Multimodal Treatment of Cholangiocarcinoma

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Abbreviations:
ALPSS : Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy
CCA : Cholangiocarcinoma
EGFR : epidermal growth factor receptor
HBV: hepatitis B virus
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
HER2-neu: Human growth factor receptor 2
LTX: liver transplantation
PDT: photodynamic therapy
PSC: primary sclerosing cholangitis
PVE: portal vein embolization
RFA: radiofrequency ablation
SBRT: stereotactic body radiation
SIRT: selective internal radiotherapy
TACE: transarterial chemoembolization
TAE: transarterial embolization
VEGF: vascular endothelial growth factor

Abstract

Cholangiocarcinomas (CCA) belong to a heterogeneous group of malignant tumours, which arise from the biliary tree via malignant transformation of cholangiocytes, hepatocytes or from hepatic progenitor cells. Even though clinical diagnosis and management of CCA improved significantly during the last decades, this malignant disease is still associated with a dismal prognosis. More and more multimodal therapeutic strategies are integrated into the treatment schedule. Treatment allocation should be based on a personalized medicine rather than guideline-based medicine by a multidisciplinary board. Whenever feasible surgical resection should be aspired in curative intend, in selected cases also liver transplantation may represent a curative option. However, often resectability is not given so that endobiliary (stenting, photodynamic therapy or intraductal radiofrequency ablation), chemotherapeutic or radio (chemo) therapeutic approaches are performed. For intrahepatic CCAs also locoregional treatment procedures such as transarterial embolization (TAE), transarterial chemoembolization (TACE) and selective internal radiotherapy (SIRT) may represent a treatment option. This review summarizes the current epidemiology, classification, diagnosis and management of CCAs, illustrates controversial areas of therapeutic strategies and recommends the optimal course of treatment.

Keywords: *cholangiocarcinoma, ALPSS, liver transplantation, radiofrequency ablation, transarterial chemoembolization, chemotherapy*

Introduction

Cholangiocarcinomas are rare tumours, which are often challenging to diagnose and to treat. Several risk factors are known and epidemiologic studies describe an increasing incidence of intrahepatic CCAs. Diagnosis of CCAs is complex and integrates clinical findings, different imaging methods, cytology/histology and serum tumour markers. The majority of patients are no candidates for curatively-intended surgical resection at first diagnosis because of local inoperability or distant metastasis. Treatment schedule is multimodal and involves surgical, radiotherapeutic, systemic and liver directed therapies.

Epidemiology

Worldwide, the incidence of cholangiocarcinoma (CCA) represents the second most frequent primary malignant tumour of the liver after hepatocellular carcinoma with 20 % and it accounts for 3 % of all gastrointestinal cancers [1]. In Europe, USA and Australia the incidence is low compared to others tumours (0.1-3.4/100000), however there are some countries with high incidence up to 113/100000 including Chile, some regions of China, Thailand and South Korea [1-4]. This is due to special, region-dependent risk factors like parasitic infections of the biliary tree or genetic predispositions. In some regions of the world like in the UK, CCA- induced mortality is even higher than that of hepatocellular carcinoma [1, 5]. The male to female ratio is 1.3-1.5:1 and CCA mainly occurs in the seventh life decade [6-7].Worldwide incidence of intrahepatic CCA (iCCA) increased over the last decades, while extrahepatic CCA (eCCA) decreased slightly [8]. However, if this is a real increase in incidence of iCCA or it is due to misclassification of perihilar CCA (pCCA) is still discussed controversial [9]. Gallbladder carcinoma and carcinoma of the ampulla vateri represent distinct tumour entities, which do not belong to the group of classical cholangiocarcinoma, and are therefore excluded in this review.

