

Review article: the modern diagnosis and therapy of cholangiocarcinoma

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SUMMARY

Cholangiocarcinomas are epithelial neoplasms that originate from cholangiocytes and can occur at any level of the biliary tree. They are broadly classified into intrahepatic tumours, (extrahepatic) hilar tumours and (extrahepatic) distal bile duct tumours. In spite of well-understood predispositions, most cholangiocarcinomas arise in the absence of risk factors. In suspected cases, the diagnosis can be established with non-invasive imaging studies.

Biliary invasion should be reserved for patients with obstruction. In high-risk patients, advanced cytological tests of aneuploidy (digital image analysis and fluorescent *in situ* hybridization) aid early diagnosis. In the absence of primary sclerosing cholangitis, curative surgical resection has 5-year survival rates of 2–43%, higher survival observed in patients with clear surgical margins and concomitant hepatic resection for hilar tumours.

Patients with unresectable cholangiocarcinoma or pre-existing primary sclerosing cholangitis should be considered for liver transplantation with neoadjuvant chemoradiation, in specialized centres.

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INTRODUCTION

Cholangiocarcinoma refers to an epithelial cell neoplasm with biliary epithelial cell differentiation; current concepts suggest that these cancers arise from cholangiocytes, the cells which comprise the biliary epithelium. This diagnosis encompasses three very distinct tumours by location, and probably by biology as well. These are intrahepatic cholangiocarcinoma, hilar cholangiocarcinoma and distal extrahepatic bile duct cancers. Cholangiocarcinoma is the second most common primary hepatic cancer. Though the overall incidence is low, it is on the rise globally. Risk factors for development of cholangiocarcinoma are age, primary sclerosing cholangitis (PSC), chronic choledocholithiasis, bile duct adenoma, biliary papillomatosis, Caroli's disease, choledochal cyst, thorotrast, smoking, parasitic biliary infestation and chronic typhoid carrier state. However, most cholangiocarcinomas arise in the absence of underlying risk factors. Many intrahepatic cholangiocarcinomas present as mass lesions. The diagnosis of hilar and distal extrahepatic bile duct cancers is suspected in patients with symptoms of biliary obstruction, right upper quadrant pain and cholangitis. Biliary visualization is essential for the diagnosis of these cancers and can be performed invasively or non-invasively. Magnetic resonance imaging with concurrent magnetic resonance cholangiopancreatography is the radiological modality of choice to assess the extent of disease. Biliary instrumentation is recommended only in the setting of either biliary obstruction or to sample suspicious lesions. Newer cytological techniques have improved the diagnostic yield of biliary sampling. Endoscopic ultrasound (EUS) is useful to assess the extent of disease and perform fine needle aspiration of regional lymph nodes. The natural history is of a rapidly progressive disease, with a median survival of months, if untreated. Surgical resection has been the mainstay of treatment with curative intent. There is renewed interest in orthotopic liver transplantation with neoadjuvant chemoradiation, single centre 5-year survival rates are >80% in a highly selected patient cohort.

DIAGNOSIS

The anatomic location of cholangiocarcinoma determines the optimal diagnostic strategy. About 50–60% of tumours occur at the bifurcation of the left and right hepatic ducts (hilar cholangiocarcinoma, 'Klatskin'

tumour), 10% are intrahepatic and 20–30% are extrahepatic distal bile duct tumours.¹ Hilar lesions are further classified, based on location, as suggested by Bismuth-Corlette (Figure 1). Most (>95%) cholangiocarcinomas are histologically adenocarcinomas. They are pathologically classified into sclerosing, nodular and papillary intraductal cancers.² A more recent pathological classification applies to both intrahepatic and extrahepatic cholangiocarcinomas, dividing them into mass-forming (nodular), periductal-infiltrating (sclerosing) or intraductal-growing (papillary) cholangiocarcinomas.³ Extrahepatic lesions commonly present with features of biliary obstruction, jaundice, pale stool, dark urine and pruritis. Fever, night sweats and weight loss may occur as well, in the absence of cholangitis. Intrahepatic cholangiocarcinoma presents with right upper quadrant pain. Rarely, the evaluation of abnormal liver tests, leads to the diagnosis of asymptomatic cholangiocarcinoma. In the past, diagnosis was made at an advanced disease state. Increasingly, at tertiary centres, patients with suspicious lesions are being referred early, aiding the early diagnosis. In patient with risk factors, the index of suspicion should be higher and advanced techniques need to be employed earlier to effectively diagnose and potentially cure the disease.

