Bile Duct Malignancies

Malignity žlučových cest

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Summary

Bile duct malignancies include intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), gall bladder carcinoma (GC) and carcinoma of Vater's ampulla (ampulloma). Bile duct neoplasms are rare tumours with overall poor prognosis. The overall incidence affects up to 12.5 per 100,000 persons in the Czech Republic. The mortality rate has risen recently to 9.5 per 100,000 persons. The incidence and mortality have been remarkably stable over the past 3 decades. The survival rate of patients with these tumours is poor, usually not exceeding 12 months. The diagnostic process is complex, uneasy and usually late. Most cases are diagnosed when unresectable, and palliative treatment is the main approach of medical care for these tumours. The treatment remains very challenging. New approaches have not brought much improvement in this field. Standards of palliative care are lacking and quality of life assessments are surprisingly not common. From the scarce data it seems, however, that multimodal individually tailored treatment can prolong patients' survival and improve the health-related quality of life. The care in specialized centres offers methods of surgery, interventional radiology, clinical oncology and high quality supportive care. These methods are discussed in the article in greater detail. Improvements in this field can be sought in new diagnostic methods and new procedures in surgery and interventional radiology. Understanding the tumour biology on the molecular level could shift the strategy to a more successful one, resulting in more cured patients. Further improvements in palliative care can be sought by defining new targets and new drug development. The lack of patients with bile duct neoplasms has been the limiting factor for any improvements. A new design of larger randomized international multicentric clinical trials with prompt data sharing could help to overcome this major problem. Defining standards of palliative care is a necessity. Addressing health-related quality of life could help to assess the real benefit of palliative treatment.

Key words

bile duct neoplasms – cholangiocarcinoma – gallbladder cancer – palliative treatment

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Souhrn

Malignity žlučových cest zahrnují intra- a extrahepatální cholangiokarcinomy, karcinom žlučníku a karcinom Vaterské papily. Jsou to vzácné nádory s celkově špatnou prognózou. Incidence dosahuje 12,5/100 tis. obyvatel a mortalita 9,5/100 tis. obyvatel, obojí byly v posledních 30 letech pozoruhodně stabilní. Celkové přežití pacientů s těmito nádory je žalostné, většinou do 12 měsíců. Diagnostika má různá úskalí a velmi často přichází pozdě. Většina případů je při diagnóze neoperabilních, proto je zde hlavní modalitou paliativní léčba. Ta je však stále problematická, nové postupy mnoho nepřinesly. Chybí standardy paliativní péče a hodnocení kvality života je překvapivě velmi málo časté. I z nečetných dat se zdá být zřejmý pozitivní efekt multimodální individualizované léčby na přežití a kvalitu života pacientů. Ve specializovaných centrech zahrnují léčebné možnosti metody chirurgické, intervenční radiologii, klinickou onkologii a metody kvalitní podpůrné péče. Tyto metody jsou rozebírány v článku podrobněji. Zlepšení lze očekávat od nových diagnostických metod a nových postupů v chirurgii a intervenční radiologii. Také lepší poznání biologie nádorů na molekulární úrovni snad přinese více vyléčených pacientů. V paliativní léčbě lze zlepšení očekávat v nalezení nových cílových struktur a vývoji nových léčiv. Malé počty pacientů jsou limitující pro jakýkoli pokrok v tomto odvětví. Lze doufat, že nový volnější design mezinárodních randomizovaných multicentrických studií s pružným sdílením dat tento hlavní problém překlene. Nezbytným dalším krokem je definice standardů paliativní péče a hodnocení kvality života přinese pohled na skutečný přínos paliativní léčby pro pacienty.

Klíčová slova

nádory žlučových cest – cholangiokarcinom – nádory žlučníku – paliativní terapie

Introduction

Malignant tumours of biliary tree form a small group of malignancies with overall poor prognosis. The assessment and treatment is associated with some special aspects. There are several specific features in behaviour, diagnostic process and treatment of these tumours that make them different from others.

Epidemiology and pathogenesis

History and epidemiology

Bile duct cancer (cholangiocarcinoma), first described by Maximilian de Stoll in 1777, was presented in modern history by Altemeier in 1957. It is a group of relatively rare tumours, presenting in older patients, mainly at the age of 65+. Maximum incidence appears in the eight decade of life [1].

Incidence of GC is approximately the same, presenting mainly in seventh decade of life, more common in women. It has shown certain racial, ethnical and geographical predispositions (high incidence in Chile, North-East Europe, Israel, in Native Americans and Americans with Mexican origin, in some parts of Asia– e. g. Thailand or Japan) [2].

In 2006 (most recent published data), in the Czech Republic there were 325 men and 646 women reported as new cases with malignant tumours of biliary tract. That is 9.5 per 100 000 persons. The number of patients with ICC is uncertain, estimated approximately 300 new cases. That is approximately 3 new cases per 100 000 persons. They form 6.7 % of all reported malignancies in the Czech Republic. Incidence of biliary tree malignancies in the Czech Republic has been remarkably stable over past three decades [3] (Pict. 1).

The real incidence is probably much higher with a large number of tumours remaining undiscovered, as some pathological studies have shown [4].

To demonstrate a different level of importance in different regions – in above mentioned north-east Thailand, incidence is highest in the world- as high as 96 per 100 thousand inhabitants. That is higher than any solid tumour (apart from non-melanoma skin malignancies) in western countries.

There were 722 reported deaths due to cancer of gallbladder (GC) and extrahepatic cholangiocarcinoma (ECC) in the Czech Republic in 2006 (8 per 100,000 and 2.9% of all reported deaths due to malignancies).

Worldwide there has been reported a marked increase in mortality from ICC in last decade (estimated average annual percentage change approximately +7% in men, +5% in women). Mortality from extrahepatic biliary tree malignancies is decreasing (average annual minus 0.3% in men, minus 1.3% in women) in most countries [5].