Classification:

Cholangiocarcinomas comprise a heterogenous group of tumors, which may arise from hepatic progenitor cells, biliary epithelial cells but also from hepatocytes [10-12]. Cholangiocarcinomas (CCA) are divided into intrahepatic cholangiocarcinoma (iCCA) arising in the branches of the biliary tree inside the liver parenchyma proximal to the secondary biliary radicals and extrahepatic cholangiocarcinoma (eCCA), which are located in the bile ducts outside the liver. Later can be further subdivided into perihilar CCA (pCCA) and distal CCA (dCCA) separated by the insertion of cystic duct.

Tumours of the perihilar region can be further classified according to the Bismut-Corlette classification (table 1) [13]. Most common are pCCA with 50-60 %, followed by dCCA with 20-30 % and iCCA with 10-20 % [14].

Table1: Bismuth-Corlette Classification

Type of Bismuth Corlette classification	Definition
Type I	Tumour is below the confluence of the left and right hepatic duct
Type II	Tumour reaches the confluence of both hepatic ducts
Type III	Tumour involves the common bile duct and either the right (IIIa) or left hepatic duct (IIIb)
Type IV	Tumour is multicentric or involves the confluence and both hepatic ducts

Intrahepatic CCA are genetically heterogenous and can be classified into a proliferative and an inflammatory subcategory [12]. Genomic alterations differ between iCCA and eCCA. While gene fusions of the fibroblast growth factor receptor 2 (FGFR2) can be found in 11-41% in iCCAs, these are rare in eCCA. Similarly, mutations in isocitrate dehydrogenease 1 and 2 (IDH1/IDH2) are overrepresented in iCCA as compared to pCCA and dCCA (15). In contrast, gene fusions of components of the protein kinase A pathway have been described in pCCA and dCCA (15). These findings are of interest, since inhibitors of FGFRs and IDHs are available and may allow targeted therapies in the future (15).

Histology

About 95 % of all cholangiocarcinoma are adenocarcinomas, while the other 5 % of all carcinomas represent squamous cell tumours. A rare subtype of CCA is a combined hepatocellular-cholangiocarcinoma [16-17].

Risk Factors

There are a variety of known and definitely established risk factors for development of CCAs, however they account for less than 30 % of all cases. In most cases CCAs occur sporadically [7]. Established risk factors are listed in table 2. Further on, there are less established risk factors discussed like obesity, smoking, alcohol, specific genetic polymorphisms and inflammatory bowel disease independent of PSC.

Table 2: Risk factors for CCA development

Established risk factors
Biliary tree disorders: • Bile (choledochal)-duct cysts (e.g Caroli syndrome) • Primary sclerosing cholangitis (PSC) with estimated risk for CCA of 9 % after 10 years (independent of diagnosis of concomitantinflammatory bowel disease [18] • Hepatolithiasis
Infections with hepatobiliary flukes Opisthorchis viverrini (O. viverrini) and Clonorchis sinensis (C. sinensis) in South East Asia
Toxins like thorotrast and dioxins
Hepatitis B and C especially for iCCAs
Liver cirrhosis especially for iCCAs
Hereditary Nonpolyposis Colorectal Cancer Syndrom (HNPCC)
Multiple biliary papillomatosis

Clinical presentation

Patients with early stage CCAs are often asymptomatic; in locally advanced or metastatic CCAs patients are suffering from fatigue, malaise, weight loss, probably jaundice and/or abdominal pain. Especially, pCCAs and dCCAs present with obstructive cholestasis and painless jaundice [4].

Prognosis

At the time point of diagnosis most patients are not resectable because of early lymph node metastasis and distant metastasis, and the median survival is about 6 months [19-20]. In meta-analysis and reviews the median 5-year survival rate after resection of CCAs ranges between 10-40 %, despite R0 resection rates up to 44 % [21-22].

Diagnosis and staging

The diagnostic confirmation of CCA is complex, depends on the subtype of CCA and uses different diagnostic tools. For local tumor evaluation MRT in case of pCCC or dCCC with cholangiopancreaticography is gold standard, in case of iCCC CT or MRT is recommended. EUS can be useful for detecting regional lymph nodes (see table 3) [23-24].