Serological testing is of limited utility. Liver test abnormalities reflecting obstruction are usually observed; however, aminotransferases may be normal. Several tumour-associated markers have been examined, including CA 19-9, carcinoembryonic antigen (CEA) and CA-125.⁴ CA 19-9 is most useful of these three. A value of >100 U/mL in patients with PSC has a sensitivity of 89% and specificity of 86% for the diagnosis of cholangiocarcinoma and in patients without PSC, the sensitivity is 53%.^{5, 6} Strikingly elevated CA 19-9 values in symptomatic patients usually signify advanced disease. CEA and CA-125 are also elevated in patients with cholangiocarcinoma but because of low sensitivity and specificity are not diagnostic. Furthermore, cholangitis and hepatolithiasis commonly lead to increased levels of all three tumour-associated markers. Cholangiocarcinoma should not be diagnosed on the basis of these tests alone. They should be used in conjunction with other individual patient characteristics.

Non-invasive imaging modalities are useful to visualize the location and extent of disease. Ultrasound is usually the first investigation performed for biliary obstruction. Intrahepatic cholangiocarcinomas may be identified as mass lesions, and bile duct dilatation may be seen proximal to the obstructing lesion.⁷ In PSC,

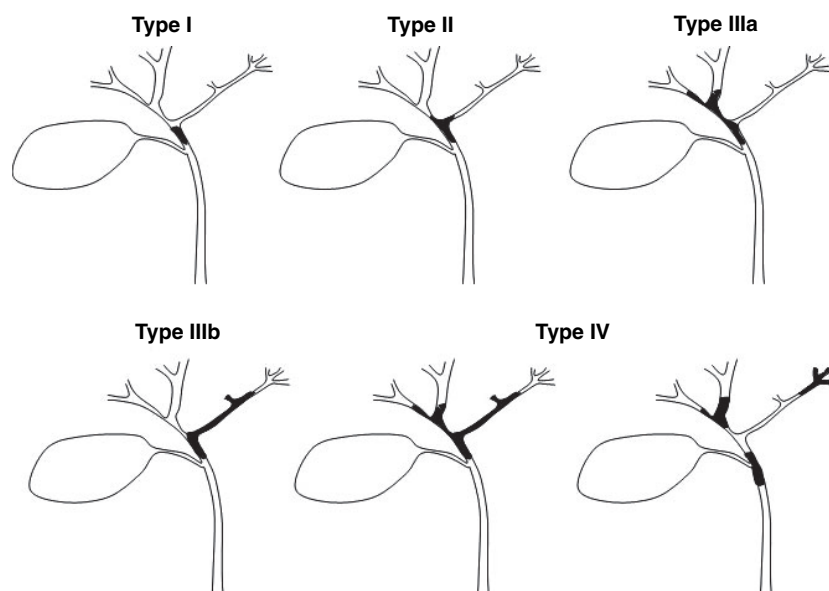


Figure 1. Bismuth-Corlette classification of hilar cholangiocarcinoma. Type I affects the common hepatic duct, distal to the confluence of the left and right hepatic ducts. Type II affects the confluence of the right and left hepatic ducts. Type IIIa affects the right hepatic duct in addition to the confluence. Type IIIb affects the left hepatic duct in addition to the confluence. Type IV refers to cholangiocarcinoma involving the confluence and both right and left hepatic ducts or to multifocal cholangiocarcinoma.

