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Opisthorchiasis and Cholangiocarcinoma in the Northeast Thailand : Treatment by Surgery

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โรคพยาธิใบไม้ในตับ และมะเร็งทางเดินน้ำดี กับการรักษาทางศัลยกรรม

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บทคัดย่อ

ในบางพื้นที่ภาคตะวันออกเฉียงเหนือมีพลเมืองที่ติดเชื้อพยาธิใบไม้ในตับสูงถึง 70 เปอร์เซ็น อัตราการเป็นโรคมะเร็งของทางเดินน้ำดีของประชากรในภูมิภาคนี้มีอัตราสูงกว่า ประชากรชาวตะวันตก ถึง 50 เท่า ทั้งการศึกษาทางระบาดวิทยา และการศึกษาในสัตว์ทดลอง หนูไซเรียน โกลเดิล แฮมสเตอร์ พบว่าปัจจัยที่เป็นสาเหตุของการเกิดโรคมะเร็งที่จำเป็นในการก่อให้เกิดโรคมะเร็งทางเดิน น้ำดี คือ สารที่ก่อให้เกิดโรคมะเร็งไนโตรสามินส์ และพยาธิใบไม้ในตับร่วมกัน

อายุของผู้ป่วยที่มารับการรักษาโรคนี้ที่มากที่สุดอยู่ระหว่าง 45 และ 65 ปี ชายต่อหญิง ในอัตรา 4.5:1 อาจแบ่งผู้ป่วยออกเป็น 2 กลุ่ม คือ กลุ่มที่มาด้วยตัวเหลืองตาเหลือง (กลุ่มกลาง) 60 เปอร์เซนต์ และกลุ่มที่ไม่มีตัวเหลืองตาเหลือง (กลุ่มริม) 40 เปอร์เซนต์ พยาธิสภาพที่พบในระหว่างผ่าตัดส่วนใหญ่มีพยาธิสภาพที่เป็นมาก หรืออยู่ในระยะท้าย ๆ

วิธีการรักษาทางศัลยกรรม ขึ้นอยู่กับพยาธิสภาพที่พบระหว่างผ่าตัด ซึ่งรวมถึงการผ่าตัดเอาก้อนมะเร็งปฐมภูมิออก และต่อทางเดินน้ำดีกับทางเดินอาหารให้ใหม่ หรือการต่อทางเดินน้ำดีกับทางเดินอาหาร เลี่ยงการอุดตันของก้อนมะเร็งปฐมภูมิ หรือการผ่าตัดตับข้างใดข้างหนึ่งที่เป็นพยาธิปฐมภูมิ ออกในรายที่ไม่มีตัวเหลือง ตาเหลือง โดยทั่วไป ผลการรักษาของกลุ่มที่ไม่มีตัวเหลือง ตาเหลือง (กลุ่มริม) ดีกว่ากลุ่มที่มีตัวเหลือง ตาเหลืองมาก ในกลุ่มที่มีตัวเหลือง ตาเหลือง อัตราตายของการ ผ่าตัดมีสูงถึง 15-20 เปอร์เซนต์ และอัตรารอดชีวิต 3 เดือน 1 ปี และ 5 ปี มี 50, 15 และ 1 ถึง 2 เปอร์เซนต์ ตามลำดับ ส่วนในกลุ่มที่ไม่มีตัวเหลือง ตาเหลือง อัตราตายของการผ่าตัดเอาตับข้างใดข้างหนึ่งที่มีพยาธิสภาพออก น้อยกว่า 2 เปอร์เซนต์ และอัตรารอดชีวิต 1 ปี, 2 ปี และ 5 ปี 75, 50, และ 15 เปอร์เซนต์ ตามลำดับ

Abstract

An estimation as high as 70% of the population in certain region of the Northeast Thailand is infected with Opisthorchis viverrini and the incidence of cholangiocarcinoma among this population may be 50 times higher than in Western countries.

Epidemiological and experimental studies suggested that dietary contamination with carcinogen may be the essential causative factor : synergistic effects of nitrosamines and Opisthorchis inducing cholangiocarcinoma was found experimentally in Syrian golden hamster.

The peak age of presentation Opisthorchiasis infestation and cholangiocarcinoma for surgical management is between 45 and 65 years males : females with a ratio of 4.5:1. There are two forms of presentation : the jaundiced (central) 60% and the non-jaundiced (peripheral) 40%. The pathological findings at operation are usually very advanced stage of Opisthorchiasis or cholangiocarcinoma.

The surgical procedures are dictated by the pathology found at operation which include tumour excision and reconstruction of enterobiliary continuity, bypass procedure for jaundiced patients; and hepatectomy to remove the diseased lobe in the non-jaundiced.

