LEADING ARTICLE

CHOLANGIOCARCINOMA UPDATED

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Cholangiocarcinoma (WHO) is a synonym for carcinoma of the bile duct, and may arise from any part of biliary system. It can be classified according to the site of occurrence : 1) peripheral cholangiocarcinoma arises from the small intrahepatic bile duct; 2) Hilar cholangiocarcinoma arises from the major intrahepatic bile duct including the hilum; 3) Extrahepatic bile duct carcinoma is found outside the liver[1]. Intrahepatic bile duct carcinoma has been known by several other names like alveolar carcinoma, cholangioma, malignant cholangioma, cholangiocellular carcinoma, etc. It is sometimes difficult to differentiate a small hilar type cholangiocarcinoma of the liver near the hilum from an extrahepatic cholangiocarcinoma at the hepatic duct within the portahepatis as described by Klatskin[2]. Gallbladder cancer invading the surrounding structure can also cause a problem. Bile duct carcinoma do have a tendency to infiltrate extensively in the submucosal plane and typically invades local tissues early. Ten percent of bile duct tumours are thought to be multicentric.

Cholangiocarcinoma is a rare tumour first reported in 1840[3]. Sako reported a frequency of 0.01-0.46% on autopsy[4] and Neibling found one in about 200 operations involving the biliary tree[5]. In Japan, it accounts for about 10% of all primary liver cancers[6]. Locally Lee et al noted that only 121 cases (about 1/12 of the Hepatocellular carcinoma cases) were reported during a 15-year period[7]. The highest frequency is found in the sixth and seventh decades of life and men have a slight predominance over women. With the advances in diagnostic methods, surgical techniques and radiation therapy, the diagnosis and management of patients with primary bile duct cancer remain difficult.

The cause of bile duct carcinoma is unknown. Recent data suggest that obstruction of the bile duct has a role as a tumour promoter though it is not clear whether this is a direct effect of the bile/bile acid or a secondary effect of obstructive jaundice on the reticuloendothelial system[8]. Gallstones and hepatolithiasis are seen in 20 to 50% of patients[9,10]. An association between ulcerative colitis especially those with pancolitis with and without sclerosing cholangitis and bile duct carcinoma has been reported[11-13] and the ages of these patients were 20 to 30 years younger than the median age of ductal cancer patients without ulcerative colitis[12]. Patients suffering from sclerosing cholangitis have a more than 31 times greater risk of developing cholangiocarcinoma than the general population[14]. Chronic clonorchis infestation can lead to a adenomatous hyperplasia of the bile duct epithelium and to cholangioma[15]. However, the significance of parasitic infection in the development of bile duct cancer is still debatable. Cystic diseases of various kinds, namely, congenital fibrosis of the liver, Caroli's syndrome, choledochal cyst and polycystic liver may be associated with cholangiocarcinoma[16, 17]. The incidence of carcinoma arising from congenital bile duct cysts is reported to be between 2.5% and 15%.

Obstructive jaundice is the most common presentation and it is usually progressive. Other symptoms like upper abdominal pain, weight loss, fever, abdominal distension have been observed. Some patients present with acute cholecystitis or mucocele of the gall bladder. Pancreatitis can occur secondary to pancreatic duct obstruction. There is no specific diagnostic laboratory tests for bile duct carcinoma. Carcinoembryonic antigen (CEA) and CA 19-9 are both elevated. Ultrasonography being non invasive, should be done as the first investigation for the elucidation of obstructive jaundice. Combined with the Doppler facility in centres where it is available, ultrasound is a superb tool in experienced hands. For better anatomic definition, endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) would be necessary. Computed tomography (CT) and arteriography may be used for evaluation of difficult cases especially hilar lesions. Magnetic resonance imaging may improve resolution compared with CT in the evaluation of proximal bile duct tumours. Endoscopic ultrasound has not yet been shown to have major advantages in diagnosis compared with other modalities. Surgical exploration remains the principal method of diagnosis. Though non-operative percutaneous aspiration of tumour or cytology of biliary fluid can be done, histologic diagnosis can be difficult due to scarring around the tumour and also due to patchy nature of the disease. Preoperative biliary decompression by ERCP stenting or PTC drainage improves liver function and gives time to improve nutritional state of the patients. The mortality rate is however not affected[18-20].

Surgery is the only hope for cure in this condition. However, by the time of diagnosis, one-third of the patients have lymph node metastasis, one-third have involvement of liver and hilar structures and one-half have nerve sheath involvement. The first bypass procedure for this condition was performed in 1896[21]. It was not until 1903 that the first successful resection of a primary bile duct carcinoma was performed[22]. Tumours of the distal common bile duct are usually amenable to resection by pancreatoco-duodenectomy (Whipple procedure). Lesions located in the upper third of the common bile duct are usually unresectable and, when resected are often incompletely removed. Recent attempts at more extensive and aggressive surgery have resulted in improved survival[23-26]. Boerma reviewed 581 resections of hilar bile duct tumours described in 40 papers from 1954 to 1989[27]. Marked improvement in operative mortality and 1- and 5-year survival were reported in publications after 1980 though the average figures

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do not approach the good survival reported in those published recently[27]. Better patient selection for major procedures probably contributed to the improved recent figures for major resections. Nimura et al reported that curative resection was possible in 70% of patients with an operative mortality of 6.4% and morbidity 41.3%. The 3-year and 5-year survival were 55% and 40.5% respectively[23]. Comparing the outcome of patients treated by radical resection with curative intention and those treated with palliative surgery, a review of 552 extrahepatic bile duct tumours managed in France showed an operative mortality of 9.5% for curative resection compared with 30.9% for palliative resection. The 1-year survival was 68% in patients who underwent curative resection and 31% in those with palliative surgery[24].

For some patients, palliation is the only option because of the extent of the tumour and/or general debility. Endoscopic or percutaneous stenting or a surgical bilienteric bypass will relieve symptoms. However good palliation should not only relieve symptoms, it should also reduce hospitalisation and avoid additional morbidity. In previous years, the debate in the management of bile duct tumours concentrated on the role of surgery versus stenting. It now seems clear that except in the very debilitated patients, operative bilienteric bypass provides the best palliation for inoperable tumours[28]. If the tumour is resectable, the best survival results are from specialist centres where very extensive resections and reconstructions can be accomplished relatively safely. This holds hope for the future in the treatment of patients with this difficult tumour.

Preliminary results seem to show post-operative irradiation improved survival in patients who underwent palliative tumour resection[29]. However prospective studies are warranted to establish the value of radiation therapy in cholangiocarcinoma. The role of chemotherapy is not known though Oncology Group (ECOG) showed that it is not recommended in inoperable bile duct carcinoma after performing several clinical trials[30]. The use of chemotherapy, either alone or combined with radiation therapy, must be further investigated.

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