Pergamon

European Journal of Cancer, Vol. 34, No. 12, pp. 1845–1851, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(98)00166-X

Review

Biliary Cystadenocarcinoma of the Liver: the Need for Complete Resection

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We report on a patient with biliary cystadenocarcinoma and review 112 previously published cases of this rare cystic hepatic neoplasm. This tumour mainly occurs in women at a ratio of 62% (female) to 38% (male), and at an average age of 56.2 years (range 18–88 years). The origin of these neoplasms is intrahepatic in 97% of cases and extrahepatic in the remaining 3%. The clinical symptoms are non-specific and are not distinctive from benign cystic liver lesions unless invasive growth of the tumour occurs or distant metastases are present. Sonography and computed tomography (CT), as well as magnetic resonance imaging (MRI) demonstrate the multilocular nature of the tumour with septal or mural nodules. Discrete soft tissue masses, thick and coarse calcifications and varying density on CT or intensity on MRI within the loculi are additional non-specific imaging findings. The best therapeutic result with a 5-year survival rate of 100% and a recurrence rate of only 13% was achieved by complete excision ($n = 16$). Surgical removal of the tumour by complete excision is, therefore, the treatment of choice for biliary cystadenocarcinomas.

Key words: biliary tract, cystadenocarcinoma, cystadenoma, malignant, neoplasm, liver, cyst
Eur J Cancer, Vol. 34, No. 12, pp. 1845–1851, 1998

INTRODUCTION

BENIGN BILIARY cystadenomas and cystadenocarcinomas are rare cystic neoplasms which usually arise in the liver or, less frequently, in the extrahepatic bile ducts or the gall bladder. The first case of cystadenocarcinoma was documented by Willis [1] under the title 'Carcinoma arising in congenital cysts of the liver'. Since then, over 100 cases have been published in the world literature. Clinical manifestations are non-specific, and include upper abdominal mass, local pain, jaundice and weight loss. Some patients are asymptomatic, and the exact diagnosis, therefore, has generally been made on the basis of histopathological examinations on surgical or autopsy material. Morphological findings include septa and multilocular cystic masses lined by mucus-secreting epithelium with papillary infolding and containing mucoid fluid. Based on such findings, diagnosis can be suspected preoperatively in some rare cases. However, only microscopic investigations can reliably differentiate between biliary cystadenoma and its malignant counterpart, cystadenocarcinoma. Therefore, complete surgical resection of these cystic tumours should be mandatory in order to identify reliably the tumour's degree of malignancy.

In the present study, we report on our own case of biliary cystadenocarcinoma of the liver and review the current knowledge of this unusual tumour by analysing 112 cases published so far. The difficulties of pre-operative imaging assessment and histopathological differential diagnosis are discussed, and the importance of extended resectional procedures for these rare hepatic tumours is emphasised. If detected early and radically resected as a curative attempt, excellent results can be achieved compared with other primary hepatic tumours.

CASE REPORT

A 69-year-old Caucasian female was admitted with acute epigastric pain. Ultrasonography showed multiple bile duct calculi and a cystic mass with a diameter of 2 cm in the left

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Received 2 Dec. 1997; revised 16 Mar. 1998; accepted 3 Apr. 1998.

liver lobe. An abdominal computed tomography (CT) scan confirmed a well-defined solitary and unilocular cyst in segments II and III of the liver (Figure 1) which was believed to be a benign liver cyst. A fine needle aspiration (FNA) was performed which revealed no malignant cells. No positive markers for hepatitis A or B were recorded. Endoscopic retrograde cholangiopancreaticography (ERCP) with papillotomy and extraction of multiple calculi from the common bile duct were carried out. A mild pancreatitis was reported after ERCP. The patient was regularly followed-up using CT scans.