due to generalized periductal inflammation and fibrosis, bile duct dilatation may not occur. In suspected cholangiocarcinoma magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) should be performed next (Figure 2).^{8–10} This modality is optimal for visualization of both intrahepatic and extrahepatic cholangiocarcinomas which appear as hypointense lesions on T₁-weighted images and hyperintense on T₂-weighted images. Image enhancement can be observed using superparamagnetic iron and delayed gadolinium images.^{11, 12} The location and extent of biliary involvement can be visualized via MRCP. MR angiography can be performed to assess vascular involvement.¹³ Computerized tomography (CT) permits identification of bile duct dilatation, assessment of hepatic parenchyma, lymph nodes, and CT angiography is superb for detecting vascular encasement.^{14–16} Endoscopic ultrasound guided lymph node fine needle aspiration facilitates staging of disease in addition to visualization of the biliary tree.¹⁷ EUS with fine needle aspiration of hilar lesions has also been advocated as a diagnostic technique to obtain a tissue diagnosis. The authors do not support this approach in patients with potential curative options due to the risk of peritoneal tumour seeding. Also, in the authors' anecdotal experience, hilar

masses are seldom observed by EUS even when present on cross-sectional imaging studies. Endobiliary ultrasound has not been incorporated into routine practice. Positron emission tomography (PET) with [18F]-fluorodeoxyglucose may be utilized to rule out metastatic disease although it should be interpreted with caution due to false-positives in inflammatory lesions, and a normal PET scan does not exclude cancer.¹⁸

Direct cholangiography via endoscopic or percutaneous routes allows bile duct sampling. Bile duct biopsies are subject to histological analysis. Brushings are analysed by cytological techniques. Routine cytology is positive in approximately 30% of suspected cases, and combined biopsy and cytology are positive in 40–70% of suspected cases. In one study, the sensitivity of routine cytology varied from 9% to 24% and specificity varied from 61% to 100%, reflecting a high degree of interpathologist variation.¹⁹ Two advanced techniques have been incorporated into the cytological evaluation of bile duct brushings to aid routine cytology in the diagnosis of cholangiocarcinoma, digital image analysis (DIA) and fluorescent *in situ* hybridization (FISH).^{20, 21} DIA is a technique that quantitates nuclear DNA as a ratio of normal ploidy (2N). FISH uses fluorescent probes to identify chromosomal amplification (i.e. the actual number of a given

