	%
Collapsed	33	26.4
Hydrops	38	30.4
Distended	26	20.8
Inflamed	4	3.2
Empyema	8	6.4
Gangrenous	2	1.6
Tumor-invaded	2	1.6
Blood-filled	1	0.8
Contracted	5	4.0
Removed	6	4.8

Clinical picture

OV-CCA affects men more than women; the ratio is about 2-3 : 1. The peak age-group is 46-60 years and nearly all are natives of "Esan" who live in rural villages. Very few cases live in urban areas and we have never seen a single case in Vietnamese or Chinese. Eighty-five percent of the patients are farmers and all are regular consumers of "Plarah", the food that is very rich in nitrosamine compounds.

There are six forms of clinical presentation:

1. Obstructive jaundice. This is the most common presentation. Eighty to ninety percent of malignant obstructive jaundice cases in Northeast Thailand are caused by OV-CCA and the common picture is a walking jaundice case with a large liver. The gall bladder may be palpated or not depending on the site of obstruction. Most of them have history of jaundice and dark urine for more than 2 weeks, half of them has abdominal pain, about one third present as a complicated obstructive jaundice such as acute cholangitis, septic shock, acute renal failure, hepatic failure and spontaneous bleeding. This form of presentation accounts for about 60-70% of OV-CCA.

2. Liver mass. This is the second most common form of presentation and accounts for about 20-30% of OV-CCA cases. The tumors may be solitary or multiple and have to be differentiated from hepatomas but 90-95% of the primary liver tumor cases in "Esan" are peripheral-type cholangiocarcinoma. Alfa fetoproteins are negative in OV-CCA, but most of the cases have high nonspecific CEA levels and are not related to hepatitis B virus. Age and sex patterns a re the same as obstructive jaundice cases and also present in late stages. Most tumor sizes are larger than 6 cms in diameter and have already invaded surrounding structures especially the diaphragm. This form of presentation is increasing.

3. Hydrops of the gall bladder. The patient is non-jaundiced but has a tensed palpable gall bladder. Formally this form of presentation was believed to be an earlier phase of obstructive jaundice but this is not true. The stage of the tumor is often advanced. Components of cystic duct obstruction are more dominant than common bile duct obstruction.

4. Acute acalculous cholecystitis. In endemic areas of OV-CCA this presentation is not uncommon. The common victims are middle-aged men. This condition has a sex ratio of about 4:1 and OV-CCA is often missed because the surgeon usually concentrates on removing the diseased gall bladder and is unaware of the latent bile duct obstruction and this often reveals itself 2-4 weeks after "successful cholecystectomy."

5. Incidental findings. This presentation is explained by the fact that small liver tumors do not cause any symptoms in most of the cases and central type tumors take a long time before they completely obstruct the bile duct and cause obstructive jaundice. These lesions may cause only dyspepsia or upper abdominal discomfort but these symptoms are minor and nonspecific.

Nevertheless some of these small and latent tumor may cause bizarre presentations.

6. Miscellaneous. There are a group of presentations caused by distant metastatic lesions, such as:

- pathological fracture of the long bone
- subcutaneous nodules
- brain and retrobulbar metastasis
- lytic lesion of the right twelfth rib
- lytic lesion of the skull or the pelvis
- paraplegia due to cord compression

Some tumors release humoral substances that cause

- pyrexia
- deep vein thrombosis

Treatment

Up to now the mainstay of treatment of OV-CCA has been surgery. The surgery aims to remove as much as possible of the tumor tissue and maintain the function of hepatobiliary system. Other modalities of treatment are not promising.

In obstructive jaundice cases, curative treatment is unlikely because of late presentation and because the nature of the tumor makes complete removal of the tumor very difficult. In Only 21 of 125 cases (16.8%) could the tumors be removed, but surgery offers good and reasonable palliative treatment.

The common surgical operations are

1. tumor resection and bypass;
2. bypass alone using many variety of enterobiliary anastomosis;
3. external drainage. This is usually the last resource in surgical treatment.

The surgery in unselected patients has high morbidity and mortality so pre-operative risk factors should be identified. A prospective study was conducted on 125 unselected patients (whose data is the main source of information for this handout) by using univariate analysis. Eight pre-operative risk factors were identified (Table 3). But from multivariate and serum alkaline phosphatase are the factors that can predict the outcome of surgery.

Table 3

Preoperative risk factors in 125 obstructive jaundice cases from cholangiocarcinoma.

1.	Hematocrit $\leq$ 30%
2.	Neutrophil in white cell count > 80%
3.	Serum albumin $\leq$ 2.7 g%
4.	Prothrombin activity $\leq$ 85%
5.	Serum creatinine > 3.0 mg%
6.	BUN > 30 mg%
7.	Serum alkaline phosphatase > 10 SU.
8.	Serum SGOT > 150 IU.