Pathogenesis

Several general mechanisms of cholangiocarcinoma development have been identified. They include chronic inflammation processes, reactive oxygen species occurrence, changes in defensive cell detoxicating mechanisms and dysregulation of processes running cell proliferation at the gene level (tumour suppressor genes and apoptosis genes malfunction or oncogenes activation) [6].

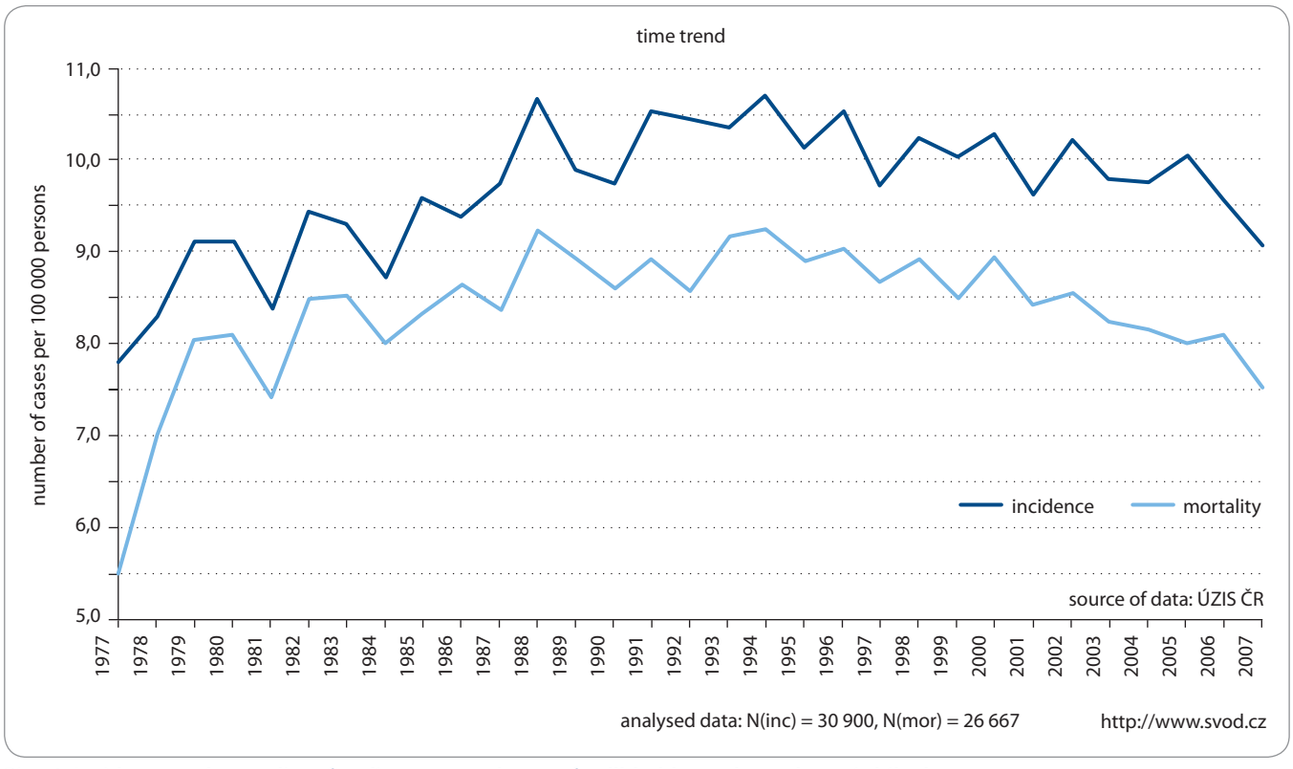
Cholangiocarcinomas express interleukin IL-6 receptor. In vitro IL-6 stimulates tumour growth [7]. They also express Fas ligand inducing lymphocyte apoptosis [8]. Cholangiocarcinomas evade immune response activated by inflammation, by the means of the inhibitor of Fas mediated apoptosis (Fas-associated death domain-like IL-1b-converting enzyme inhibitor – I-FLICE) [9].

Especially interleukin-6/STAT-3 signalling pathways have been identified and studied, offering a potential to new diagnostic and prognostic markers and targets for cholangiocarcinoma therapy [10].

Specifically, there have been identified several factors – primary sclerosing cholangitis as the most frequent connecting tissue disease in western world [22], choledochal cysts, chronic bile duct inflammation either of bacterial or parasitic origin (e. g. *Fasciola hepatica, Clonorchis sinensis, Opisthorchis viverrini* [11] prevailing in East Asia) and further hepatic infections. More risk factors would be cancerogens as radioactive radon, thorium [12], nitrosamines, dioxines and azbestos.

Recently, chronic viral hepatitis C has been identified as a possible risk factor for development of intrahepatic cholangiocarcinoma in Japan [13]. It may be one of possible factors causing increase in intrahepatic cholangiocarcinoma (ICC) in western countries.

Chronic inflammation is a risk factor of GC development, as well. There have been several connecting infections identified: Salmonella typhi [14], *Esche-*



Pict. 1. Incidence and mortality of malignant neoplasms of gallbladder and extrahepatic bile ducts.

richia coli and *Helicobacter* species [15]. In *S. typhi* carriers there is a risk of gallbladder cancer development 167times greater than in controls. Incidence of GC depends, up to certain amount, on cholelithiasis – mainly cholesterol type, however causality remains unclear. An increased risk has been proven when using methyldopa [16], oral contraceptives [17], isoniazid [18] and rubber industry chemicals exposure [19].

Some studies suggest that it be rather inflammatory process than cancerogens themselves that triggers a cancer development cascade [20].

Recently, molecular markers suggest that GC, intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) differ in more qualities than it was thought before. These markers are under investigation. It seems wise, though, for future clinical trials, to discriminate these entities and consider them separately.