On the whole, results of treatment for non-jaundiced patients are far better than these who are jaundiced. Among the jaundiced patients, the perioperative mortality rate is 15-20% and the survival rates at 3-month, 1-year and 5-year are 50%, 15% and 1 to 2%, respectively. In the non-jaundiced, the perioperative death of hepatectomy is less than 2%, one year survival 75%, two years survival 50% and five years survival 15%.

Keywords ; Opisthorchiasis, Cholangiocarcinoma, Northeast Thailand, Surgery

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In the Northeast of Thailand where raw fresh water and uncooked fermented and salted fish are consumed daily as the mainstay diet and estimation as high as 70% of the population is infected with Opisthorchiasis viverrini. The incidence of cholangiocarcinoma of the population in this area is among the highest in the world ; may be fifty times higher than in Western countries [1]. Epidemiological and experimental studies suggested that dietary contamination with carcinogen may be the essential causative factor. Synergistic effects of nitrosamines and Opisthorchsis viverrini inducing cholangiocarcinoma in Syrian golden hamster are found but the administration of chemical carcinogen or fluke infection alone does not cause the cancer [2]. Although the infestation of the fluke actually begins in childhood, the clinical mainfestations occur in the middle age and after.

Presentation

In our recent study of 450 cases (1988-1991) there are two main forms of presentations namely the jaundice and the non-jaundice. They are :

Table 1 Clinical presentations of 450 patients with cholangiocarcinoma secondary to opsithorchiasis infestation in Thailand.

Presentations	No. of patients 5	Percentage
(I) Jaundice:		
Malignant biliary obstruction	246	54.6
(II) Non-Jaundice:		
Liver mass	135	30.0
Hydrops of gall bladder	30	6.7
Acalculous cholecystitis	31	6.8
Miscellaneous	8	2.0
Incidental finding at Laparotomy		
Liver abscess		
Pyrexia of unkown origin		

(1) The jaundice :

Central type intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma.

(a) Elective Obstructive Jaundice : Although malignant biliary obstruction and clinical jaundice serious ascending cholangitis has not yet occurred, physical findings may include firm hepatomegaly, palpable gall bladder and detectable ascites. Serum bilirubin is often high, above 15 mg%, while total serum protein and serum albumin are low. Most patients are chronically ill with poor nutritional status. But there is time for adequate preoperative preparation including correction of blood coagulopathy and total serum protein and albumin.

(b) Urgent obstructive janundice : associated cholangitis. In addition to the above presentation there are recurrent high fever and chills, diminished urinary output and frequent severe septic shock. We regard this type of presentation as "acute abdomen" of Opisthorchiasis or cholangiocarcinoma : the clinical picture of recurrent ascending cholangitis with raised BUN and creatinine, and low serum albumin. The total bilirubin may be as high as 40 mg% or more.

In 1989 out of 135 cholangiocarcinoma operated upon, 32 were "acute abdomen" (25%) : eight were septicemia, twenty-two were ascending cholangitis and two were gereralised bile peritonitis. Thereare appreoximately twenty to thirty such cases admitted through the accident and emergency department of Srinagarind Hospital each year.

(2) The Non-Jaundice :

Peripheral type of cholangiocarcinoma. This may present as palpable mass over the right and not uncommonly the left subcostal margin, R:L 3:1 [3], hepatomegaly, palpable gall bladder of various degree from just palpable to huge hydrops of gall bladder. A picture of an acute abodmen in the form of acte cholecystitis either calculous or acalculous cholecystitis is encountered.

Surgery

Useful diagnostic investigations and localization of the tumour lesions now include ultransonography, PTC, ERCP and perhaps CT for detection of para-aortic involvement.

The surgical pathology found at operation of Opisthorchias in our area is almost always advanced and is already associated with cholangiocarcinoma. The patient presentations are due to the complications of this condition. We rarely encounter the histological report of the tumour mass or stenotic bile duct excised as benign fibrotic granuloma without malignancy. However the general picture of the rest of the liver in case of obstructive jaundice is greenish congested liver with typical superficial bile lake dilitation and white fibrotic pattern of periductal fibrosis over the liver surface a characteristic opisthorchiasis pattern [4].

Surgical procedures are dictated by the surgical pathology seen intra-operatively. One can formulate the aims of these palliative procedures as follows:

(1) to relieve obstructive janundice;

(2) to remove the tumour mass as much as possible;

(3) to remove the diseased gall bladder and other sources of sepsis.

Surgery for Obstructive Jaundice

The locations of tumour causing obstructive may be at the (1) Porthaepatis (Klatskin tumour) or the (2) Extrahepatic duct which may either be (a) common hepatic duct or (b) common bile duct.