There are conditions that complicate the pre-, peri-and postoperative courses of obstructive jaundice patients from OV-CCA.

1. Bleeding tendency. This common condition is due to coagulopathy from prothrombin complex deficiency. The second cause is prolonged PTT from hepatocholangitis secondary to biliary sepsis. The bleeding tendency is very rarely caused by platelets dysfunction due to azothemia and usually had a poor prognosis.

2. Biliary sepsis. This condition, if uncontrollable or poorly managed, may lead to other complications. Suppurative cholangitis is a consequence of long-standing obstruction or small and obstructed enterobiliary anastomosis. A common causative organism is *E. coli.* The second most common is *Klebsiella.* In immunocompromised hosts or poorly managed cases super-infection by *Candida albicans* is not uncommon.

3. Renal failure. This condition may be caused by inadequate hydration, use of aminoglycosides and biliary sepsis. Endotoxin theory seems to fit well in OV-CCA cases.

4. Upper GI hemorrhage. Commonly caused by gastritis secondary to stress or sepsis. Uncommonly caused by bleeding from a pre-existing peptic ulcer. Coaggulopathy makes the treatment of this complication very difficult. Rare bleeding from gastric varices or duodenal varices has a very poor prognosis.

5. Hepatic failure. This complication is usually due to a neglected case of obstructive jaundice and nearly all of them have biliary sepsis. Surpisingly this complication is uncommon.

The principle causes of death in OV-CCA are

1. uncontrollable biliary sepsis
2. massive upper GI hemorrhage
3. acute renal failure

Long term survival in obstructive jaundice from OV-CCA is rare. Most surgery is palliative. Nevertheless, at least 2 cases of 125 cases had 5 years' survival. The quality of life in the first months after surgery were satisfactory and well-accepted by the patients and their families.

As for the survival curve from 125 unselected patients, including those who died postoperatively, 50% proportional survivality is about 90 days. The one year survival rate is around 15% The factors that predict better prognosis are type and stage of the lesion, and proper internal bypass (Figs 2, 3, 4). Skip and diffused lesions, external drainage, and unilateral peripheral bypass have very poor prognosis.

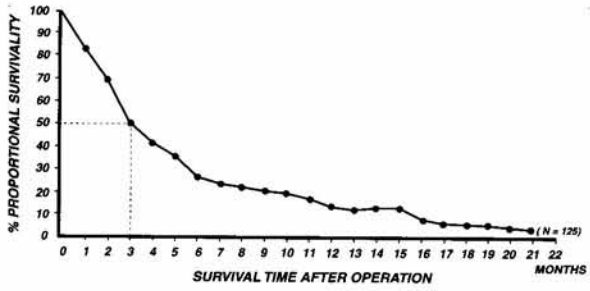

Fig 2 - The survival curves of 125 obstructive jaundice cases from OV-CCA Nov 1982-Nov 1985.

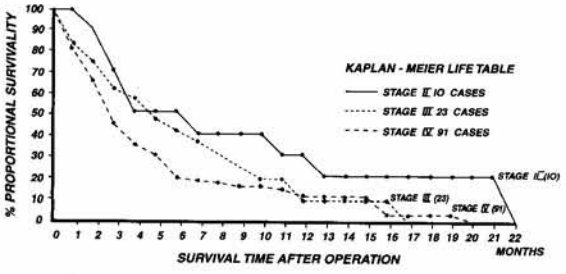

Fig 3 - 125 Obstructive jaundice cases from cholangiocarcinoma Nov 1982 - Nov 1985.

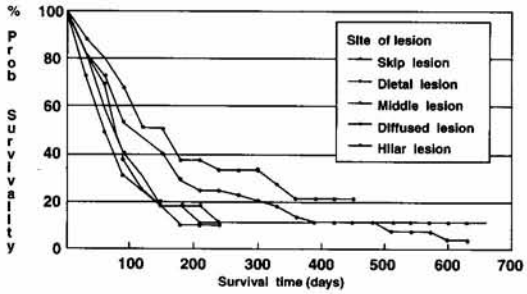

Fig 4 - Obstructive jaundice from OV-CCA. 125 personal cases Nov 1982 - Nov 1985.

Treatment of liver mass is surgical removal of the mass by varieties of hepatectomy. In general this has better prognosis than obstructive jaundice cases. Postoperative morbidities and complications are few and postoperative mortality are rare. This may be due to proper selection of the patients and good surgical technics. Hepatectomy are done even in the cases that had distant metastases or where the tumor had invaded the diaphragm.

But where the size of the tumor is larger than 6 cms or has already invaded surrounding structures, recurrence of the tumor is common. The tumour spreads more rapidly than in properly resected cases.

Much progress have been made during the last 3 years, especially in unstanding the process of carcinogenesis, but there are many things still to be learned.

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