Pathology and staging

Bile duct malignancies arise from epithelium anywhere in the bile duct and can be divided in gallbladder carcinoma, intrahepatic (ICC) and extrahepatic cholangiocarcinomas (ECC) and the carcinoma of Vater's ampulla (ampulloma). The carcinoma of Vater's ampulla may be considered as a separate entity by some authors or included thank to similar diagnosing and treatment [21].

Intrahepatic localization appears in approximately 10% tumours. Extrahepatic occurrence is more frequent, can be distinguished into two types – proximal (hilar) and distal. Extrahepatic hilar cholangiocarcinoma of proximal choledochus or bifurcation may be referred to as Klatskin tumour, named after Nicolas Klatskin who first described it in 1965. Multifocal or diffuse pattern is also possible, presents in less than 10%.

Staging may be very difficult and in many cases impossible at all. This is due to very common stealthy tumour spread along bile ducts and vessels that may not be noticeable on imaging techniques. This statement is strongly supported by official statistics.

Cholangiocarcinomas tend to invade organs in proximity and lymph node metastases can be present in 1/3 of cases. Besides lymphatic spread, haematogenic spread and occurrence of implant metastases, tumours quite often tend to spread via nerves, perineural or subepithelial spaces. This spread may be not distinguishable by imaging and understaging or cases of uncertain stage are quite common.

In the Czech Republic, in more than 52% of reported cancers of GC and ECC was clinical stage recorded as uncertain [22].

Macroscopic presentation may be divided in three types. Most common are sclerosing cholangiocarcinomas. These are firm tumours, often thickening bile ducts in circular pattern. Nodular cholangiocarcinomas are firm as well, often prominent into bile duct lumen. Papillary cholangiocarcinomas (approx. 10% of cholangiocarcinomas) are soft and frail tumours, more frequently found in distal localizations. They are often less invasive, thus offering somewhat better prognosis. It is possible to find more types combined, especially first two types (nodular-sclerosing tumours).

Even though there have been over 10 various histological subtypes described in literature, vast majority (over 98%) of tumours are adenocarcinomas [23], often well differentiated and mucin producing. Other histological types are rare (e. g. carcinoid tumours).

GC are in majority also adenocarcinomas histologically, less common are papillary, rarely squamocellular or anaplastic carcinomas. They tend to infiltrate (scirrhotic tumour) gallbladder wall, later gallbladder bed in hepatic hilus. Spread into nearby organs is possible, as well. Metastases usually spread into regional hilar lymph nodes.

Clinical presentation and diagnostics

Clinical presentation

Unfortunately most of the clinical signs of bile duct malignancies appear relatively late. Obstructive icterus is present in more than 90% of patients. Other clinical signs are less specific: abdominal pain or discomfort, loss of weight, fever, pruritus present in about 1/3 of the patients [24]. Information about intermittent icterus may suggest obstruction in distal part of choledochus. Usually clinical signs are no different from other tumour signs from this area (e. g. pancreatic malignancies) or may be not specific for malignancy at all. That makes early diagnosis even less possible.

Imaging

Basic imaging methods for hepatobiliary tumours are ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). Further methods include endosonography, cholangiography (endoscopic or percutaneous), positron emission tomography (PET), cholescintigraphy and angiography. Each method presents its advantages and limitations [25].

Transabdominal ultrasonography (US) is a method relatively compromised by subjective error of the performing radiographer. Its sensitivity is between 25 a 50%, maybe increasing with new hardware and better resolution. This method is relatively cheap and non-invasive. Especially duplex ultrasonography may be able to determine size of the tumour, vascular invasion and resectability, lobar atrophy, bile duct obstruction extent, and can achieve no worse sensitivity and specificity as CT angiography [26,27]. Quite promising are methods with organ specific contrast (e. g. SonoVue), however may not be in wide routine use yet [28].

Computed tomography (CT) is a method with sensitivity approximately 70%. Its main limitation is ionizing radiation growing with level or generation of CT machine. Standard is two- or three-phase contrast investigation. Besides imaging liver in the late portion of the arterial phase and venous phase (approx. 35 and 70 seconds after intravenous contrast bolus), it can be useful to record pancreatic phase (approximate 45–second delay). For patients with suspected cholangiocarcinoma, delayed images during the equilibrium phase (10–15 minutes delay) are helpful due to late washout of the contrast material from desmoplastic tumours [29]. 3D reconstructions are possible, giving to a clinician a better understanding and possibly making staging little easier [25].

Magnetic resonance imaging (MRI) offers again several options. There are some non specific and organ-specific contrasts in use, dynamic imaging, MR cholangiography (MRC), or 3D-reconstruction. Main advantage is non-invasivity, absence of radiation, better soft tissue contrast. Disadvantage is higher cost, lower availability, longer imaging time. In many cases it substitutes for endoscopic or percutaneous cholangiography, describing better obturated bile ducts, vascular patence in hepatic hilus and presence of lymph node or distant metastases [30].

In **cholangiography** (percutaneous or endoscopic) has sensitivity been described between 80 and 90%, specificity though 62 % only [31]. The main limitation is the invasiveness of this method. Necessary manipulation with bile ducts always means artificial infection induction and high morbidity and perioperative mortality [32]. On the other hand, its accuracy and reliability to assess the borders of cholangiocarcinoma are better than with MRI [33].

Positron emission tomography (PET) determines tumours about 1cm in size. That is for high fluorodeoxyglucose (FDG) utilization in tumour cells [34]. Its higher cost has been limiting, nevertheless, there has been a remarkable increase in use in staging over past couple of years. Its main use remains in preoperative staging and exclusion of distant metastases. The sensitivity of fluorodeoxyglucose positron emission tomography is limited in small, infiltrative, and mucinous cholangiocarcinomas [35]. In bile duct malignancies, there have been better results with high sensitivity with PET/CT. Better sensitivity has been recorded in ICC than in distal tumours. Distant metastases are better detected than regional lymph node metastases [36,37].