Table 3: Diagnostic procedures for CCA

Tumor localisation	Diagnostic tool
iCCA	• (contrast-enhanced) transabdominal ultrasound • MRT or CT (often peripheral ring-like contrast enhancement in arterial phase) • Biopsy (CT or ultrasound-guided)
pCCA	• (contrast-enhanced) transabdominal ultrasound • MRT with cholangiopancreaticography • Histological confirmation of diagnosis by biopsies or biliary brush cytology via ERCP (or PTCD) • probably cholangioscopy
dCCA	• (contrast-enhanced) transabdominal ultrasound • Endoscopic ultrasound (probably with fine needle aspiration) • MRT with cholangiopancreaticography • Histological confirmation of diagnosis by biopsies or biliary brush cytology via ERCP(or PTCD) • probably cholangioscopy

MRT: magnetic resonance tomography; CT: Computed tomography; ERCP: Endoscopic retrograde cholangiopancreaticography; EUS: Endoscopic ultrasound.

CCA can be classified according to their growth pattern and macroscopic characteristics into mass forming, periductal-infiltrating or intraductal tumours [25]. In case of iCCA radiological or sonographic approaches macroscopically mostly show tumours forming nodules. In pCCA and dCCA radiological or ultrasound imaging often fails to identify the underlying tumour, rather showing obstructive cholestasis as consequence of tumour growth. Macroscopically pCCAs or dCCAs can form a nodule, however more often they show diffuse periductalar infiltration and to lesser extent an intraductal growth pattern [26].

Histological diagnosis is a prerequisite for non-surgical therapeutic procedures e.g. chemotherapy. In case of curatively-intended surgical resection histological diagnosis is not absolutely needed if radiological and/or ultrasound features are characteristic for CCA, however, whenever possible histological diagnosis should be acquired in order to distinguish from hepatocellular carcinoma or metastatic disease. Needle biopsy is easily feasible in nodule-forming iCCAs in order to exclude hepatocellular carcinoma or metastasis of different origin. Especially in case of pCCA or dCCA histological validation might be unsuccessful depending on growth pattern (intraductal or extraductal) and tumour extent. Specificity and sensitivity of cytologic examination with fluorescence in situ hybridization (FISH) via ERCP/PTCD is about 70 % in pCCA and dCCA [27]. Biopsies for histological diagnosis slightly increase the diagnostic sensitivity [28].

67-80 % CCA lead to an increase of the tumour marker carbohydrate antigen (CA) 19-9, however, cholangitis per se and other gastrointestinal or gynaecological tumours also can lead to a significant increase [29-31]. Interestingly, in iCCA elevated CA19-9 is an independent risk factor for poor survival [31].

In the future, plasma cell free-DNA may be of value to diagnose both pCCA and iCCA [32].

For staging after revealing diagnosis of CCA computed tomography of abdomen and thorax is needed in order to exclude distant metastasis. However, for planning treatment schedule performance status, comorbidities and liver function have to be taken into account [23]. In western countries staging was carried out to TNM classification of the 7th edition of the AJCC/UICC staging manual from 2010, which separate between iCCA, pCCA and dCCA [33]. In January 2017 the 8th classification of the AJCC/UICC staging system was published, which will change prognostic stage groups [34].

Treatment of cholangiocarcinoma

CCAs often present in an inoperable state at first diagnosis because of local inoperability or distant metastasis, however surgery and for some patients liver transplantation may represent curative treatment options [22]. Treatment allocation should be determined by a multidisciplinary board and ECOG performance status, liver function and comorbidities of patients have to be considered. In the last decades multimodal and individualized concepts have increasingly been integrated into the management of CCA. Three stages of tumour disease can be defined; resectable early stage, irresectable locally advanced and metastatic stage (figure 1).