Five years later, the patient was re-admitted to our department. A physical examination demonstrated a painful epigastric mass. Neither fever, weight loss nor ascites were found. Biochemical tests were unremarkable, and both alphafetoprotein (AFP) and carcinoembryonic antigen (CEA) levels were within normal range. Abdominal ultrasonography demonstrated the non-homogeneous cystic mass in the left lobe of the liver to now measure 10×15 cm. The lesion had a liquid core and showed an infiltrating pattern. Abdominal CT scan confirmed the presence of a cystic mass with a small hypodense satellite lesion in segments II, III and IV (Figure 2). A FNA of the mass yielded well-differentiated cuboidal cells of a mucinous adenocarcinoma. A body scintigram with ^{99m}Tc was performed to exclude bone metastases. Chest radiography, colonoscopy and gastroscopy failed to visualise other neoplasms. Our pre-operative imaging assessment of resectability [2] demonstrated an expanding hepatic tumour of unknown degree of malignancy and origin in segments II, III and IV.

At laparotomy, a large mass with multiple satellite lesions was found in the left liver lobe. Although the neoplasm was adjacent to the hilum of the liver, it had not infiltrated it. Intra-operative ultrasonography did not reveal any lesions in the right liver lobe. Complete resection of the tumour was achieved by a left hemihepatectomy, after which the patient had an uneventful postoperative course and remains asymptomatic 30 months postoperatively without disease recurrence.

Gross and histopathological findings

Macroscopically, the centrally cystic, unilocular tumour measured 11×9×4 cm. Histology showed a moderately differentiated adenocarcinoma with a papillary growth pattern (Figure 3A). The papillary structures were lined by columnar

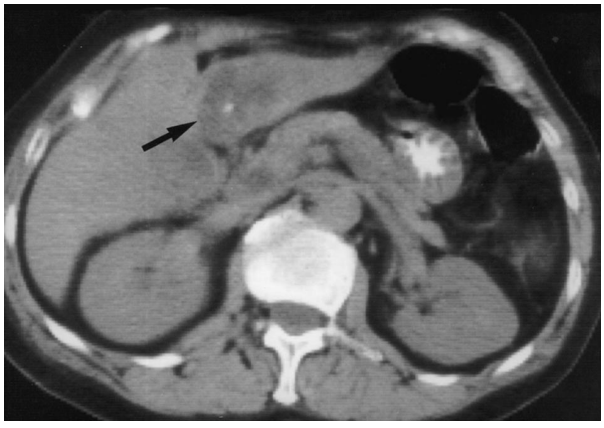


Figure 1. Non-enhanced computed tomography of the liver demonstrates a low density mass in the left lobe with a thick calcification (arrow). The lesion was erroneously considered to be a benign liver cyst.

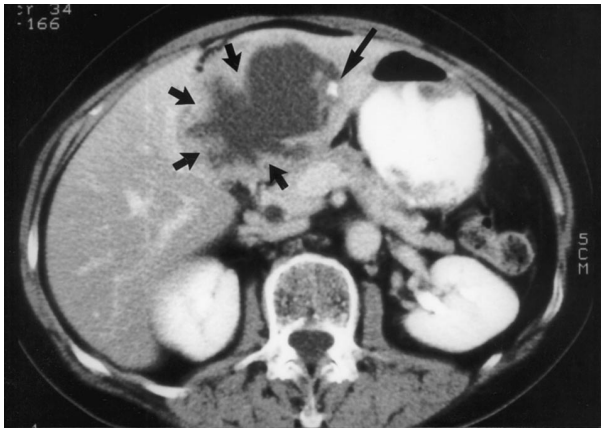
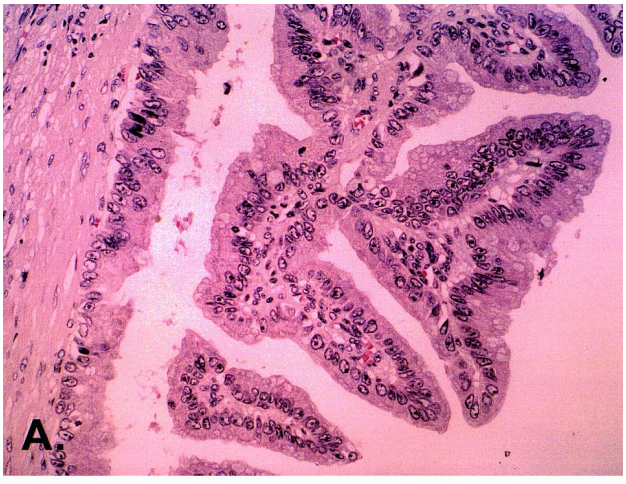


Figure 2. Enhanced computed tomography, 5 years after Figure 1, shows enlargement of the liver lesion, which now involves segments II, III and IV. Note that the calcification, in eccentric position, is thick and coarse (long arrow). Note the thick, peripheral, incomplete septa, that are enhanced (short arrow).