Cholescintigraphy using 99mTc-labeled imino-diacetic acid analogue (e. g. HIDA) enables to visualize hepatocyte uptake, transport, and excretion pathways of bilirubin. It is not dependent on secondary signs such as ductal dilatation [38]. Function quantification of gallbladder ejection fractions and biliary transit times are used to assess safety and extent of possible liver surgery or regional methods especially embolization.

Upper GI tract **endoscopy** may be useful in ampullomas, as a tumour can be visible in duodenum and biopsy easily obtainable.

In other bile duct malignancies, **endoscopic ultrasound** may be a helpful guide for fine needle biopsy of a tumour or enlarged lymph node sampling before surgery.

Intraductal ultrasound is less common, increasing sensitivity and specificity of ERCP.

Optical coherence tomography (OCT) is a new method producing cross-sectional images using infrared light. Preliminary studies have demonstrated the ability of OCT to generate high resolution images of the biliary tree that seem to correlate with histological findings [39,40].

Tissue sampling

Obtaining tumour tissue sample can be difficult or may be impossible at all. There are clinical situations where therapy has to be commenced before clear histopathological reading obtained. Sample obtaining can be performed endoscopically (ERCP, choledochoscopy), or via

percutaneous catheterization/drainage (PTC-PTD), or through CT-guided biopsy or surgery (laparoscopy or laparotomy).

Endoscopic brushing or cytology is not sensitive enough. Negative result is of no significance. A negative percutaneous biopsy may be technically difficult due to small size of tumours. However, it is usually possible in larger or inoperable tumours.

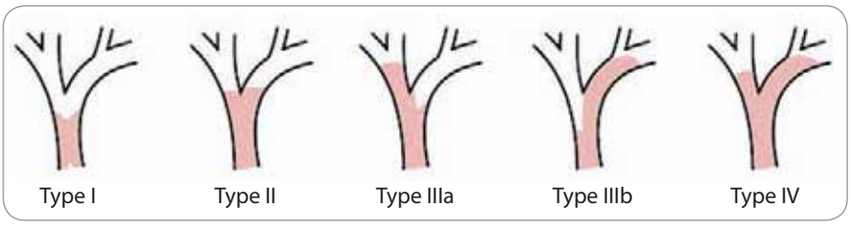
Laboratory findings

In blood count we usually find light anaemia – the chronic diseases type.

Coagulation is affected by impaired liver synthesis and biliary obstruction, when malabsorption of K-vitamin from intestine influences K-dependent coagulation factors, resulting in prolonged INR.

Liver function test may be elevated due to liver metastases (transaminases). An elevation of markers of biliary epithelial injury, such as alkaline phosphatase (ALP) and gamma-glutamyl transferase (GTT or GMT) is very common, especially in biliary obstruction, even clinically inapparent.

Serum tumour markers linked to bile duct carcinomas are carcino-embryogenic antigen (CEA) and carbohydrate antigen CA 19-9 [12]. The latter has for values above 100 U/mL a sensitivity of 75 % and specificity of 80 % [41].



Pict. 2. Bismuth-Corlette classification of hilar cholangiocarcinoma.

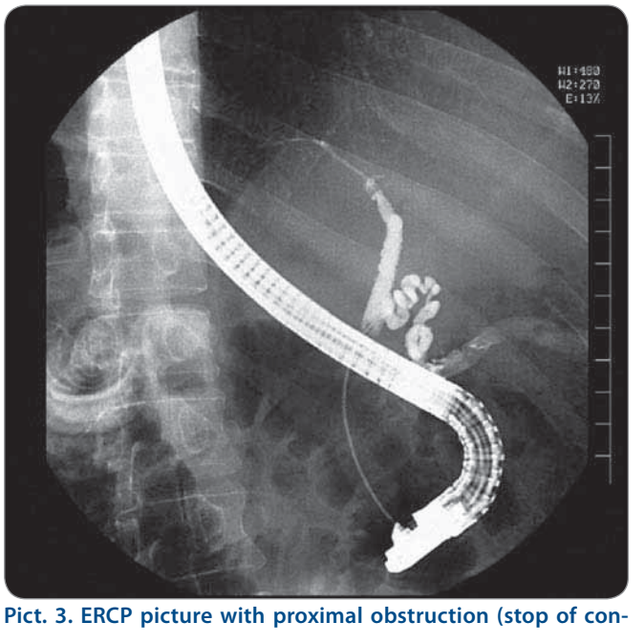
Tab. 1. MSKCC staging system (from Ustundag and Bayraktar) [99].

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

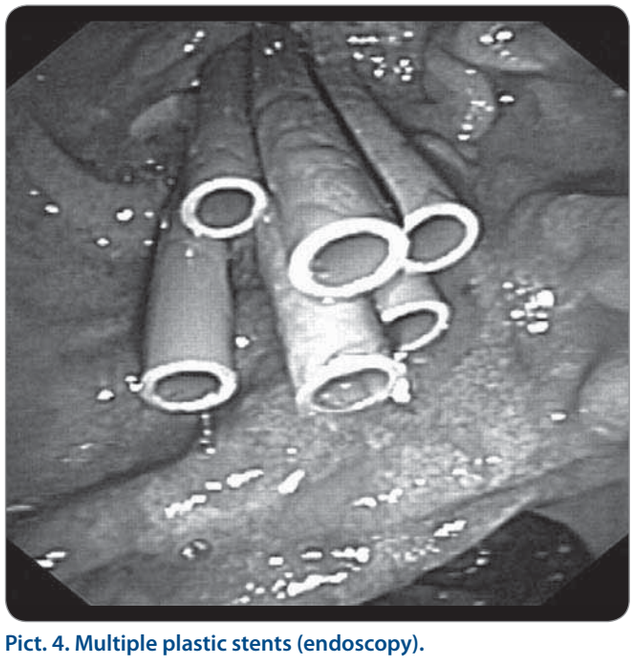
In some studies, CA 19-9, in fact its values above 100 U/mL were defined as poor prognosis indicator [42]. In another study higher values correlated with better chemosensitivity [43].