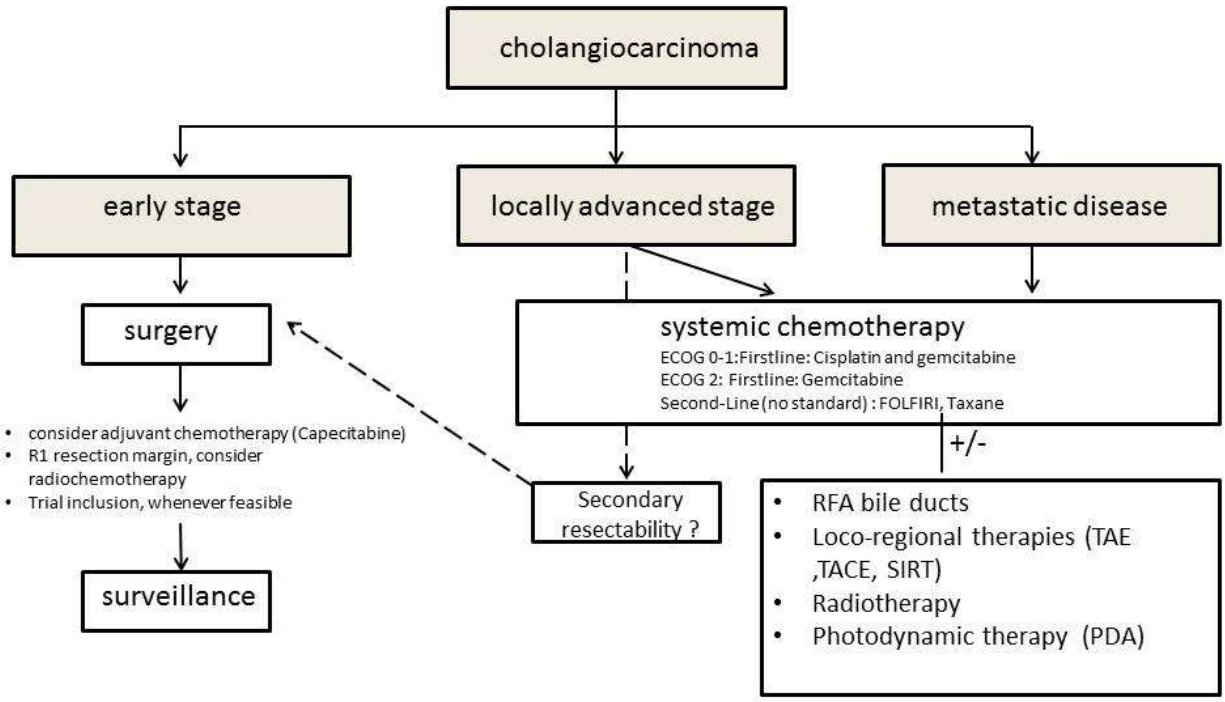

Figure1: Therapeutic Management of CCA

Surgical resection

Only 1/3 of all patients are candidates for curatively-intended R0 resection at diagnosis [35-37]. Importantly, resectability has to be evaluated by an experienced hepatobiliary surgeon. Resectability rates are higher in distal CCA than in intrahepatic or perihilar CCAs, because they become symptomatic earlier and therefore are diagnosed in earlier stages. All over resectability rates of CCAs increase irrespective of their origin because of more aggressive operative approaches. Recurrence after curatively-intended resections of CCAs might be local within the liver or peritoneum or distant as metastatic disease [38]. In up to 1/3 of all patients staging laparoscopy detects occult metastasis of cholangiocarcinoma mainly in the peritoneum or liver [39]. Laparoscopy might be recommended in high-risk patients with large tumours or long standing percutaneous stents. Criteria for irresectability are summarized in table 4 [40-41].