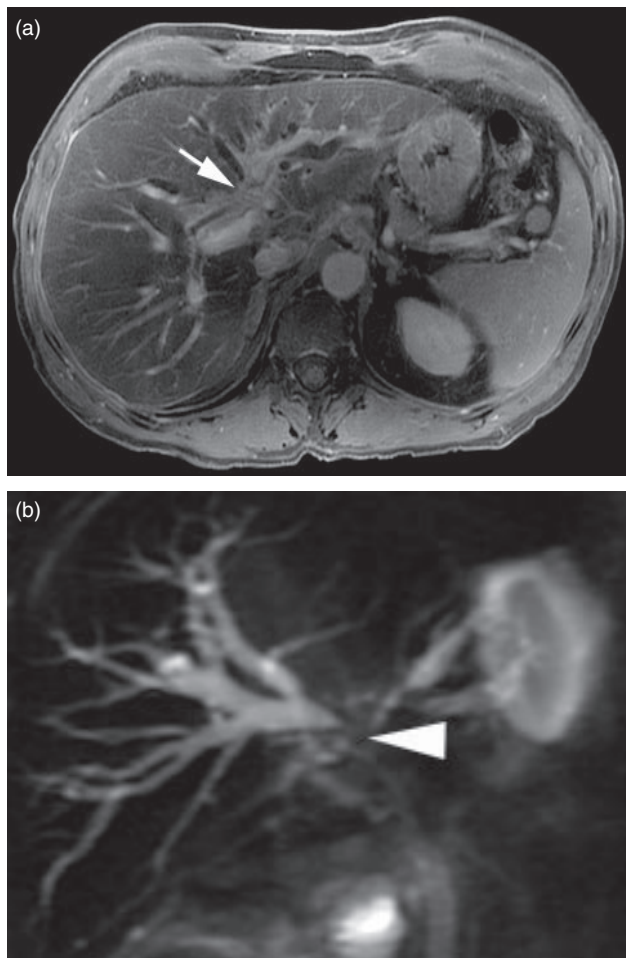


Figure 2. Hilar cholangiocarcinoma. (a) Gadolinium-enhanced magnetic resonance imaging (MRI) scan of the liver with Feridex demonstrates an enhancing mass in the portahepatis that encases the proximal hepatic duct and extends along both the right and left hepatic ducts (white arrow) consistent with a hilar cholangiocarcinoma. (b) Magnetic resonance cholangiopancreatography (MRCP) shows hilar stricture (white arrowhead) and bilateral (right > left) intrahepatic bile duct dilatation.

chromosome in a cell). Both techniques identify aneuploidy, a hallmark of chromosomal instability and cancer. The use of DIA to quantitate aneuploidy, in addition to routine cytology increases the sensitivity without compromising the specificity for diagnosis of cholangiocarcinoma. Furthermore, FISH is significantly more sensitive than routine cytology. The combination of DIA and FISH offers the highest sensitivity for the diagnosis of malignant biliary stricture, both in patients with PSC and in patients with proximal strictures in the absence of PSC, in a single centre experience. In patients with PSC the combination of

DIA and FISH was found to have a sensitivity of 22% in patients with normal cytology for the diagnosis of cholangiocarcinoma while retaining a specificity of 98% (Dr L.E. Moreno-Luna, personal communication).

Recent advances in tumour biology have delineated cellular and molecular abnormalities seen in cholangiocarcinoma. The detection of telomerase in biopsy specimens and bile had a high sensitivity without any false-positives for the diagnosis of cancer, in a small case series.²² Several growth regulatory molecules are overexpressed in cholangiocarcinoma, including receptor tyrosine kinases, c-erbB-2 and c-met.^{23, 24} Cyclooxygenase-2 is overexpressed and implicated in tumour growth as well.²⁵ Indeed, other abnormalities in tumour-suppressor genes also occur.²⁶ Though these are characterized, the molecular fingerprint of cholangiocarcinoma is not used for diagnostic or therapeutic purposes yet. These tests may be one means of diagnosing early cancers in high-risk populations, a premise that needs to be tested further. It may also provide the basis for highly tumour-specific individualized therapies.

The diagnosis of cholangiocarcinoma, therefore, should be based on a combination of all of the above features. The absence of positive cytology does not exclude cancer. Patients with underlying risk factors such as PSC or liver fluke infestation (*Opisthorchis viverrini* or *Clonorchis sinensis*) should be followed serially with repeated brushings and biopsies over time. The timing of intervention should be governed by clinical features rather than arbitrary intervals. Though clinical features may reflect the underlying disease process rather than cholangiocarcinoma, patients with persistently elevated CA19-9, high-grade strictures visualized by non-invasive imaging techniques (MRCP), changes in their biochemical profile are ideal candidates for advanced cytological testing. Many centres monitor CA19-9 values and MRCP annually in these high-risk patients. More frequent surveillance in asymptomatic, stable patients is difficult to justify because of the high incidence of endoscopic retrograde cholangiopancreatography (ERCP)-induced pancreatitis in PSC patients (7%, Keith Lindor, personal communication). A diagnostic algorithm for patients with PSC is illustrated in Figure 3.

