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Progress Report

Cholangiocarcinoma: A position paper by the Italian Society of Gastroenterology (SIGE), the Italian Association of Hospital Gastroenterology (AIGO), the Italian Association of Medical Oncology (AIOM) and the Italian Association of Oncological Radiotherapy (AIRO)

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ABSTRACT

The incidence of Cholangiocellular carcinoma (CCA) is increasing, due to a sharp increase of the intrahepatic form. Evidence-ascertained risk factors for CCA are primary sclerosing cholangitis, *Opistorchis viverrini* infection, Caroli disease, congenital choledocal cist, Vater ampulla adenoma, bile duct adenoma and intra-hepatic lithiasis. Obesity, diabetes, smoking, abnormal biliary-pancreatic junction, bilio-enteric surgery, and viral cirrhosis are emerging risk factors, but their role still needs to be validated. Patients with primary sclerosing cholangitis should undergo surveillance, even though a survival benefit has not been clearly demonstrated.

CCA is most often diagnosed in an advanced stage, when therapeutic options are limited to palliation. Diagnosis of the tumor is often difficult and multiple imaging techniques should be used, particularly for staging.

Surgery is the standard of care for resectable CCA, whilst liver transplantation should be considered only in experimental settings. Metal stenting is the standard of care in inoperable patients with an expected survival >4 months. Gemcitabine or platinum analogues are recommended in advanced CCA whilst there are no validated neo-adjuvant treatments or second-line chemotherapies. Even though promising results have been obtained in CCA with radiotherapy, further randomized controlled trials are needed.

1. Background

Cholangiocellular carcinoma (CCA), has long been considered the "son of a lesser god" of primary liver cancers. The lower interest compared to hepatocellular carcinoma (HCC) was due to a number of reasons: lower incidence of the tumor, deriving from intra- or extrahepatic cholangiocytes; lack of association with an easily recognizable preneoplastic lesions, such as cirrhosis for HCC; the lack of clearly identified risk factors. The scenario is now changing: the incidence of the tumor is increasing and a number of preneoplastic conditions, such as hepatitis C virus (HCV) infection, are being recognized, chemotherapy with gemcitabine combinations is now accepted, radiotherapy is showing the first promising results and, finally, data regarding sorafenib in HCC and other epithelial tumors as well as preliminary *in vitro* and *in vivo* studies suggest the possibility of using multikinase inhibitors in the treatment.

The present manuscript represents a position paper reporting the standpoints of the Italian Association of Hospital Gastroenterologists (AIGO), The Italian Society of Medical Oncology (AIOM), the Italian Society of Oncological Radiotherapy (AIRO) and the Italian Society of Gastroenterology (SIGE); these scientific societies commissioned the speakers involved in a joint meeting held in Milan in the spring of 2009, during the Congress of the Italian Federation of

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Table 1
Levels of evidence from the American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines.

Levels of Evidence	Study Design Grade Definition	Grade of recommendation
I	Randomized controlled trials (RCT)/metanalysis of RCT	A
II-1	Controlled trials without randomization	B
II-2	Cohort or case-control analytic studies	B
II-3	Multiple time series, dramatic uncontrolled experiments	C
III	Opinion of respected authorities, descriptive epidemiology	C

the Societies of the Digestive System Diseases (FISMAD) to produce this work. The paper is the result of a first phase of systematic literature search and revision, which resulted in a preliminary draft. The draft was then circulated amongst the authors and a subsequent meeting was held, in which a consensus was reached on the points touched and on the final statements identified. These are presented with the respective levels of evidence, as reported in the American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines, summarized in Table 1 [1]. Even though surgical issues were not debated in the joint meeting, two short paragraphs have been introduced to summarize also the indication and results of liver resection and transplantation in patients with CCA.

2. Epidemiology

The prevalence of CCA is heterogeneously distributed amongst different racial and ethnic groups, with the highest age-adjusted prevalence in Hispanics (1.22/100,000) and the lowest in African Americans (0.17–0.5/100,000) [2–6]. In the United States, the incidence of CCA has been reported to be 0.95/100,000 for intra-hepatic (IH)-CCA and 0.82/100,000 for extrahepatic (EH)-CCA [2]. A number of recent studies have highlighted a progressive increase, in the past 3 decades, in the mortality for IH-CCA, whilst EH-CCA mortality is stable or slightly decreasing [2–10]. With the exception of Denmark [11], this scenario has been reported worldwide [2–10]. The significant increase in age-adjusted incidence of IH-CCA was confirmed even after correction for a prior misclassification of hilar CCA as IH-CCA [12]. In Europe, the increase in the IH-CCA mortality was higher in Western countries than in Central or Northern Europe. In contrast, mortality rates for EH-CCA showed a diffuse decreasing trend [6,7]. Very recently, data on mortality and incidence trend for CCA have been reported also for Italy where a 40-fold increase in mortality for IH-CCA has been documented from 1980 to 2003 [13]. For EH-CCA, in contrast, mortality rates were stable or slightly decreasing in the last 10 years [13]. Thus, as described in most countries, also in Italy the increased mortality for CCA mainly involves the intra-hepatic form, thus suggesting different etiologic and risk factors for IH- and EH-CCA. It is however of interest that in all epidemiologic studies concerning primary liver malignancies, a high percentage (about 40%) of primitive liver cancers are classified as adenocarcinoma and therefore excluded from the group of either CCA or hepatocellular carcinoma. This probably accounts for a significant underscoring of IH-CCA incidence and mortality since, it is a common clinical opinion that most primary liver adenocarcinomas are indeed CCA [14,15]. Biological, immunohistochemical or genetic markers could definitively allow an exact diagnosis and classification of primary liver cancers and avoid these classification biases.