Table 4: Criteria for unresectability of CCAs

Criteria for irresectability:
• Distant liver or organ metastasis • Invasion/encasement of the main portal vein or main hepatic artery, however some centers even perform vascular reconstructions • Ipsilateral lobar atrophy with contralateral encasement of the lobar hepatic artery or portal vein branch • Retropancreatic nodal metastasis • extrahepatic adjacent organ invasion • Low remnant liver parenchyma • Bilateral hepatic duct involvement up to secondary radicles bilaterally

In case of R0-resection overall 5-year survival rates of 10-40 % are reported [8, 35-37]. The main prognostic factors after curative intended resections are lymph node metastasis and status of resection margins. Lymph node positive disease goes along with a poor prognosis, with five year survival rates of less than 10 % compared to 38 % in patient without lymph node metastasis for extrahepatic CCAs [42]. Furthermore, positive resection margins are associated with decreased prognosis with five year survival rates of 13 % [43-44]. Often resectabilitiy is ultimately determined at the time point of explorative surgery.

Patients with pCCA and planned extended liver resections with an estimated future liver remnant < 30 % should be considered for surgical liver augmentation procedures [45-46]. There are two approaches existing: portal vein embolization (PVE) or ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy) [45]. ALPSS is a two-step technique, with initial in-situ transection of liver parenchyma and portal vein ligation, followed by hepatectomy about 10 days later. For HCC it is an established method, however recently a study published a 48 % 90-day mortality after ALPPS for pCCA [47]. The authors concluded that portal vein embolization (PVE) should remain the preferred method to increase future remnant liver volume in patients with pCCAs. Preoperative, ipsilateral PVE can induce hypertrophy and a volume increase from up to 8-10 % of the future liver remnant (FLR), going along with increased resectability rates in patients with pCCA and better liver functions [45].

The surgical procedure for resection of the tumour is dependent on location of the tumour:

Intrahepatic cholangiocarcinoma: Radical resections with tumour free margins are indicated for curative treatment in patients with iCCAs, whenever feasible. These patients require segmental liver resections or hemihepatectomy [48]. Benefit of lymphadenectomy at the level of the hepatoduodenal ligament is not clearly proven, but especially in case of central localized tumours recommended [49-51].

Perihilar cholangiocarcinoma: Assessment of resectability according to the Bismuth classification by imaging might predict resectability. Radiographic criteria, which suggest local irresectability are bilateral hepatic duct involvement up to the secondary radicles, encasement or occlusion of the main portal vein and involvement of bilateral hepatic arteries [52] (see table 4), however often surgical exploration is needed for determination of operability. Depending on tumour dissemination lobectomy or extended right hemi-hepatectomy with resection of extrahepatic bile ducts is necessary for curative resection. In some cases, especially type I lesions upon the Bismuth classification,

en bloc resection of the extrahepatic bile ducts (and gallbladder) inclusive regional lymphadenectomy and reconstruction with Roux-Y hepaticojejunostomy is sufficient. In some cases portal vein embolization is needed for induction of hypertrophy of segment II and III in order to achieve sufficient future liver remnant. Segment I has to be removed also, because it drains into the ductal bifurcation. Lymphadenectomy has to be performed and in some (rare) cases vascular resections can be done [53].

Distal cholangiocarcinoma: This type of CCA requires resection of the pancreatic head usually as (partial) pancreaticoduodenectomy. In this case, bile duct resection is performed up to the hilum and includes lymph node dissection and reconstruction of the stomach and the remaining pancreas.

30 day-mortality after resection of CCA differs from 2-25 % in various case series [54-56]. Overall recurrence rates remain high with 49-65 % and occur mostly within 2-3 years after resection [for review see 57].