STAGING

Several staging systems have been proposed for both intrahepatic and ductal cholangiocarcinoma. Okayabashi *et al.*, proposed a system for staging intrahepatic cholangiocarcinoma that correlates with survival after

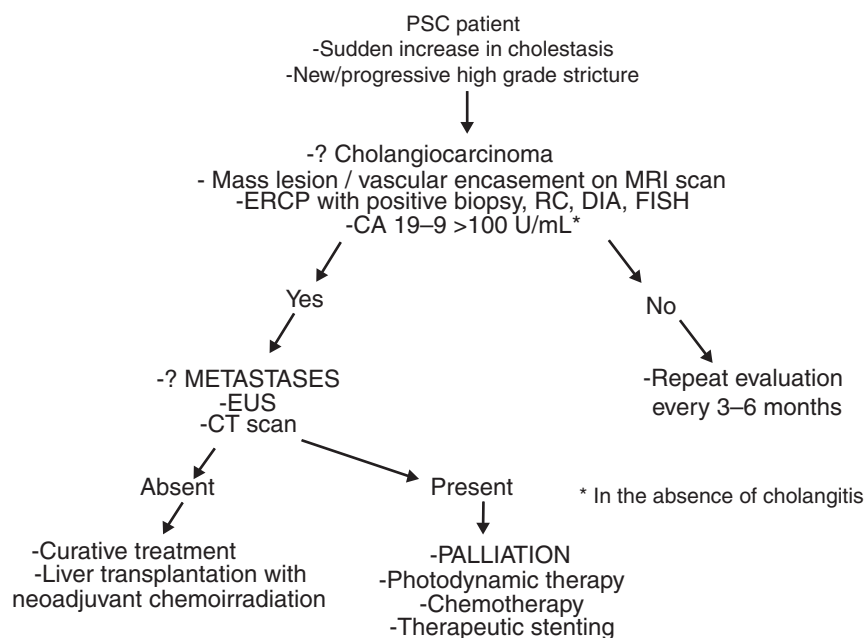


Figure 3. Proposed diagnostic algorithm for cholangiocarcinoma in patients with primary sclerosing cholangitis (PSC). Patients with sudden change in cholestasis or progressive or new high-grade bile duct obstruction should be evaluated by an hepatobiliary magnetic resonance imaging (MRI) scan as well as ERCP with bile duct brushings for routine cytology, digital image analysis (DIA) and fluorescent *in situ* hybridization (FISH), and CA 19-9. If a diagnosis of cholangiocarcinoma is clinched, local and systemic spread of disease is assessed next. In patients with early, locally contained disease, liver transplantation with neoadjuvant chemoirradiation is recommended. In patient with locally advanced or metastatic disease, palliative options should be individualized.

hepatic resection.²⁷ Stage I disease was defined as a solitary tumour without vascular invasion, Stage II disease was defined as a solitary tumour with vascular encasement/invasion, Stage IIIA disease was defined as multiple tumours with or without vascular involvement, Stage IIIB disease was defined as any tumour with regional lymph node metastasis and Stage IV disease was defined as any tumour with distant metastases.

The goal of staging for hilar cholangiocarcinoma should be to determine resectability. A pathological staging system has been developed by the American Joint Committee on Cancer Staging (AJCCS; Table 1). The major drawback of this staging system is that it does not correlate with resectability. On the other hand, the Memorial Sloan-Kettering staging system (Table 2) is based on the extent of biliary and vascular involvement, and correlates with resectability and survival. However, the goals of clinical staging should be to determine the local and distant extent of disease as it impacts surgical resectability. Furthermore, in patients with PSC, cholangiocarcinoma is often multifocal, and a staging system based on the index lesion would underestimate the burden of disease.