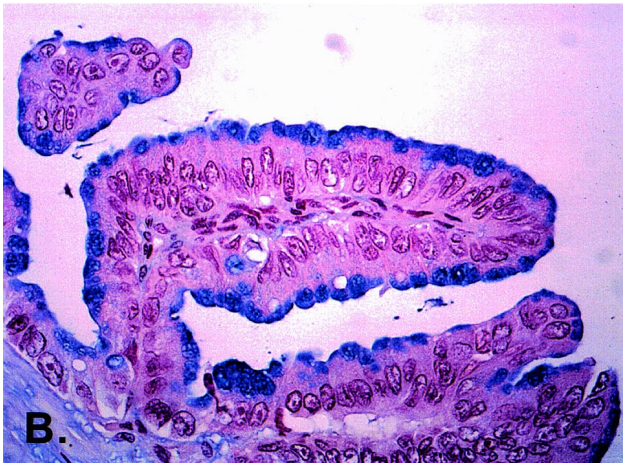


Figure 3. (A) Cystadenocarcinoma of the liver, histological details. Note the papillary growth pattern with slender vascular axes lined with cylindrical epithelial cells (haematoxylin and eosin stain; ×180). (B) With this glycoprotein stain, mucus formation and storage in the apical parts of tumour cells are demonstrated (alkaline alcian blue stain; ×250).

cells with apical mucin accumulation (Figure 3B). The mitotic rate was moderately high. The tumour had a peripheral fibrotic border facing atrophic liver parenchyma.

Immunohistochemically, the tumour cells were strongly reactive for cytokeratins 8, 18 and 19, and for epithelial membrane antigen (EMA), but much less so for CEA. The diagnosis of moderately differentiated biliary cystadenocarcinoma was established.

REVIEW OF REPORTED CASES

Demographic

A total of 113 patients (including our own) with biliary cystadenocarcinomas of intra- and extrahepatic origin have so far been reported in the English, Japanese, French, German and Italian literature. Although some of the older reports [3, 4] describe the typical pattern of biliary cystadenocarcinoma, they have not been included in this survey, because their detailed histological features were lacking. The neoplasms mainly occurred in women at a ratio of 62% (female) to 38% (male), and at a mean age of 56.2 years (range 18–88 years).

Presentation (Table 1)

The clinical manifestations were non-specific and variable. 51 patients (57%) complained of diffuse abdominal discomfort or severe constant pain in the region of the right upper quadrant or epigastrium, and 27 patients (30%) complained of an abdominal mass that was confirmed by physical examination. 23 patients (26%) were admitted with an elevation of one or more of the liver function tests alkaline phosphatase, glutamine-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), gammaglutamyl transpeptidase or bilirubin. 16 patients (18%) had a history of intermittent or constant jaundice. Less common symptoms at initial presentation were fever in 13 patients (14%), weight loss in 10 patients (11%) and ascites in 5 patients (6%). The mean duration of symptoms prior to final treatment was 29.3 months and the range varied from 1 day [5] to 12 years [6, 7] in the 46 patients for whom it was reported.

Diagnosis (Table 2)

A total of 189 radiological examinations were reported in 64 patients. Abdominal ultrasound, performed in 47 patients, revealed a well-demarcated, mostly multilocular hypoechogenic mass in all patients. Papillary projections into the tumour wall were reported in 9 patients, and in 10 there was an intrahepatic bile duct dilatation. CT scans confirmed the hypodense cystic lesions in the livers of all 45 patients on whom it was performed. Internal papillary projections and septum formations, better seen after contrast administration, were found in 11 patients. Intrahepatic bile duct dilatation was described in 6 patients. Angiography, performed in 26 patients, revealed an avascular or hypovascular mass, although the lesion did present in a neo- or hypervascular pattern in 6 patients. ERCP, performed in 9 patients, and percutaneous transhepatic cholangiography in 11 patients, showed obstruction of the biliary tree in 16 cases, and dilatation of the intrahepatic in 5 and of the extrahepatic in 2 individuals. 2 patients had a communication between the cyst and the intrahepatic bile ducts [8, 65]. 11 patients underwent radionuclide liver scans which demonstrated a cold area in 10 cases. MRI investigations of the abdomen confirmed the presence of a cystic mass in the liver of all 4 patients on whom it was performed. 3 patients underwent an oral cholecystogram which was normal in 1 [9], failed to visualise the gall bladder in 1 [10] and showed a downward displacement of the gall bladder in 1 [11]. Plain film of the abdomen and of the chest showed an elevation of the right diaphragm in 2 patients [8, 9].