Preoperative biliary decompression: Whether patients with extrahepatic CCAs and obstructive jaundice need preoperative biliary stenting or not, is controversially discussed [58-61]. Supporters of preoperative drainage hypothesize that preoperative stenting will improve hepatic function and reduce the risk of cholangitis and postoperative liver failure [59], while opponents describe a higher risk of tumour seeding and higher perioperative morbidity [58]. A recent meta-analysis published no differences in postoperative mortality and postoperative hospital stay; however, overall postoperative complication rates and infectious rates were higher in the group of patients with preoperative stenting [62]. Furthermore, it is also unclear if biliary stenting should be performed with endoscopic or percutaneous transhepatic procedures [63-64]. Guidelines recommend to refrain from preoperative stenting when feasible [23,65]. Biliary stenting is recommended in patients with significant cholangitis or cholangiosepsis, hepatic insufficiency, patients requiring portal vein embolization (PVE), jaundice with bilirubin > 10 mg/dl and if extended liver resection is planned in order to drain future remnant liver, when it is less than 30 % [23,65-68].

Adjuvant treatment after surgical resection:

The evidence for adjuvant chemotherapy or radiochemotherapy is very low, meta-analysis suggests an increase in survival rates for adjuvant chemotherapy in nodal positive stage and radiochemotherapy in R1-resected tumours [69]. Probably other high risk tumours with vascular invasion or perineural invasion might also benefit from adjuvant chemotherapy. For R1/R2 resected iCCAs or eCCAs systemic chemotherapy with gemcitabine/cisplatin or gemcitabine/capecitabine followed by conventional 5-FU based radiochemotherapy is recommended, however data are very weak (NCCN Guidelines). Recently a randomized study was published, which showed an increase in median survival in patients with R0-resected biliary tumours (82 % CCAs, 18 % gallbladder cancer) and adjuvant treatment with capecitabine monotherapy up to 51 months compared to 36 months in the observation arm. This is the first randomized study, which clearly showed survival benefit of an adjuvant therapy in patients with cholangiocarcinoma after R0 resection [70] and this therapy may become standard of care. However, another randomized phase III trial, which evaluated the treatment with gemcitabine and oxaliplatin in patients with biliary cancers could not find any difference in relapse-free survival compared to surveillance [71]. Further trials are needed for analysing the role of adjuvant (radio) chemotherapy in patients with resected CCAs.

Neoadjuvant treatment of locally advanced, primarly unresectable tumours

In selected cases, borderline resectable or primary unresectable tumours might be downsized by a neoadjuvant therapy in order to induce secondary resectability. There are only some small series reporting secondary resectability after initiation of a neoadjuvant therapy [72-73]. Randomized trials are missing so that optimal therapy schedules cannot be recommended (see also section palliative therapy).

Liver transplantation

Usually liver transplantation is not recommended in Europe to treat CCA. However, there are consistent data for perihiliar CCAs that suggest a role of liver transplantation in selected patients. In these trials candidates for LTX showed no evidence of lymph node or distant metastasis and they have tumours less than 3 cm diameter. In these patients often neoadjuvant radiochemotherapy was administered followed by liver transplantation. These patients showed 5 year survival rates greater than 70 %. However about 30 % develop tumour progression while awaiting transplantation resulting in exclusion from the protocol [74-79]. Whenever feasible, patients should be treated within clinical trials. For intrahepatic CCAs role of LTX is discussed much more controversial because of small numbers of patients and heterogeneity of neoadjuvant treatment schedules.

Palliative treatment

There are no clearly established recommendations for an optimal therapy of locally advanced cholangiocarcinomas because randomized trials are missing. Options might be chemotherapy alone or radiochemotherapy for intra- and extrahepatic CCAs. For intrahepatic CCAs also hepatic intraarterial chemotherapy, radiofrequency ablation, embolization with and without chemotherapy or radioembolization can be offered. These multimodal approaches might even be combined or at least sequentially applied during the course of disease. A multidisciplinary board should provide the treatment schedule on basis of a personalized medicine rather than guideline-based medicine for each individual patient.