TUMOUR RESECTION

The procedure commonly performed is the resection of tumour mass and reconstruction of entero-biliary continuity by either hepatico-jejunostomy, hepatico-jejunostomy or choledochojejunostomy depending on the location of the tumour to be excised. Cholecystectomy is usually included in the procedure due to its diseased condition as the result of chronic obstruction, direct invasion of the tumour or associated gall stones.

BY-PASS PROCEDURE

This is done in the situation whereby the tumour resection is not advisable due to extensiveness of tumour invasion either deep into the hilar or the high risk of damaging the main blood vessels the portal vein or inferior vena-cava. In such a situation the alternative procedures of a central by-pass or a peripheral by-pass could be made.

THE CENTRAL BY-PASS

If the central tumour of the porta or the extrahepatic tumour of common hepatic duct or common bile duct cannot be safely resected, the proximal dilatation from the obstruction site will be used for biliary enteric by-pass. The usual procedure performed depend on the site of tumour obstruction from the porta downwards to the ampulla.

These are :

(1) left hepatico-jejunostomy;

(2) right hepatico-jejunostomy;

(3) bilateral hepatico-jejunostomy;

(4) hepatico-docho-jejunostomy;

(5) choledocho-jejunostomy.

THE PERIPHERAL BY-PASS

Where there is a gross pathology at the portahepatis or frozen porta, an access to the central dilatation of the duct is sometimes not possible. To relieve obstruction peripheral by-pass is an alternative procedure. This is done by wedging or hepatotomy into segment III, IV, and V along the edge of the liver and suitable dilated peripheral bile ducts are searched for. A Roux-en-Y or defunctioning loop cholangio-jejunostomy anastomosis is then performed.

It will be emphasised here that bilateral lobe drainage either centrally or peripherally is preferable to unilateral lobe drainage expecially when there is a complete obstruction between the right and left hepatic duct.

Surgery for the Non-Jaundice

In cases of hepatomegaly, ultrasonography may show cholangiocarcinoma confined to one or both lobes of the liver without biliary obstruction or jaundice. In case of unilateral lobe involvement which is much more common on the right than the left (3:1)[3] hepatectomy is performed. This procedure not only removes the diseased lobe of the liver but reduces the huge space occupying mass causing great discomfort to the patient. The tumour lobes removed weighing to two or three kilograms in weight are not uncommon. Those of hydrops of gall bladder and acute acalculous cholecystitis, intraoperative search of early associated cholangiocarcinoma must be made. Both conditions are regarded as sinister signs of latent cholangiocarcinoma. Cholecystectomy is recommended in both conditions. When cholangiocarcinoma is incidentally found it should be dealt with accordingly either with resection or by-pass surgery if potentially obstructive. Occasionally cases of pyrexia of unknown origin are encountered. Ultrasound finding may demonstrate small liver abscess and associated cholangiocarcinoma, segmentectomy or hepatectomy is then recommended.

Result : Fig. 1

The result of surgery of obstructive jaundice cases including both elective and urgemt types the peri-operative mortality is around 15-20%, three months survival at 50%, one year survival at 15% and five year survival at 1-2%. There is no different in terms of survival time between central and peripheral by-pass. However the result of the non-jaundice case is far bettter than the jaundice. The peri-operative mortality rate of our liver and tumour resection is less than 2%, for one year survel is 75%, two year survival is 50%, and five year survival is 15%. Amongst the five-year survival rate, the surgical pathology is usually unilateral lobe with no regional node involvement[3].

Discussion

An association between chronic trematode infection and cholangiocarcinoma was first proposed by Katsurada (1987) in his report of primary liver cancer occurring with Clonorchiasis[5]. Chronic infection due to Opishorchis viverrini results in bile duct epithelial changes including adenomatous hyperplasia, goblet cell metaplasia and periductal fibrosis. Dysplasia as well as carcinoma in situ arising in conjunction with fluke induced non-neoplastic duct lesions have been demonstrated[1]. In all our surgical specimens as well as the ultrasonographic pictures in those who present for surgical management, the combination of Opisthorchiasis pattern and cholangiocarcinoma are always seen. We then regard the cholangiocarcinoma as a complication or as the progress of Opisthorchiasis pathology. This is further supported by the evidence of either living flukes or fluke ova found in green bile almost in eight out of ten of our patients[4]. However the finding of living flukes or ova in white bile are far less in our observation. White bile represents prolonged obstruction: one may postulate that the environment of prolonged obstruction or white bile may be unsuitable surrounding for the flukes to survive.