The AFP serum level was elevated in 2 of 25 patients (8%). CEA and CA 19-9 were measured in 22 and 11 patients, respectively, and showed raised levels in 3 (14%) and 4 (36%) patients, respectively. On the basis of imaging assessment and FNA, cystadenocarcinoma or cystadenoma was suspected pre-operatively in 13 patients.

Surgical therapy (Table 3)

All except 10 patients underwent an exploratory laparotomy for final diagnosis and treatment. The mass was confined to the left liver lobe in 55 patients (49%) and to the right lobe in 35 patients (31%). Both lobes were involved in 13 patients (12%) and the porta hepatis in another 4 patients (4%). In 2 patients (2%), the tumour originated from one of the hepatic ducts and extended into the liver parenchyma. Extrahepatic tumour growth into the hepatoduodenal ligament [12], the gall bladder [13] and the common hepatic duct [14] was observed in 3 patients. The origin of the tumour was unknown in 1 patient [14].

Treatment and follow-up information was not available in 30 patients. For the other 83 patients, at the time of the primary operation, a left or right hepatic lobectomy was

Table 1. Clinical presentation [1, 5–65]

Presentation	% of patients ($n = 90$)
Abdominal pain or discomfort	57
Abdominal mass	30
Elevated liver function test	26
Jaundice	18
Fever	14
Weight loss	11
Ascites	6
General fatigue	4
Nausea, vomiting	3
Chills	3
Others	16
No symptoms	11
Unknown	23

Table 2. Radiographic evaluation [1, 6, 8–12, 20, 21, 23–26, 28–33, 35, 36, 38, 40–45, 47–50, 52–58, 60–65]

Test	No. of patients	% of positive findings
Ultrasound	47	100
CT scan	45	100
Angiography	29	97
ERCP and PTC	20	100
Upper GI	13	62
Liver scan	11	91
IVP	5	20
MRI	4	100
Oral cholecystogram	3	33
Tomogram	3	100

CT, abdominal computed tomography scan; ERCP, endoscopic retrograde cholangiopancreaticography; PTC, percutaneous transhepatic cholangiography; GI, gastrointestinal series; IVP, intravenous pyelogram; MRI, magnetic resonance imaging.

Table 3. Treatment and long-term survival [1, 5–65]

Treatment	2-year survival rate (Kaplan–Meier)	No. of patients re-operated for recurrence
Hepatic lobectomy ($n = 24$)	65%	2
Complete excision ($n = 16$)	100%	2
Hemihepatectomy ($n = 11$)	68%	1
Partial excision ($n = 9$)	71%	6
Segmentectomy ($n = 6$)	100%	3
Drainage ($n = 3$)	Indeterminable	1
None ($n = 4$)	Indeterminable	–
Autopsy finding ($n = 3$)	–	–
Chemo- and/or radiotherapy ($n = 3$)	33%	–
Paracentesis ($n = 2$)	50%	1
Ligation of the inferior vena cava ($n = 1$)	Indeterminable	–
OLT ($n = 1$)	Indeterminable	–
Unknown ($n = 30$)	–	–

OLT, orthotopic liver transplantation.

performed in 24 patients (29%), 16 patients (19%) underwent total excision of the mass, 11 patients (13%) required a left or right hemihepatectomy and a partial excision was carried out in 9 patients (11%). A further 6 patients (7%) underwent a segmentectomy. Percutaneous drainage of the cyst was performed in 3 patients [15–17], either as drainage alone [17] or in combination with systemic chemotherapy and radiation [16] or infusion of 5-fluorouracil (5-FU) into the cyst [15]. No treatment in any form was given to 4 patients [10, 13, 18], and in another 3 patients [7, 19] diagnosis was made on autopsy. 3 patients had only chemo- and/or radiotherapy [20–22]. Paracentesis without any further intervention was carried out in 2 patients [1, 18] and another patient [18] underwent ligation of the inferior vena cava. In the final patient [23], an orthotopic liver transplantation was performed.

