

Management of cholangiocarcinoma

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Cholangiocarcinomas (CCK) are enigmatic tumours arising from the epithelial cells that are covering both intra and extra-hepatic bile ducts. More than 90% of these cancers are tubular adenocarcinomas, generally well differentiated. Infrequently, they are adenosquamous carcinomas or lympho-epithelial tumours.

Although rare, it remains the second most common hepatobiliary cancer. About 8000 new cases/year are reported in the United States. Its worldwide incidence is now increasing probably due in part to the improvement of diagnosis and to a better knowledge of the disease.

Based on anatomic localization, cholangiocarcinomas can be divided into three categories: intra-hepatic tumours and extra-hepatic tumours these latest including hilar distal locations. These different forms are distributed as follows: about 5-10% for intra-hepatic form, 60-70% for hilar tumours and 20-30% for common bile duct tumours.

Another classification, based on tumour morphology and growth pattern, describes three different categories: mass forming (nodular), periductal-infiltrating and intraductal-growing, these latest being able to produce mucus.

The intra-hepatic form appears as unique or multiple hepatic masses mimicking metastases and needs to be differentiated by histologic analysis. It is also the most aggressive form which is growing rapidly invading the surrounding liver, blood and lymphatic vessels and can give hepatic, pulmonary and peritoneal metastasis. Hilar form is the most common form (about half of the tumours) occurring at the biliary convergence and endoscopically classified according to Klatskin and Bismuth and Corlette. These tumours are more indolent, growing slowly with perihilar sclerous infiltration, often without any visible mass; they can invade hilar adenopathies and the liver by direct extension. All the extra-hepatic tumours can cause obstructive jaundice, which represents the most classic clinical presentation.

Epidemiology

Worldwide, cholangiocarcinoma is the second most common hepatobiliary cancer. The incidence in the USA is about 1-2 cases per 100000 without clearly identified ethnic predisposition. There is a slight male preponderance and peak incidence occurs around 65-70 years old.

While the vast majority of the cases are sporadic, several risk factors associated with chronic inflammation of the biliary epithelial cells have been identified. Primary sclerosing cholangitis is one of these well known predisposing factors. Parasitic biliary infections (liver flukes), especially with *Opisthorcis viverrini* have been suggested, supported by epidemiologic data in patients suffering for fibropolycystic liver disease disclose a higher risk to develop cholangiocarcinoma, at an average age of 34. Chronic exposure to DNA-damaging chemical agents has been reported, notably well documented for the thorium dioxide (Thorotrast), a radiological contrast agent that has been removed from sale. Chronic bile stasis (lithiasis, Caroli's disease, presence of congenital biliary abnormalities) seems to be a potential cofactor for the development of cholangiocarcinoma. Finally, as recently demonstrated, cirrhosis, HCV and HBV infections are also risk factors for developing cholangiocarcinoma

Diagnosis

The most common clinical presentation for cholangiocarcinoma is jaundice. Sometimes, biliary obstruction leads to cholangitis. Patients may present mild and diffuse abdominal pain, weight loss, decreased appetite and fatigue, or being completely asymptomatic.

The diagnosis of cholangiocarcinoma is based on a combination of imaging techniques and tumour tissue sampling.

Serum CEA and CA19.9 may be increased, especially for the latest in case of cholestasis. They can be useful in the further evaluation and follow-up of the patient (treatment response, recurrence) but are not specific enough to achieve a definite diagnosis.

Cholangiography is the step point of the diagnostic strategy. It can be obtained by MRCP, ERCP or CT, the latest being weaker in this case. Both MRCP and ERCP provide imaging tools leading to a diagnostic accuracy of 70 to 80%. If ERCP is more aggressive than MRCP and at risk of failure and complications (cholangitis), it has the key advantage to allow tissue sampling by brush-cytology or biopsy of the suspected biliary stenosis. With the development and high accuracy of MRCP, ERCP is less and less used preoperatively in patients with obvious diagnosis candidate to surgical resection. Histologic proof is of course mandatory for the definitive diagnosis, but it can be difficult to obtain, especially for sclerous and fibrosing forms. The yield of intraductal biopsies and brush cytology remains poor. ERCP-guided biopsies and brush cytology can provide a diagnosis in only 36 to 46 % of the cases. Nodular intra-hepatic tumours should preferentially be biopsied percutaneously under US guidance. EUS is another rising technique able to provide tissue sampling, especially with newly designed forward viewing therapeutic scope.