Table 1. Staging of ductal biliary cancers (except periampullary cancers)

TNM classification	Extent of tumour spread	Stage
T1a	Bile duct mucosa	I
T1b	Muscular layer of bile ducts	II
T2	Periductal connective tissue	III
T3	Vessel or organ invasion	IVA
M1	Distant metastases	IVB
N1a	Lymph node involvement: hepatic, cystic, common duct and hepatoduodenal ligament	
N1b	Distant lymph node involvement	

THERAPY

Curative surgical resection

Surgical resection has been the mainstay of curative treatment for cholangiocarcinoma in the absence of PSC.¹ Resection in patients with PSC is discouraged as

Table 2. Memorial Sloan-Kettering T stage for hilar cholangiocarcinoma

Stage	Criteria
T1	Tumour involving biliary confluence \pm unilateral extension to second-order biliary radicals
T2	T1 + ipsilateral portal vein involvement \pm ipsilateral hepatic lobar atrophy
T3	Tumour involving biliary confluence + bilateral extension to second-order biliary radicals; or unilateral extension to second-order biliary radicals with contralateral portal vein involvement; or unilateral extension to second-order biliary radicals with contralateral hepatic lobar atrophy; or main or bilateral portal venous involvement

cholangiocarcinoma is often multifocal in this setting, the underlying parenchymal disease may preclude resection and recurrent disease with death following resection occurring in >90% of patients. In PSC patients with early cholangiocarcinoma, liver transplantation is the preferred definitive therapy (vide infra). Choice of surgical procedure is determined by location of the tumour following the schema of intrahepatic or extrahepatic tumours, and dividing extrahepatic tumours into hilar lesions and non-hilar lesions. Surgical resection is recommended for solitary intrahepatic lesions. This involves partial hepatic resection with removal of the involved bile ducts. Neoadjuvant therapy or adjuvant therapy with radiation or chemotherapy has not been proven to prolong survival. The absence of lymph node involvement, negative tumour margins up to 1 cm, solitary lesions, and lack of microscopic vascular invasion correlate with survival. Perineural involvement and tumour site do not affect survival. Data from surgical series for resection of intrahepatic cholangiocarcinoma are presented in Table 3 (5-year survival ranges from 27% to 48%). Careful patient selection, primarily exclusion of patients with extrahepatic disease accounts for improved survival in some studies. Multiple intrahepatic lesions represent haematogenous metastasis precluding curative surgery.

In the absence of local or distant metastases, resectability of extrahepatic lesions is determined by the extent of involvement of the biliary tree and hepatic vasculature. In general, unilobar involvement even with ipsilateral encasement of the hepatic artery or portal vein branch, and/or involvement of ipsilateral secondary biliary radicals with associated lobar atrophy is considered resectable. In contrast, bilateral hepatic artery encasement, bilateral portal vein branch encasement, involvement of the main portal vein and bilateral involvement of secondary biliary radicals all preclude surgery. Patients requiring a lobar resection

Table 3. Survival following resection for intrahepatic cholangiocarcinoma (1995–2006)

Author	Number of resections	Survival (%)		
		1 year	3 years	5 years
Jan <i>et al.</i> ⁵³	187	32.5	9.2	4.1
Yeh <i>et al.</i> ⁵⁴				
Intraductal-papillary (IP)	40	72.9	41.2	24.7
Non-IP	94	43.3	6.0	2.0
Nakagohri <i>et al.</i> ⁵⁵	14	84	52	43
Han <i>et al.</i> ⁵⁶	12	55	35	20
El Rassi <i>et al.</i> ⁵⁷	19	83	16.5	
Isaji <i>et al.</i> ⁵⁸	36	44.4	24.4	24.4
Harrison <i>et al.</i> ⁵⁹	32	76	58	42
Madariaga <i>et al.</i> ⁶⁰	34	67	40	35
Casavilla <i>et al.</i> ⁶¹	34	60	37	31
Berdah <i>et al.</i> ⁶²	17	67	32	32
Cherqui <i>et al.</i> ³⁷	14	58	32	