Outcome (Table 3)

For the patients who had a left or right hepatic lobectomy, both the 2- and 5-year survival rates (Kaplan–Meier) were calculated to be 65%. 2 [9, 24] required further surgery for recurrence of the tumour. All patients who underwent total excision of the mass were alive after 2 and 5 years, but 2 patients [11, 14] needed another procedure for recurrence. After a left or right hemihepatectomy there was a 2-year survival rate of 68% with just one re-operation for recurrence [25]. Although there was a 2-year survival rate of 71% after partial excision, the 5-year survival was only 36% and 6 of these patients (67%) had a recurrence of the tumour requiring surgery. Patients who had a segmentectomy had a 2-year survival rate of 100%. 3 [22, 65] experienced a recurrence necessitating surgery. It was not possible to distinguish from the literature whether the procedures hepatic lobectomy, hemihepatectomy or segmentectomy resulted in either complete or incomplete tumour excision. Patients with chemo- and/or radiotherapy alone had a 2- and 5-year survival rate of 33%. Paracentesis alone resulted in a 2-year survival rate of 50% with 1 recurrence [18]. The patient who had a ligation of the inferior vena cava died 2 days postoperatively of cardiac arrest. The patient with an orthotopic liver transplantation died of a ruptured aneurysm of the arterial anastomosis 2 months after the operation. Because of the lack of data it could not be ascertained if all deaths were tumour related. No follow-up data were available from the patients who had percutaneous drainage of the cyst or those without treatment.

Definition, pathology and histogenesis

Definitions of benign and malignant cystic biliary tumours are given in the updated WHO classification [66] and in a recent article proposing a parallel classification of biliary tract and pancreatic neoplasms [67]. Cystic biliary tumours comprise serous and mucinous cystadenomas and mucinous cystadenocarcinoma. Serous cystadenomas of the biliary tract are rare tumours characterised by small cysts lined with clear cuboidal cells. Unilocular or multilocular mucinous cystadenomas are apparently benign cystic tumours lined with a single layer of mucin-secreting, well differentiated columnar cells which frequently form papillary structures. Interestingly, many of these tumours present with a cellular, 'ovarian-type' stroma [68] leading to the term, cystadenoma with mesenchymal stroma (CMS) [69]. This feature also occurs in cystic tumours of the pancreas and has resulted in the suggestion that these neoplasms represent the 'benign' end of an adenoma–carcinoma sequence [67]. Most mucinous biliary cystadenomas arise in the liver, and only very few are observed in the extrahepatic bile ducts and the gall bladder [13, 70]. The biliocyte origin of the tumours is underlined by the expression of cytokeratin 19, and the tumours are thought to originate from smaller ducts in the liver and from periductal glands in extrahepatic ducts [67]. Even though the term adenoma implies a benign behaviour, there is current debate with respect to the biology of those cystic tumours which exhibit cellular atypia (dysplasia). In the pancreas, mucinous cystic tumours with moderate dysplasia are classified as borderline [66], whereas the current classification of biliary cystic tumours offers no borderline designation, even though this situation is, as such, recognised [71].

Biliary cystadenocarcinomas consist of a similar biliocyte-derived epithelial cell population which has, however, atypical and, at least in some of the cases, visible invasive growth. In our study, malignant papillary epithelium coexisting with foci of benign columnar epithelium was observed in 91%, whereas in 9% exclusively malignant epithelium was found. These tumours may develop into large masses, the size of which ranged from 1.2 to 30 cm (mean 12.4 cm) [13, 16]. The cysts were multiloculated in 84% and uniloculated in 16%, which included our patient. With respect to invasion, our study revealed that, of 63 patients, tumour growth was confined to the cysts in 30 cases (48%), whereas invasive extension into adjacent liver or neighbouring organs was seen in 33 cases (52%). Distant metastases were found in 15