Staging

Assessment of vascular encasement is a key step for the staging of this tumour, and angiography can be performed by angio- MRI or CT scan, the former having the potential of providing "all in one" staging method combining mass evaluation, cholangiography and angiography.

Chest X-ray and abdominal CT scan must be done to evaluate the presence of metastases, and to evaluate regional lymph nodes. If lymph node invasion remains doubtful, US or EUS guided sampling may be useful.

¹⁸F-FDG-PET can be helpful for the staging of these tumours, but is not yet considered in the standard work-up.

Staging of the tumour is the crucial point for directing therapeutic approach. Unfortunately, both the Bismuth-Corlette and the American Joint Committee on Cancer (AJCC) staging systems are based only on the extent of ductal involvement, lymph nodes involvement or distant metastasis. They do not account for other important factors such as vascular invasion, resectability of the tumour or liver function (atrophy).

Oncologic and hepatic criterias of unresectability include: liver, pulmonary and peritoneal metastasis, encasement of main portal vein or hepatic artery, Bismuth IV tumours, lymph node extension (histologically proven N2 lymph nodes), liver atrophy and cirrhosis. Poor clinical status and comorbidities precluding surgical resection are also important factors to be evaluated. According to their clinical experience and multifactorial analysis, Jarnagin et al have proposed a new classification for hilar tumour which fits more than Bismuth-Corlette and AJCC classifications by considering tumour resectability, secondary biliary extension, liver atrophy and portal encasement (Table 1).

Surgery

A complete surgical resection with histologically negative resection margins (R0 resection) is the only way to cure patients. A multidisciplinary discussion is mandatory before operating any patient. Assessment of resectability must be done as well as evaluation of comorbidity and operability of the patient.

Even with careful staging, selection and surgery at curative intent, five year survival for hilar cholangiocarcinoma ranges from 20 to 40%, and the best predictor of survival is R0 resection (Table 2). For intrahepatic tumors, five years survival ranges from 20 to 43% and relevant prognostic factors are R0 resection, absence of vascular invasion and N0 status.

Multimodal therapy

Regarding poor survival and high rate of recurrence after surgery, many treatments have been attempted in the neoadjuvant and in adjuvant settings.

To date, no adjuvant treatment after curative surgery, neither chemotherapy and/or radiation (external or intra-ductal), has ever proved any survival benefit and are not recommended outside a trial. Poorly designed or -powered trials have been reported without giving any clear conclusion regarding peri-operative therapy and clearly, there is a need for adequately designed trials in the setting of biliary tract cancer.

Neoadjuvant treatment exploring new chemoradiation options or regimens have been proposed before surgery of a resectable tumour and also for downstaging and downsizing of unresectable non-metastatic lesions, or before liver transplantation (see below). To date no clear data are emerging, and such approach is not routinely recommended.

Liver transplantation:

In the particular case of PSC, liver transplantation is preferred to resection because tumour is often multifocal and also because recurrence of the biliary disease after resection occurs in more than 90% of the cases.

Liver transplantation can also be an option for patients with unresectable tumour without hilar lymph node involvement and without metastasis. In this setting, neoadjuvant chemoradiation has been considered. Two series, including 28 and 38 patients respectively, have reported a similar 5 year survival of 82% after neoadjuvant chemoradiation followed by transplantation (Table 2). This approach requires a preliminary staging by laparoscopic evaluation of the peritoneum and the hilum but has to be considered as a valuable option in experienced centers.

Treatment of biliary obstruction

In hilar and common bile duct tumours, biliary obstruction is the major problem and cause of morbidity and its palliation is a priority. Aims are relief of jaundice and related pruritis, prevention of cholangitis and hepatic dysfunction, and improvement of quality of life.

This can be achieved endoscopically, surgically (biliary-enteric bypass) or percutaneously. The different techniques have been compared and showed equal palliation of jaundice and survival. However, nonsurgical procedures offer significantly lower morbidity, mortality and cost.

The type of endoscopic palliation depends essentially on life expectancy of the patient and location of the tumour in the biliary tree.

In Bismuth type I and distal CCK, placement of a single biliary stent is required. In Bismuth II, III and IV hilar tumours, unilateral versus multiple biliary stenting remains strongly controversial.

For distal tumours, metal stents provide a longer patency and are more cost-effective for patients surviving at least 3 months. Patency of hilar plastic stent is less than 4 weeks and they are at high risk of distal migration. Covered metal stents are not appropriate for hilar lesions since they would induce an obstruction of the contralateral lobe. When placing open mesh metal stents, the question of single vs multiple stenting has also been raised, the latter being probably to be recommended when all the lobes or segments have been opacified but being technically more demanding. In this case, a combination of endoscopic and percutaneous approaches is necessary in one third of the patients.