who have contralateral vascular encasement are also unresectable. Recently, partial hepatic resection with concomitant *en bloc* resection of vascular structures and accompanied by reconstruction along with biliary excision has been advocated for complex hilar tumours.^{28, 29} The advantage likely stems from tumour-free margins in patients undergoing more extensive resection, indeed partial hepatectomy was found to be the only predictor of outcome in patients with a negative surgical margin.²⁹ Portal vein embolization with compensatory contralateral hypertrophy of the future liver remnant has been attempted to enable extended hepatectomy (resection of ≥ 5 hepatic segments).^{30, 31} Distal bile duct tumours require more extensive surgery with concomitant pancreatoduodenectomy. In addition to local extent of disease, the presence of cirrhosis, comorbid conditions and the patients performance status impact the surgical decision. Careful preoperative staging is therefore manda-

tory to select optimal candidates for curative surgery. Even with careful selection and curative intent, the 5-year survival for hilar cholangiocarcinoma ranges from 30% to 40% (Table 4). Tumour-free surgical margin is the best predictors of survival. Several staging schemes have been proposed and none correlates with respectability. Neoadjuvant therapy with several modalities, including radiation, photodynamic therapy and chemotherapy, again is not of clear benefit.^{32, 33} Five-year survival for distal bile duct cancers is around 37%. Lymph node involvement and tumour-free surgical margin are predictors of survival.³⁴

Transplantation

Liver transplantation is an emerging therapy for unresectable cholangiocarcinoma. Initial case reports were discouraging as tumour recurrence in the transplanted organ was the norm and disease-free and overall survival were no different from resection. Recent data, though, have lead to a resurgence in orthotopic liver transplantation for unresectable, albeit locally contained cholangiocarcinoma. Excellent disease-free 5-year survival (82%) has been reported in carefully selected patients that underwent neoadjuvant external beam radiation therapy, trans-catheter intrabiliary radiation, chemotherapy and pretransplant staging exploratory laparotomy.³⁵ However, these data originate from a single centre with specialized interest in this disease; the generalizability of this experience remains untested.

Adjuvant therapy

External beam radiation therapy and chemotherapy have been administered as adjuvants to surgical resection. In the setting of complete resection, radiation does not improve survival,³⁶ and may even lead to hepatic decompensation.³⁷ Adjuvant chemotherapy has been associated with improved survival^{34, 38} in some studies and no benefit in others.³⁹

Palliative therapy

Symptom resolution and improvement in quality of life have been the goals of established palliative therapy. For hilar tumours, symptoms stem from biliary obstruction. This can be decompressed percutaneously, endoscopically or surgically. Surgical biliary bypass is associated with a high perioperative morbidity and mortality in this patient population. Endoscopic biliary

Table 4. Survival following curative resection for hilar cholangiocarcinoma (2000–2006)

Author	Number of resections	Survival (%)		
		1 year	3 years	5 years
Silva <i>et al.</i> ⁶³	45			
R0* resections		83	58	41
R1† resections		71	24	24
Jarnagin <i>et al.</i> ⁶⁴	106			
Papillary	25	100	80	45
Nodular-sclerosing	81	85	45	30
Otto <i>et al.</i> ⁶⁵	43	90	46	
Kondo <i>et al.</i> ⁶⁶	40			40
Rea <i>et al.</i> ⁶⁷	46	80	39	26
Ebata <i>et al.</i> ⁶⁸				
With PVR‡	52			9.9
Without PVR	108			36.8
Neuhaas <i>et al.</i> ²⁸	133			
R0*	80	70	42	36
Capsusotti <i>et al.</i> ⁶⁹	36		40.8	27.2
Munoz <i>et al.</i> ⁷⁰				
With PVR‡	10	60	22	22
Without PVR	18	70	47	38
Nagino and Nimura ⁷¹	58		23	8
Bathe <i>et al.</i> ⁷²	19		47	
Figueras <i>et al.</i> ⁷³	20	44	21	21
Havlik <i>et al.</i> ⁷⁴	29			20
Tabata <i>et al.</i> ⁷⁵	75	56.4	30.5	22.5
Nimura <i>et al.</i> ⁷⁶				
Biliary resection only	8	64	31	16
Biliary resection + hepatectomy	100	75	43	26
Gazzaniga <i>et al.</i> ⁷⁷	46	68	30	17.5
Tsao <i>et al.</i> ⁷⁸				
Nagoya cohort	122			25
Lahey cohort	25			43

* R0 denotes clear surgical margins.