Obstructive icterus is quite often associated with false CA19-9 elevation even in benign conditions [44].

The role of the tumour marker CA 19-9 in differentiating benign from malignant masses in chronic pancreatitis has been assessed in a study with 84 patients who had mass lesions in chronic pancreatitis. The overall sensitivity and specificity of CA 19-9 for cancer was 68% and 70%, respectively. There was a higher positivity of CA 19-9 in cancers than in benign masses (23/34; 68% versus 15/50; 30%, $P < 0.01$) with cut-off values of 37 U/mL. Values over 300 U/mL were 100% specific for malignancy, but occurred in only 5 (of whom had distant metastases) of 34 patients [45].



Pict. 3. ERCP picture with proximal obstruction (stop of contrast), quidewire passing through. Winding cystic duct.



Pict. 4. Multiple plastic stents (endoscopy).

The real clinical utility of CA 19-9 remains controversial.

Staging and prognosis

Staging

Preoperative staging is not accurate. It can be problematic perioperatively, as well. Cryobiopsy of resection borders may be needed. Unfortunately, very frequent perioperative finding is an unresectable tumour. It has been described in up to 30 % patients previously classified as resectable on imaging.

Most patients (50–90%) patients are diagnosed with advanced/metastatic disease [46].

There are several staging systems in use. TNM system (see International Union against Cancer staging manual) deals with primary tumour extent (T), presence and extent of tumorous lymphadenopathy (N) and distant metastases (M).

Bismuth classification (modified Bismuth-Corlette system) dealing with hilar cholangiocarcinomas (Klatskin tumours) divides these according to bile duct involvement (Pict. 2). It is preferred by many surgeons as clinically more relevant. Neither of these systems is useful in survival prediction.

An ideal staging and classification system would consider resectability, it would predict the extent of necessary surgery (liver resection), and it would correlate with survival after resection. One such system has been designed in Memorial Sloan-Kettering Cancer Center (MSKCC) and it is based on primary tumour classification (T stage) (Tab. 1) [51].

There are four basic radiological signs for unresectable tumours. One is the extent of the tumour in the bile duct tree, in fact second level bile duct involvement on either side. The second is the vascular invasion, actually main portal vein involvement or occlusion before bifurcation. The third sign is the hepatic-lobar atrophy with contralateral portal vein involvement or hepatic-lobar atrophy with contralateral second-level bile duct involvement. The fourth sign is the presence of distant metastases (liver, lungs, peritoneum etc.) [22].

Prognosis

When untreated, carcinomas of biliary tree lead to swift death with median survival below 6 months. Survival more than 12 months is according to literature quite rare [24,47,48,64].

Death is usually caused by liver failure or biliary sepsis [49–51].

Only patients with incidental findings of localized stage of GC (T1N0M0) survive 5 years in nearly 100%.

An American review of 2500 patients showed 5 year survival of GC 60%, 39%, 15%, 5% and 1% for stages 0–IV respectively [52]. Another analysis showed median overall survival 10.3 months for all stages and 12 and 5.8 months for stage IA-III and IV, respectively [53].

Another study has shown survival rate for patients with unresectable GC as low as 2 to 4 months [54]. Patients with this cancer on palliative chemotherapy survive 7–12 months in median [55–58].

In literature, median survival rate for the patients after resection of intrahepatic and hilar cholangiocarcinoma ranges between 15 and 37 months. After resection for distal cholangiocarcinoma, median survival ranges between 20 and 33 months.

For unresectable cholangiocarcinoma on palliative chemotherapy, median survival ranges between 2 and 14 months [59–61].

Five-year survival rate of patients with ampulloma has been recorded around 40 % in some studies. Depending on the stage of disease it varies from 5-year survival of 90 % after resection of early stages carcinomas [62] to a survival less than 2 years in disseminated disease.

Prognostic factors and markers

Prognostic factors are the completeness of resection, lymph node involvement [63] and tumour differentiation. These influence the long-term survival essentially. Especially lymph node status is considered an independent and substantial prognostic factor for long term survival after resection [64]. When affected, the risk of relapse and tumour related death is nearly 7times higher.

Molecular genetic prognostic markers are being developed with increasing understanding of molecular level of cancerogenesis. In cholangiocarcinomas, several markers have been identified: oncogene K-ras mutation, p16, PCNA proliferation marker enhanced expression, tumour cells aneuploidy, increased vascular endothelial growth factor (VEGF) expression and angioinvasion, further oncoproteins overexpression (RCAS115, S100A4) [65]. L1 cell adhesion molecule has been identified as a poor prognostic factor, associated with perineural invasion [66].

Some markers may be helpful in differential diagnosis. Cholangiocarcinomas express p53, bcl-2, bax, and COX-2. Intrahepatic tumours were significantly more frequently bcl-2+ and p16+, whereas extrahepatic tumours were more often p53+ [67].

The serum levels of interleukin 6, trypsinogen, mucin-5AC, soluble fragment of cytokeratin 19 and the platelet-lymphocyte ratio have also been recently shown to help in the diagnosis of cholangiocarcinoma as well as certain prognostic value. Insulin-like growth factor 1 has shown a capability of discriminating cholangiocarcinoma from benign biliary disorders and pancreatic cancer [68].

There have been also attempts to define a set of genes to produce a signature useful predictor of survival (similar to already existing pattern in breast cancer). This set contains molecular biomarkers including mdm2, p27, matrix metalloproteinases and vitamin D receptor [69]. These markers are still experimental and none of them is being used routinely.

Treatment

Treatment can be curative (with intent to cure, aiming for long term survival) or palliative (aiming to prolong survival and/or improve life quality and postpone disease symptoms).

The only standard curative option is the complete surgical resection.