Clinicopathological observation has verified that biliary cancer associated with liver flukes occurs not only at the site where the flukes have established chronic infection but at the peripheral part of the liver and extrahepatic bile duct as well[6]. Both intra and extrahepatic tumour (30%) may be multifocal. Intrahepatic tumour may be classified as : central

(60%), peripheral (20%) and diffuse (20%)[7]. The central will always presents with obstructive jaundice. The peripheral and the diffuse are usually present as hepatomegaly and non-jaundiced. Unilateral lobe is the type of non-jaundice with relatively good prognosis when compared with the jaundice of Klaskin type of tumour.

There is no reason to assume that the non-jaundiced peripheral unilateral lobe type is the early pathology of the jaundiced central or Klatskin type of tumour. One can only postulates that without jaundice its better prognosis may be due to the minimal damage it makes to the rest of the liver and the tumour is only confined to either certain lobe or segments. The most common segments involved are segment VII and segment VIII[3].

After excision of the diseased lobe by either right of left hepatectomy, the remainning lobe is usually macroscopically free of tumour and still retains adequate liver function. This may then account for the favourable prognostic factors of the non-jaundice.

Up to date, surgery is still the main stay of the management of complicated Opisthorchiasis or cholangiocarcinoma and only palliative result could be expected. Unless means of early detection and screening survey amongst the population of the endemic area of Opisthorchiasis are available, the improvement of surgical result is obviously difficult.

At present there is no specific early detection or tumour marker as comparable with a-fetoprotein in hepatocellular carcinoma. Only suggestive tests such as persistent raised alkaline phosphatase, CEA and ultrasonography are available. Prevention of Opisthorchis infestation is then the logical means to deal with this local public health problem.

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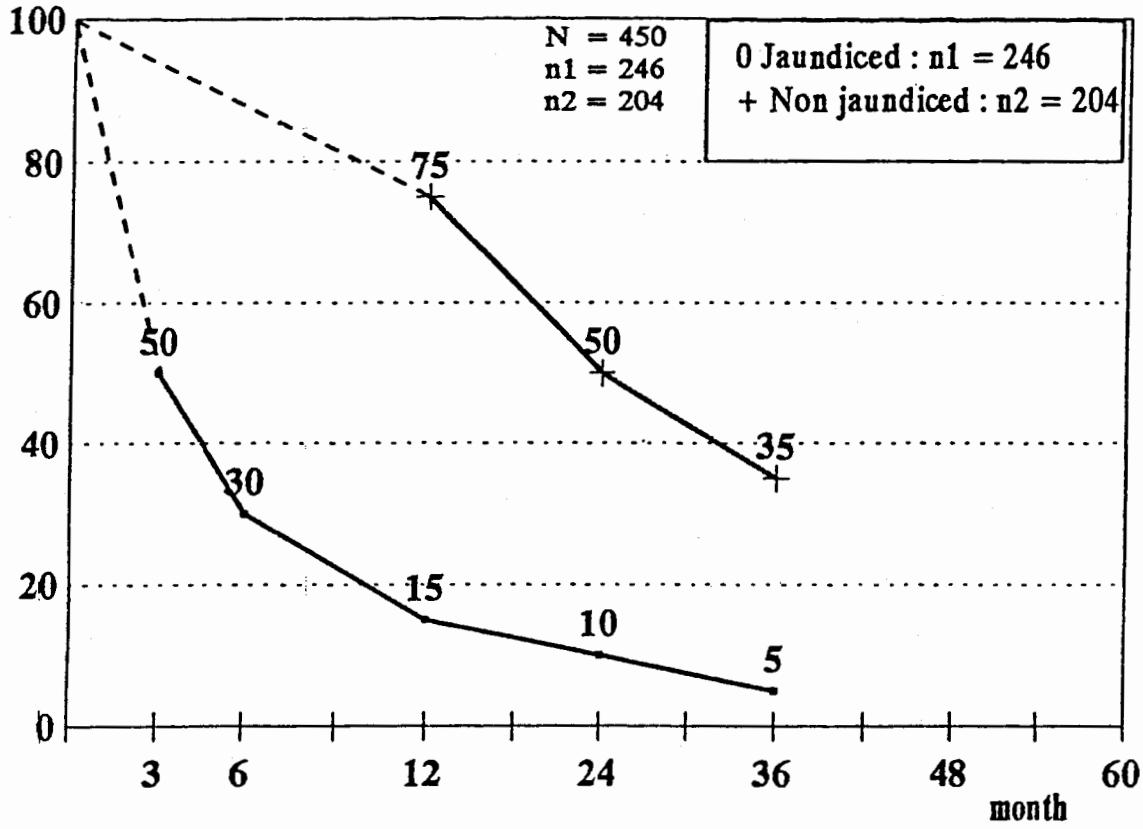
Fig. 1



Cholangiocarcionma (1988-1991)
Comparison of survival curve of the jaundiced and the Non-jaundiced