† R1 denotes microscopic involvement of the surgical margin.

‡ Portal vein resection.

stenting offers many advantages. It is usually an outpatient procedure, without associated mortality. Partial biliary drainage of a nonatrophic lobe is usually adequate. Unilobar stenting is more easily attained and is associated with lower rates of cholangitis than bilobar stenting.⁴⁰ The choice of stent is limited to plastic vs. metal, and bare vs. coated. In general stents can migrate, become occluded from biliary sludge or tumour, or cause cholecystitis from mechanical cystic duct obstruction. Metal wall stents offer longer patency, and are preferred in patient with an

anticipated survival >6 months, but they cannot be removed or manipulated.⁴¹ Plastic stents have a higher frequency of occlusion, they need replacement every 3–4 months. Coated metal stents remain patent longer than bare metal stents. Percutaneous stenting may be necessary for high-grade lesions that cannot be cannulated endoscopically. Intestinal obstruction from distal bile duct tumours can similarly be relieved by endoluminal stenting.

Tumour palliation

Photodynamic therapy, radiation and chemotherapy are all available as palliative options. Photodynamic therapy relies on systemic administration of a photosensitizer such as a haematoporphyrin derivative that accumulates specifically in malignant cells. Endoscopic application of red laser light leads to photoactivation and destruction of malignant cells. Improvement in biliary drainage and quality of life has been reported in case series.^{42–44} In a randomized-prospective study photodynamic therapy lead to significantly improved survival.⁴² Radiofrequency ablation has been performed in patients with small intrahepatic cholangiocarcinoma.^{45–47} Transcatheter arterial embolization has also been shown to have some survival advantage in case series.⁴⁸ Hepatic arterial chemoinfusion via a pump device placed surgically or fluoroscopically offers convenient site-directed chemotherapy.⁴⁹ Case series utilizing this modality for chemotherapy have demonstrated its safety.⁵⁰ This offers a significant logistical advantage for the chemotherapy du jour. A clinical trial of intraluminal brachytherapy showed improved stent patency in the irradiated group.⁵¹ Chemotherapy with gemcitabine has minimal response rates and can be considered in patients with non-

resectable cholangiocarcinoma. There have been several Phase II clinical trials in patients with bile duct cancer of gemcitabine alone and in combination with other agents such as cisplatin, and 5-fluorouracil, although like most other palliative options it has not been analysed in a prospective randomized-controlled trial.⁵² The combination of gemcitabine ± cisplatin is now in Phase III trials. Other agents in Phase I/II trials include exatecan mesylate, sorafamib, rebeccamycin analogue, the use of hyperthermia in conjunction with chemotherapy (cisplatin + gemcitabine), allogenic peripheral blood stem cell transplant to name a few. Directed biological therapy targeting epidermal growth factor-receptor (EGF-R) is another promising area. Indeed, given the frequent amplification of chromosome 7 in this disease, which contains the EGF-R gene, EGF-R targeted therapy, likely in combination with other therapies, is an especially attractive approach.

Search strategy

A Medline search was performed for cholangiocarcinoma from 1966 onwards. Relevant references from selected papers were also reviewed. Medline was searched for peripheral cholangiocarcinoma and resection from 1995 onwards for tabulation of data (Table 3), and hilar cholangiocarcinoma and resection from 2000 onwards for tabulation of data in Table 4. The registry of clinical trials <http://www.clinicaltrials.gov> was searched for cholangiocarcinoma. This yielded 27 trials, many of which are mentioned above.

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