patients (20%), including regional and extrahepatic lymph nodes in 8 patients (13%), bones in 3 patients (5%), lungs in 2 patients (3%), and omentum, mesenterium, pancreas, stomach and kidneys in one patient each. Peritoneal spread may occur [26]. Based on detectable invasion, two prognostic groups of biliary cystadenocarcinoma were proposed [27], i.e. a non-invasive type and an invasive type. Although mucin histochemical and immunohistochemical techniques did not demonstrate any difference between the two groups, there was a difference in prognosis. In contrast, Devaney and colleagues [13] could not ascertain any distinction between these two groups with respect to outcome. These authors, however, proposed three distinct types of cystadenocarcinoma. The first type, arising in pre-existing cystadenoma of the CMS type, occurs exclusively in females and follows a relatively indolent course in most instances. The second type is not associated with adenoma, mainly occurs in males and has an extremely aggressive course. The third type consists of cystadenocarcinoma lacking the dense stromal component and occurs in females; no information on the clinical course in these patients was given. There are too few patients with biliary cystadenocarcinoma described in the literature to generate accurately information about the prognostic value of either tumour invasion or the presence of distinctive mesenchymal stroma. Finally, a further classification of cystic lesions has been proposed by Kawarada and associates [28], which suggests that isolated biliary cystadenocarcinoma bears a worse prognosis than carcinoma arising in a simple cyst of the liver.

DISCUSSION

Biliary cystadenocarcinoma is a rare cystic neoplasm and is classified as one of the malignant epithelial tumours of the liver. According to Takayasu and colleagues [29], the incidence of biliary cystadenocarcinoma among hepatic malignant epithelial tumours is as low as 0.41%. The clinical presentation is usually mild and not distinctive from other lesions of the liver (Table 1). Some of the reported cases remained undiagnosed until autopsy [7, 19]. 1 patient with a huge mass obstructing the inferior vena cava and the right portal vein did not notice the mass, probably due to the very slow growth of the neoplasm [29]. In another reported case, osseous metastasis from liver cystadenocarcinoma occurred 1 year before the discovery of the primary lesion [21]. Rarely, severe abdominal pain as a result of intracystic haemorrhage or rupture may occur. Although the tumour size ranges from 1.2 to 30 cm in the largest diameter, most of them are large (mean diameter 12.4 cm) which accounts for the most common presenting symptoms, such as abdominal pain or discomfort (57%) and palpable mass (30%). Less commonly, the patients suffer from intermittent or constant jaundice (18%), fever (14%), weight loss (11%) and ascites (6%). In general, ascites and jaundice are late symptoms, owing to recurrence or metastases. Jaundice may occur as a result of progressive displacement of the liver parenchyma by the neoplasm, obstruction of the major bile ducts by external pressure of the tumour [14, 30, 65] or by mucus hypersecretion [6]. Fever may be caused either by consecutive cholangitis or by the neoplasm itself.

The aetiology of biliary cystadenocarcinoma remains largely unknown. One of the proposed theories is that it develops from ectopic remnants of primitive foregut sequestered within the liver [18, 29, 69]. Another recent report has suggested an origin from ectopic rests of embryonic gall bladder tissue [72]. However, the demonstration of benign epithelium in over 90% of the cystadenocarcinomas makes it highly probable that they arose in previously benign cystadenomas. Craig and colleagues [65] described a malignant transformation of cystadenomas in 25% of cases. Further indirect support for this hypothesis is provided by the observation that the mean age of patients with cystadenomas was approximately 5 years younger than those with cystadenocarcinomas [31]. Rarely, biliary cystadenocarcinoma has been reported to arise from a congenital cyst [1, 5, 32] or extrahepatically from the hepatoduodenal ligament [12], the gall bladder [13] or the common bile duct [14].

Ultrasonography and CT scans show the cystadenoma as a multiseptal cystic mass that frequently has mural nodules at the periphery (Table 2). At CT, after intravenous administration of contrast agent, enhancement of the septa and mural nodules can be seen. Mural or septal nodules, discrete soft-tissue masses and possibly thick or coarse calcifications increase the likelihood of a cystadenocarcinoma. MRI complements the other imaging modalities by displaying the mass in multiple planes and by characterising the content of the different locules not as serous fluid but as a complicated collection of bile, proteinaceous material and haemorrhagic debris. This material produces the heterogeneous signal intensities seen in the T1 or T2 weighted sequences on MRI.