Photodynamic therapy

The principle of phototherapy (PDT) is to administer a photosensitizer agent which accumulates within the neoplastic tissue and which becomes cytotoxic when the tumour is directly exposed to low-energy light of a specific wavelength during ECRP therapy. The only randomized trial, comparing PDT using Photofrin[®] plus stenting vs stenting alone, has been prematurely stopped due to a significant survival advantage in the group of PDT (493 vs 98 days, $p < 0.0001$). Quality of life was also significantly improved in this study. Main side effect of this treatment is skin photosensitivity. Although survival in the control group was particularly low in this trial, it has raised enthusiasm for application of PDT in the setting of palliation.

The role of PDT was confirmed by the prospective study of Witzigmann, showing that PDT + stenting resulted in significantly ($p < 0.01$) longer survival than stenting alone and that survival of patients treated with PDT + stenting was similar to those treated by surgery resulting in R1 and R2 resections, reaching 12 months (Table 3).

Combining PDT and stenting is therefore a promising palliative therapy that twofold aims to treat cholestasis and reduce tumour growth, with little invasiveness and low complication rate.

Palliative radiotherapy

Palliative radiotherapy has been proposed for patients with unresectable non-metastatic tumours. In all published trials, but unfortunately not in controlled studies, externalbeam radiation therapy (EBRT) was applied alone or in combination with brachytherapy. Currently, no survival benefit has been

demonstrated but the proper use of conformal radiation ± new chemosensitizing agents likely deserves further evaluation.

Systemic chemotherapy and new targeted agents

Until the recent trial by Valle et al, chemotherapy has had limited impact on the course of this disease, both in the adjuvant and the advanced setting. There was clearly no standard regimen identified that prolongs survival and this relatively rare disease was poorly considered for large phase III trials exploring new drugs.

Fluoropyrimidines were considered as the cornerstone of palliative chemotherapy despite limited response rate (around 5-10%) and 5FU-based chemotherapy was shown to improve quality of life for biliary cancer patients versus best supportive care. The combination of gemcitabine and cisplatin is now considered as the new standard of care since the publication of the phase III trial showing a clear survival advantage for the combination as compared to gemcitabine alone. Targeted therapies are also under development.

Growth factor receptors Her-1 (25-87%) and Her-2 (0-82%) have been shown to be overexpressed in biliary tract cancers and can be targeted by different agents such as monoclonal antibodies (cetuximab, panitumumab, trastuzumab) or small molecules such as erlotinib (Her-1, tyrosine kinase inhibitor), lapatinib (Her-1/Her-2 kinase dual inhibitor), sunitinib or sorafenib.

This newer approach however will require a translational evaluation of the therapeutic intervention in order to better identify the responders and the benefit to treat.

Conclusions

Cholangiocarcinoma is a rare tumour, but its incidence is increasing over these last decades as well as diagnosis and management are improving.

Accurate diagnosis and staging are key steps to determine the appropriate treatment. The only curative treatment of this cancer is surgical resection. Liver transplantation (with or without neoadjuvant treatment) can be an option for highly selected cases.

Unfortunately, these tumours are generally diagnosed at an advanced stage or are unresectable. For most of these patients, several palliative therapeutic options exist and are in development, based on the complementary approach of bile duct stenting and local tumour destruction. Systemic therapy is now based on the combined regimen of gemcitabine and cisplatin.

TABLE 1. Classification of Jarnagin

<u>T stage</u>	<u>Biliary extension</u>	<u>Liver atrophy</u>	<u>Portal encasement</u>	<u>Resectability</u>
T1	0 or unilateral	Absent	Absent	59%
T2	0 or unilateral	0 or homolateral	Homolateral	31%
T3	Unilateral Unilateral Bilateral Bilateral	0 or homolateral Contralateral Contralateral Contralateral	Contralateral Contralateral Contralateral Bilateral or troncular	0%

TABLE 2. Survival data according to therapy (5-year survival or median overall survival)

Surgery:

R0 resection: 20-40%

R1 resection: 5-10%

R2 resection: 0%

Liver transplantation after chemoradiation: 82%

Palliation:

Stenting: 6,4 months

PDT + stenting: 12 months

Chemotherapy: 4-16 months

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