3. Risk factors

Cholangiocyte proliferation is a physiological mechanism of repair after damage, which maintains the biliary tree's integrity. Accordingly, proliferation is present in most liver diseases as a consequence of chronic inflammation, particularly when associated with obstructive cholestasis and intra-hepatic biliary tree involvement.

All putative risk factors indeed share a common pathogenetic mechanism, a condition of chronic biliary inflammation which, together with an activation of the resident stem cell compartment, predispose to CCA development by favouring occurrence and accumulation of somatic mutations. This is associated with an imbalanced regulation of cholangiocyte proliferation and apoptosis, and all the above factors are necessary for CCA development and growth.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease which leads to a progressive destruction of intra- and extrahepatic bile ducts and is the major risk factor for CCA in the Western world [16]. In 50% of the cases, the diagnosis is concomitant with the identification of PSC or within the first 2 years of follow-up, with an annual incidence rate of 0.6–1.5% [16–19]. In 30–42% of PSC cases, CCA is often found incidentally at autopsy or in explanted livers of patients undergoing transplantation [16–19]. In a European multicenter study [17] including 394 PSC patients from five European countries with a median follow-up of 18 years, the majority of CCA cases (50%) was diagnosed within the first year after PSC diagnosis and in 27% of cases at liver transplantation, with no correlation between incidence of CCA and the duration of PSC. The coexistence of inflammatory bowel diseases and their duration confer an additional risk of CCA development in PSC patients. In a Mayo Clinic study [18] on 161 PSC patients followed for over 10 years, 6.8% of patients developed CCA (0.6% per year). In contrast with the European multicenter study, no association was found between CCA incidence in PSC patient and coexistence of ulcerative colitis or its duration. Also in this study, the majority of CCA cases were diagnosed during the first 2.5 years after initial PSC diagnosis [18]. Therefore, when an initial diagnosis of PSC is made, patients should be carefully screened and regularly monitored for CCA development mainly during the first 2 years of follow-up. Even though overall accuracy in surveillance is still far from being satisfactory, surveillance with CA19-9 determination and one imaging technique, either computed tomography (CT) or magnetic resonance imaging (MRI), is at present the suggested approach [19]. In PSC patients [16–19], older age at PSC diagnosis, history of colorectal dysplasia or carcinoma, smoking, and current or former alcohol use (>80 g/die), have all been suggested as additional risk factors for CCA development.

Liver fluke infestation is one of the most important risk factor for CCA in Eastern countries. Both epidemiologic and experimental data strongly support the role of parasite [20–22] or bacterial infections (particularly *Opisthorchis viverrini* but also *Clonorchis sinensis*, *Schistosomiasis* Japonica and *Salmonella typhi*) as risk factors for CCA in Asian endemic regions. Certain xenobiotics may lead to increased risk of CCA [23–25]. Exposure to thorotrast (thorium dioxide), a radiocontrast agent used in the 1950s and 60s, first led to reports of CCA in the 1970s [23,24]. Since then, hundreds of cases of CCA (as well as of other primary hepatic malignancies) due to thorotrast exposure have been described [23,24].

Miscellaneous risk factors. Any condition characterized by chronic biliary inflammation, such as Caroli disease, congenital choledocal cist, Vater ampulla adenoma, intra-hepatic lithiasis and abnormal biliary-pancreatic junction are considered to be addi-

tional risk factors for CCA [26–33]. Recent retrospective studies have suggested that an abnormal pancreatic-bile duct junction, with a common channel length of 8–15 mm, can influence the degree of pancreatic fluid regurgitation, resulting in an increased incidence of biliary tract malignancy. The abnormal junction was found in 45% of CCA compared to 6% of controls ($p < 0.01$)[33]. From a pathogenetic point of view, it has been hypothesized that lysolecithin, formed as consequence of the mixing between pancreatic juice and bile, acts as detergent on the biliary epithelium favouring chronic inflammation [34]. This mechanism has been also considered for patients undergoing bilio-enteric surgical drainage for benign diseases which represents another well recognized risk category. In contrast, patients undergoing endoscopic sphincterotomy during endoscopic retrograde cholangio-pancreatography (ERCP) do not have an increased risk of CCA, as definitively demonstrated in three different studies performed in large series of patients with long-term follow-up [35–37].