Unfortunately, most patients (nearly 90% according to some authors) are not candidates for curative treatment. It is usually for unresectable advanced/metastatic tumour. Some patients are not capable of radical surgery due to their performance status. In these and other cases that sadly form the majority of clinical situations, palliative care is the option.

Treatment of resectable tumours

Surgery

Cholangiocarcinomas

The only effective and potentially curative treatment option for distal cholangiocarcinomas is a complete resection with lymphadenectomy [70]. For a complete removal of distal cholangiocarcinomas, usually pancreato-duodenectomy is necessary. Compared to pancreatic cancer these tumours are somewhat more accessible to resection, less often with lymphatic dissemination and relatively less common is the microscopic resection border positivity.

For a complete removal of tumours lying proximally from the junction of cystic duct and main choledochus, liver resection is usually necessary. This situation occurs in about 40–60% including Klatskin tumours. Before hemihepatectomy, portal vein branch embolization on corresponding side is to be considered. The aim would be to induce an atrophy of to-be-resected liver lobe and compensatory hypertrophy of the lobe that is left.

The success of resection of distal cholangiocarcinoma is similar to duodenal cancer, somewhat better than pancreatic cancer, less favourable than neuroendocrine pancreatic tumours or ampullomas (Vater's ampulla carcinomas). Five year overall survival is usually between 20 and 40% (Nagorney et al 50%, Fong et al 27%, Wade et al 14%) [22]. Resection of distal cholangiocarcinomas is not more successful than a resection of hilar cholangiocarcinoma. When the stage and completeness of resection is considered, results are comparable. Main difficulty of hilar cholangiocarcinomas is their perineural spread, possible liver infiltration or invasion of important hilar vessels. Resection radicality is always questionable and relapses are common.

The benefit of ICC resection is similar to extrahepatic lesions. One retrospective study recorded total 5-year survival after resection 33%, for stages I, II, IIIA a IIIC median 5-year survivals 57, 33, 26 and 14 months respectively. More than half of the patients relapsed, out of these 89 % once more in liver [39].

Liver transplantation has not been recommended [71] for long time but for early stages of cholangiocarcinoma in the terrain of primary sclerosing cholangitis [41]. In this indication, autoimmune inflammation recurs in 20 % patients and relapses of cholangiocarcinoma have been described in transplanted liver where no signs of cholangiocarcinoma were observed before operation [72]. Improvement in technique, neoadjuvant treatment and staging have achieved results superior to standard surgical therapy, with 72% 5-year survival for patients with unresectable disease [73].

Gallbladder carcinoma

For GC, the only potential cure is a complete surgical resection, as well. The extent of surgery is given by the stage of the disease. In rare cases of incidental histological finding of carcinoma in tissue after cholecystectomy, it is recommended to consider re-resection of gallbladder bed. Liver resection is a necessity in cases of R1 gallbladder tumour resection.

The reason for this radicality is quite simple. There is no efficient treatment alternative for unresectable or recurrent GC.

Combination therapy

With development of new methods and multimodal approach, combination therapy has been used in radical management of bile duct carcinomas.

Methods of physical tumour destruction (cryoablation, laser or radiofrequency ablation) accompany surgery possibly in localities with poor technical accessibility.

Embolization may help visualize otherwise low-contrast tumours.

These methods, more often used in palliative setting, will be mentioned in further sections.

Adjuvant and neoadjuvant therapy

Standard regimen for adjuvant therapy after bile duct malignancies resection has not yet been defined. Usually fluoropyrimidine based chemo-radiation or chemotherapy with fluoropyrimidine or gemcitabine is recommended [70]. At present, no randomized phase III clinical trial results are available.

Neoadjuvant treatment is not a standard at present. However, there have been publications presented, showing significant increase in number of complete R0 resections after neoadjuvant chemotherapy. Even long term remissions have followed [74].

Treatment of unresectable tumours

A majority of patients with bile duct malignancies are diagnosed with unresectable tumours.

Palliative treatment aims for prolonged survival and improvement of quality of life of patients. Although it has evolved tremendously over past two decades, its results remain quite unsatisfactory. Even though palliative treatment is more common, standards are missing.

Palliative treatment is multimodal, involving surgeons, oncologists, radiologists, gastroenterologists, anaesthetists/pain managers, psychologists and others. There is no strict standard at the moment, as the effect of available treatment is questionable. Participation in clinical trials is encouraged and best supportive care remains one of legitimate options for treatment of unresectable bile duct tumours [70].

Biliary obstruction management

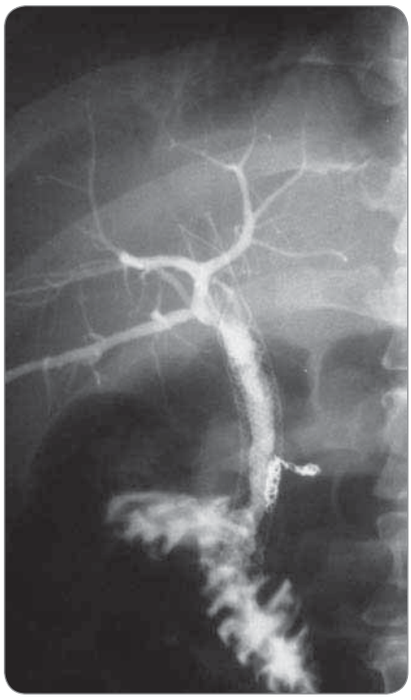
Biliary obstruction is a leading syndrome in bile duct malignancies. It may cause symptoms leading to diagnosis of a malignant tumour at the beginning or appear at any stage of patients' disease. Vast majority of patients experience biliary obstruction and connected problems at some point.

Progressing biliary obstruction leads to maldigestion, icterus, pruritus, abdominal discomfort or pain, cholangitis and sepsis, liver failure and death.

Therefore, biliary obstruction should be resolved whenever possible, even in palliative setting.