Chemotherapy is an established therapy especially in metastatic disease, however, it can be recommended also for locally advanced, unresectable tumours (see section systemic therapy). Radiochemotherapy is also considered for therapy of locally advanced, unresectable intra- or extrahepatic CCAs. There is one retrospective study, which suggests a benefit of systemic chemotherapy followed by radiochemotherapy compared to chemotherapy alone in iCCA [80]. For extrahepatic CCAs median overall survival rates of 12 months were reached by radiotherapy [81]. Newer series (retrospective or small series) show high rates of local control for iCCAs or eCCAs, which were treated with stereotactic body radiotherapy (SBRT) with or without chemotherapy [82-84].

Transarterial embolization (TAE), transarterial chemoembolization (TACE), selective internal radiotherapy using Yttrium-90 tagged glass or resin microspheres (SIRT) and percutaneous ablation (radiofrequency ablation and microwawe ablations) are techniques, which are established in treatment of hepatocellular carcinoma, but can also show effectiveness in intrahepatic cholangiocarcinoma [85-94]. For TACE survival benefit in patients with locally advanced or metastatic iCCA was reported in retrospective analysis compared to best supportive care (TACE 12-15 months overall survival vs. 3,3 months in BSC) [92-94]. Another retrospective multicenter analysis including nearly 200 patients with iCCA suggested that intra-arterial therapy was safe and this approach resulted in stable disease in 62% or partial to complete response in 26%.

The majority of these patients were treated with conventional TACE or Yttrium-90-SIRT [86]. Recently a retrospective study was published consisting of 46 patient, which were treated with (90)Y radioembolization at a single institution. Survival varied based on presence of multifocality (multifocal 5.7 months vs. 14.6 months unifocal) and tumour morphology (infiltrative tumour type 6,1 months vs. peripheral, nodule forming tumour 15,6 months). Disease was converted to a resectable status in five patients, who successfully underwent curative resection [89]. Another pooled analysis of 12 studies showed median overall survival rates of 15,5 months after Yttrium-90-SIRT. 28 % of patients showed partial response and a stable disease was confirmed in 54% of patients at three months [90].

Treatment of iCCA with radiofrequency ablation has been studied only in retrospective series with small numbers of patients. A recent meta-analysis identified 7 observational studies with 84 patients. The pooled 1-year, 3-year, and 5-year survival rates were 82% (95% confidence interval [CI], 72%-90%), 47% (95% CI, 28%-65%), and 24% (95% CI, 11%-40%). Five patients showed major complications including one patints, who died because of liver abscess and subsequent sepsis [91]. However, percutaneus radiofrequency ablation should not be performed in tumours, which are > 5 cm in diameter.

Palliative therapy of bile duct obstruction

In extrahepatic CCAs bile duct obstruction and jaundice goes along with high morbidity and mortality rates because of liver dysfunction and cholangitis. There are different strategies to resolve bile flow via stenting with plastic or metals stent by Endoscopic Retrograde Cholangiopancreatography (ERCP) or Percutaneous Transhepatic Bile Duct Drainage (PTCD). Stenting of bile duct might be combined with intraductal destruction of tumour cells by photodynamic therapy or radiofrequency ablation.

Photodynamic therapy: First injection of a photosensitizer intravenously has to be performed thereby reaching the bile duct via bloodstream, where it accumulates inside the tumour cells. A small light source with a special wavelength is applied to the tumour bed inside the bile duct by ERCP or PTCD. The photosensitizer in the tumour cells absorbs the light and produces an active form of oxygen radicals thereby destroying tumour cells. These techniques are not available in every center. However, there are also randomized trials, which showed a survival benefit for bile duct stenting in combination with PDT. First Zoepf et al. described a median survival of 21 months in patients treated with PDT compared with 7 months in the group with stenting alone [95]. Further on, Ortner et al. reported a significantly longer survival in the combination group (PDT with stenting alone [96]) with 493 days compared to 98 days in the group with stenting alone [93]. This prolongation of survival is thought to result from better resolution of biliary obstruction and not because of tumour mass reduction.