It has been generally suggested that biliary cystadenocarcinoma has a better prognosis than either hepatocellular carcinoma or cholangiocarcinoma [6, 33], as is the case in mucin-hypersecreting carcinoma of the pancreas compared with pancreatic carcinomas of usual type. The majority of these tumours are slow growing, which is reflected in a mean duration of 29.3 months between the first symptom and treatment. 2 patients had a 12 year history of fever, chills and right upper abdominal pain prior to undergoing laparotomy [6, 7]. In fact, the 3-year (5-year) survival rate (Kaplan–Meier) of all resected cases has been calculated as 74% (57%), compared with 52% (40%) in hepatocellular carcinoma [73] and 26% (22%) in cholangiocarcinoma [74].

Despite its relatively benign clinical course, the only safe attitude that can be proposed is total surgical resection of the neoplasm by a formal hepatic resection. However, two-thirds of patients who had only local or pericystic excision experienced tumour recurrence (Table 3). In contrast, just 5 of 51 patients (10%) who had hepatic lobectomy, hemihepatectomy or complete excision required further surgery for recurrence. Also, since cystadenocarcinomas are believed to arise from benign cystadenomas and differentiation of these two conditions cannot be made macroscopically, we propose radical excision of all multilocular cystic tumours of the liver. Most of the time, a complete formal resection with a margin of normal liver tissue is possible and should be performed. No further treatment is usually required if the tumour is confined to the liver.

With reference to the differential diagnosis and differential therapy of benign hepatic cystic lesions, there can be no doubt that singular benign cystic lesions are a quite distinct clinical and diagnostic entity. Their assessment can usually be made pre-operatively, and the treatment consists of a resection of the cystic roof. Insertion of an omental patch into the hepatic defect may reduce postoperative bile leakage [75].

For the multiple cystic lesions with both intraparenchymal and cystic wall abnormalities, we recommend a hepatic resection. Further, in polycystic liver disease, both unroofing of the cyst and resection as published by Vauthey and colleagues [76] are appropriate.

There remains debate whether malignant lesions of the liver should be transplanted. With a severe shortage of transplantable organs, we advocate a conservative approach, limiting the criteria to benign lesions. The experience with orthotopic liver transplantation in patients with cystadenocarcinoma is limited to a single case report. This patient died 2 months after transplantation due to a ruptured aortic aneurysm [23]. However, because of the relatively benign clinical course of biliary cystadenocarcinoma, it is our opinion that orthotopic liver transplantation is appropriate in cases of complete hepatic involvement.

In patients with metastasis (20%), chemo- and/or radiotherapy have been advocated. Castelletto and associates [22] reported on a patient in good general condition 84 months after administration of doxorubicin and 5-FU. The benefit of postoperative radiation and/or chemotherapy cannot, however, be evaluated at this time. Aspiration and sclerosing therapy, marsupialisation and internal drainage should be avoided. Although FNA or needle biopsy may be helpful diagnostic procedures, they should not be performed, since peritoneal carcinomatosis secondary to imprudent biopsy of the cystadenocarcinoma has been reported [27, 34, 35]. For the same reason, the cyst should be left intact during the surgical procedure. Despite negative cytology for tumour cells in cystic fluid, 1 patient succumbed to peritoneal carcinomatosis after accidental cyst rupture occurred during the operation [36].

CONCLUSION

Total excision of a cystadenocarcinoma of the liver is the treatment of choice when feasible. During the operation, the cyst should be left intact in order to avoid the possible spilling of cystic fluid into the abdominal cavity and development of peritoneal carcinomatosis. For the same reason, FNA or needle biopsy is, in our opinion, contraindicated. After complete excision of the neoplasm, no further treatment is usually required if the tumour is confined to the liver alone. Aspiration and sclerosing therapy, marsupialisation and internal drainage procedures should be avoided. The benefit of adjuvant chemo- and/or radiotherapy cannot be evaluated at this time.

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