Cholangitis is a very common and potentially lethal complication of biliary obstruction. It appears at any stage of the disease.

Methods of biliary drainage include surgery, endoscopy, or percutaneous methods. An optimal approach is determined by accessibility of different methods, patient clinical status and life expectancy.



Pict. 5. Metallic stent in choledochus. Contrast picturing bile ducts from periphery to duodenum. Coils in gastroduodenal artery (a patient treated with regional intraarterial chemotherapy).

Surgery is most invasive and as such should be used in selected patients with good performance status or in cases of exploratory operation finding unresectable tumour. In such setting, it can provide excellent long term biliary drainage. Usually choledocho-jejunal anastomosis is designed.

Endoscopic approach is more common, least invasive and relatively most widely accessible, enabling biliary drainage in distal bile duct obstruction. Endoscopic retrograde choledocho-pancreatography (ERCP) (Pict. 3) equipment is used for sondage, drainage and possibly placing plastic prostheses (Pict. 4) or metallic stents.

Main disadvantage of this method is a high risk of artificially induced cholangitis in obstructed segments not relieved by drainage.

Metallic stent is preferred in most indications. It has shown longer patency and lower risk of cholangitis [75].

New developing endoscopic methods include photodynamic therapy (more below) or use of high intensity intraductal ultrasound [76].

Radiological **percutaneous transhepatal catheterization and drainage** (PTC and PTD) uses fine Chiba needle insertion into liver under local anaesthetics. The aim is to visualize, using a contrast, a bile duct and gradual Seldinger sondage of larger bile ducts, eventually bypassing tumour obstruction and placing a plastic drain providing drainage. Such a drain provides outer access for washout, inner perforation before obstruction and tip perforation for bile outlet in duodenum. Hence it may be called outer-inner-inner drainage.

Sometimes it is technically impossible to bypass tumour obstruction in one session. In such a situation, outer drainage is assembled, releasing pressure in bile ducts. In a following session several days later, it may be easier to bypass the obstruction and provide more physiological outer-inner-inner drainage.

Percutaneous approach also enables placing of self-expanding metallic biliary stents. (Pict. 5) Stents are more comfortable for patients, leaving no drain on the outside of abdominal wall and no maintenance flushes needed. Their patency is also relatively better than the patency of percutaneous drains.

Stenting is not appropriate in terminal patients, may not be appropriate in patients where further frequent adjustment of drainage is expected (e.g. progressing tumour) or in patients with cholangitis. However, there are situations where stenting provides better drainage results than percutaneous drains. It is due to usually larger lumen in stent compared to limited apertures in plastic drain tube.

In rare occasions, percutaneous stenting may be used preoperatively, enabling icterus resolution and surgery. In such settings, stent may be even helpful in local orientation for the surgeon.

Palliative surgery

Besides palliative biliary drainage, surgery provides a useful option of digestive tract bypass evading tumour. It may be beneficial to patient's life quality. Most common operation type is a gastro-jejunal anastomosis assembling.

Interventional radiology

For tumours affecting liver parenchyma, other methods of interventional radiology may be considered. Being percutaneous, these methods are often quite elegant with low invasiveness and good tolerability. Liver nodules may be destroyed using application of chemicals (ethanol, acetic acid, hot saline solution), or by thermal methods (cryotherapy, laser destruction, microwaves, electric current, or radiofrequency ablation).

As mentioned above, these methods can be combined with other modalities – for example a resection of superficial liver metastasis can be accompanied by an ultrasound guided perioperative radiofrequency ablation of a deeper situated nodule.

Embolization

Using Seldinger method, it is possible to embolize tumours with sufficient vascularization. Selective catheterization of an arterial tumour bed enables a direct application of embolization material. Combination of embolization with application of chemotherapy may be favourable (TACE). Ischemia is so combined with a prolonged cytostatic effect with maximal topical action and fewer systemic side effects. According to desired outcome, with respect to liver function, sessions can be repeated. Prolonged survival has been reported in some studies [77].

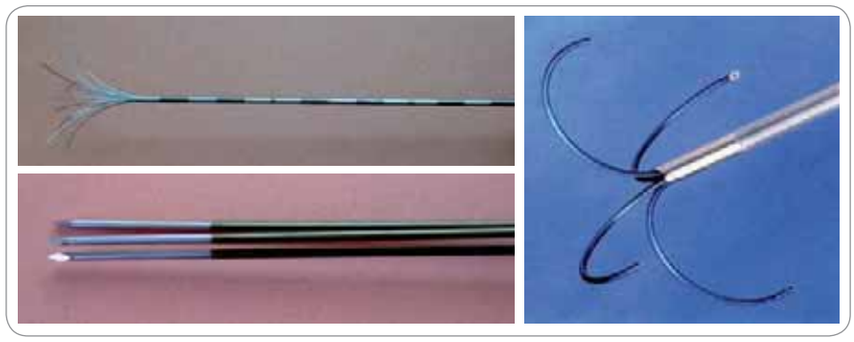
Recently, new delivery systems have been developed, using microspheres produced from a biocompatible polyvinyl alcohol (PVA) hydrogel, capable of binding and gradually eluting chemotherapeutic drugs, providing better accuracy and tolerability.

Radiofrequency ablation

Radiofrequency ablation (RFA) can be performed as percutaneous or as a part of operation. (Pict. 6) It's a physical method of thermal destruction. Tumorous nodes are destroyed by the temperature near to 100 Celsius degrees for approximately 20 minutes. With respect to the patient, the RFA session can be very demanding – painful, long and requires active cooperation of the patient. Usually,

presence of an anaesthetist is needed. Otherwise, this method is relatively safe, simple, and effective [78,79]. It is possible to destroy even by other modalities hardly accessible nodes up to 10 centimetres in diameter. It has been described even more than 10 nodes ablation in one patient [80]. RFA can also be combined with other methods and can be used repeatedly. As an example we can mention a RFA of liver nodule, followed by a chemoembolization taking advantage of reactive hyperaemia of ablated node.