Intraductal radiofrequency ablation has also been described as safe and feasible method in treatment of extrahepatic CCA [97-98] going along with reduced stent occlusions and probably improvement of survival. Prospective and randomized trials are needed for evaluation of the role of intraductal RFA in respect to a probably survival advantage.

Systemic therapy

In locally advanced, unresectable or metastatic disease classical chemotherapy is one cornerstone of treatment. It is hypothesized that eCCA respond better to chemotherapy than iCCAs [99].

Gold standard for first line therapy is the combination of gemcitabine and cisplatin as it was shown by a large randomized phase III trial. Median survival was nearly 11,7 months

for the combination therapy compared to 8.1 months with gemcitabine alone (HR 0.64; 95 % CI:0.52-0,80; p=0.001) and also the progression free survival was improved (8 months compared to 5 months, HR 0.63; 95 % CI: 0.51 to 0.77; p=0.001) (100). Similar results were obtained in a randomized phase II trial in Japan [101].

Selective studies for 1st line chemotherapy are summarized in table 5. Trials mainly follow two strategies, on the one hand they analyzed combination therapies with 5-FU or capecitabine and a platinum compound (cisplatin or oxaliplatin) or on the other hand monotherapies with gemcitabine or combinations with gemcitabine and a platinum compound were used. A pooled analysis of studies identified gemcitabine, 5-fluorpyrimidine and platinum agents to have significant antitumor activity [108]. However, with exception of the study of Valle et al. prospective randomized, placebo controlled phase III trials showing a survival benefit by combination therapies are missing [100]. If cisplatin is contraindicated because of renal insufficiency, oxaliplatin can be used instead [4] (table 5).

Study	Phase	Entities	Treatment schedule	Overall survival (months)	p-value
Valle et al. [100]	III	locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer	gemcitabine+cisplatin vs. gemcitabine	11,7 8,1	< 0,001
Glimelius et al. [102]	II	pancreatic or biliary cancer	5-FU+etoposide vs. BSC	6 2,5	< 0,001
Sharma et al. [103]	II	unresectable gall bladder cancer .	5-FU vs. gemcitabine+oxaliplatin vs BSC	4,6 9,5 4,5	0,032
Nehls et al. [99]	II	gallbladder, eCCA iCCA	capecitabine+ oxaliplatin	12,8 5,2	*NR
Ducreux et al. [104]	II	inoperable locally advanced or metastatic biliary tract carcinoma	5-FU 5-FU+cisplatin	5 8	*NR
Alberts et al. [105]	II	in advanced biliary tract and gallbladder carcinoma	gemcitabine+5-fluorouracil	9,7	*NR
Takada et al. [106]	II		5-FU+doxoruvicin+mitomycin C vs. BSC	6 3	*NR
Andre et al. [107]	II	advanced BTCs	gemcitabine+oxaliplatin	8,8	*NR

Table 5: Selected first line chemotherapies in advanced biliary cancer
*NR: not resulted, BSC: best supportive care

There is no established second line therapy after failure of gemcitabine and platinum based combination treatment. Recently a review was published, which showed very disappointing results for second line therapies with median PFS of 3.2 months, response rates of 7.7 % and a median overall survival of 7.2 months [109]. However the magnitude of the data is not compared to best supportive care, so a clear benefit is not established or excluded for a second line therapy. Potential second line therapies are mainly fluoropyrimidin-based therapies as monotherapy or combinations with oxaliplatin or irinotecan [109-110].

Up to now targeted agents addressing signaling molecules e.g. MEK, Her-2, EGFR, VEGF and mTOR showed no survival improvement [111]. Immunotherapies with the checkpoint inhibitor pembrolizumab [112], inhibitors of fibroblast growth factor receptor 2 [113] or isocitrate dehydrogenase 1 (IDH1) [114] suggest a promising response; however, phase III trials have to be awaited.

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