We have experienced RFA as a new and potentially promising method of clearing an obstruction in a biliary stent. This application of RFA needs more investigation and safety data to be widely acceptable.



Pict. 6. Examples of RFA needle electrodes.

Chemotherapy

The effect of systemic chemotherapy in cholangiocarcinoma [81] and GC [82] is very limited. No complete remission following chemotherapy has been described [83].

For many past years, fluoropyrimidines have been used and many other agents tested, with response rate lower than 30%.

Gemcitabine seems to offer better response rate with favourable toxicity profile and has become a widely accepted standard. In several small studies involving 167 assessable patients, objective response rated up to 60% (36% in the largest trial composed of 39 evaluable patients), overall survival times ranging from 6.3 to 16 months. Grade 4 haematological toxicity was rare (< or = 5%) [84].

Recently, role of other agents is under investigation, however, data is still very limited. There are no phase III randomized controlled clinical trials defining standard treatment regimen.

Chemotherapy agents supported by phase II clinical trials are: single agent gemcitabine, capecitabine, 5-fluorouracil and combinations gemcitabine/cisplatin, gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/ oxaliplatin, 5-fluorouracil/cisplatin [85]. The combination of gemcitabine/cisplatin has shown response rate of 53%, and median survival times > or = 11 months with only a slight increase in frequency and severity of side effects [84].

Other combinations have been studied with epirubicine, etoposide, leucovorin, doxorubicin, mitomycin-C; out of newer agents irinotecan and paclitaxel.

In clinical practice, it seems to be likely that a certain group of patients benefits from palliative chemotherapy more than others. This group hasn't been defined yet, nor the ideal regimen. Many predictors and markers are under investigation, possibly aiming for a gene signature predicting response to certain treatment. So far, only empiric approach is possible, aiming for a well tolerated, inexpensive and effective treatment.

For the application of regional chemotherapy it is necessary to secure an access into the hepatic artery. Chemotherapy may be administered via a Seldinger technique-inserted catheter or via an arterial port-catheter. The latter option is more convenient for repeated applications. A perioperative insertion seems to be more secure and durable. From cytotoxic agents, usage of fluoropyrimidines (5–FU or UFT), cisplatin, doxorubicin and mitomycin-C are common [86]. Most of these agents have been in use for decades [87]. The rationale of this method is to increase local chemotherapy concentration with smaller side effects. Response rate using this method has been reported around 40% [88]. There are also regimens combining regional and systemic application.

Radiotherapy

Carcinomas of biliary tree are relatively resistant to radiotherapy. Adjuvant or neoadjuvant use of radiotherapy has brought no improvement [89,90]. However, solid data is still missing.

Only combination radio-chemotherapy with fluoropyrimidines has been proven beneficial and belongs to treatment algorithm for patients with locally advanced unresectable ECC. Chemo-radiation can provide local control and even prolong survival [91,92]. However, for ICC, evidence supporting benefit of chemo-radiation is very limited.

Despite lack of valid randomized data, external beam radiotherapy or intraluminal brachytherapy are often used and seem to be useful for local control of patency of biliary stents, some show even benefit for survival [93–96].

Photodynamic therapy

A very promising method uses intravenous application of photosensitizing agents followed by intraluminal photo-activation [97]. Necrosis of tumour cells occurs in 4–6mm in depth. Improvements have been reported in quality of life, longer biliary drainage, and overall survival [98]. Main disadvantages are the risk of artificial infection of bile and photosensitivity. Photodynamic therapy was not available in the Czech Republic in year 2009.

Targeted therapy

Molecular therapies (e. g. epidermal growth factor receptor, ErbB-2, and vascular endothelial growth factor receptor antagonists) and immunotherapy using antibodies are under investigation [10]. Especially interleukin IL-6 signalling pathway including its receptor gp130 and IL-6 specific subunit gp80, activated downstream cascade JAK/STAT, PI3K/Akt

and MAPK, protein bcl-2 and other targets seems to offer more targets for specific inhibitors.

Some of the studies with these agents are reviewed in literature [85].

Supportive care

Supportive care is a mainstay in treatment of patients with bile duct malignancies. For some patients, it may be the only possibility – due to poor performance status, their wish or poor availability of other treatment methods. For all patients, however, it presents main backup for quality of life management. Health related quality of life has not yet been assessed properly in this field. Supportive care includes pain management, nutrition, treatment of cholangitis, psychological support etc.

The care is to be individualized to each patient, palliating all his/her needs if possible. In some regions, functional institutional or home-hospice care is available. In other localities, a specialist advice is to be sought.

There are more special methods (e.g. invasive pain management, special nutrition management or biliary drainage options) that may be tied to super-specialized centres. In need for such interventions, a specialist's consultation should be sought.

Conclusion

Biliary tract carcinomas are rare cancers with poor prognosis. Development in diagnostic methods and surgery hasn't changed this fact much over past decades.

The mainstay of medical care for patients with biliary tract carcinomas is the palliative treatment. The best up-to-date choice seems to be the multimodal individually tailored treatment including methods of surgery, clinical oncology, interventional radiology and other methods. These methods can prolong survival and improve quality of life to patients. This care can be found in specialized centres.

Much more needs to be done to bring more hope to this field. Improvements can be brought by new methods of diagnostic workup, surgery and interventional radiology. Understanding the tumour biology on molecular level could shift the strategy to a more successful one, resulting in more cured patients. Further improvement in the palliative care can be sought in defining new targets and new drug development.

The paucity of patients with bile duct neoplasms has been limiting to any improvement. A new design of larger randomized international multicentric clinical trials with prompt data sharing could help to overcome this major problem.

Defining standards of palliative care is a necessity. Addressing health-related quality of life could help to assess the real benefit of palliative treatment.

While waiting for the improvement with new radical methods and drugs, standards of palliative care should be defined and maintained.

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