An increased risk of CCA in patients with chronic hepatitis C virus (HCV) infection [38,39] has been recently demonstrated and, HCV RNA has been detected in the biliary epithelium of resected CCA [40]. A prospective study of 600 HCV-infected individuals in Japan detected a 2.3% incidence of CCA, well above the baseline population incidence [41]. No sound data are available on hepatitis B virus infection [42–44]. Similarly an association has been reported between CCA and alcohol use [42–44], obesity, diabetes [42–44] and smoking, however further confirmation is need.

In summary, definition of risk factors for CCA is mostly based on observational or case–control studies. With these limitations, the evidence is strong for considering as definite risk factors age, PSC, *O. viverrini*, Caroli disease, congenital choledocal cyst, Vater ampulla adenoma, bile duct adenoma and intra-hepatic lithiasis. In contrast, weak evidence still exists for obesity, diabetes, smoking, abnormal biliary-pancreatic junction and bilio-enteric surgical drainage, which all need confirmation as risk factors by additional studies. Finally, HCV, hepatitis B virus and viral cirrhosis are emerging risk factors recently considered for the increasing incidence of intra-hepatic CCA; definitive confirmation, however, requires longitudinal prospective studies.

4. Diagnosis and endoscopic therapy of colangiocarcinoma

CCAs can be subgrouped into three anatomic subsets: intrahepatic, perihilar, and distal or extrahepatic. Perihilar tumors, also known as Klastkin tumors [45], involve the hepatic duct bifurcation. Klastkin tumors were the most common, accounting for about 60–80% of CCA. Intra-hepatic tumors are about 15% and distal extrahepatic about 20% [46]. However, recent epidemiologic data indicate that the incidence of the intra-hepatic form is progressively increasing and approximates that of perihilar CCA [12,13].

The Bismuth classification is commonly used to describe the biliary tract involvement and is helpful in planning surgical intervention. Type I tumors are found below the bifurcation of the left and right hepatic ducts. Type II tumors involve the bifurcation. Type IIIa and IIIb tumors occlude the common hepatic duct and either the right or left hepatic duct, respectively. Type IV tumors are multicentric, or involve the bifurcation and both the right and left hepatic ducts [47].

More than 90% of CCAs are well-to-moderately differentiated tumors, and appear as solid masses; they may infiltrate surrounding tissues, grow intraductally, or have mixed characteristics [48]. CCA is usually silent or associated with nonspecific symptoms in early stages. Intra-hepatic CCA is usually diagnosed only by imaging tests, whilst the presence of painless jaundice suggests the diagnosis of extrahepatic CCA. When the patient has symptoms, jaundice is usually present in 85% of patients, weight loss in 35%, abdominal pain in 30%, nausea and vomiting in 20% and fever in 10%.

At laboratory investigation, alkaline phosphatase and gamma-glutamyltransferase are frequently increased and are observed specifically in the presence of obstruction of the two main intrahepatic biliary ducts, or of the common bile duct. Elevation of alkaline phosphatase or gamma-glutamyltransferase might be present without increase in serum bilirubin in the presence of unilateral obstruction.

Elevation of serum tumor markers (Ca 19-9 and CEA) supports a diagnosis of CCA, although none are diagnostic. The levels of Ca 19-9 seem to correlate with the stage of the disease, as serum levels of Ca 19-9 lower than 100 UI/mL are found in 67% of resectable CCA compared with 28% of unresectable tumors [49]. Recent data show that biliary IGF-I levels in patients undergoing ERCP for biliary obstruction may differentiate extrahepatic CCA from either pancreatic cancer or benign biliary abnormalities [50]. Other markers, such as serum levels of interleukin 6, trypsinogen, mucin-5AC, soluble fragment of cytokeratin 19, and the platelet-lymphocyte ratio have been recently shown to help in the diagnosis of CCA, but their use is far from being routine. Interesting data on proteomics of serum and bile seem promising in identifying new markers for CCA [51].

The option of ultrasound-guided biopsy should be carefully evaluated, due to the relative contraindications given by the presence of mechanical cholestasis; it is often possible only in peripheral masses or when the lesion can be reached through an unaffected portion of liver parenchyma. Endoscopic ultrasound (EUS) with fine needle aspiration biopsy (FNAB) has instead a growing importance in the diagnosis and staging of CCA. EUS provides high-resolution imaging and can visualize lesions as small as 3 mm. Hilar lesions represent a difficult localization for EUS without FNAB. EUS also provides visualization of hilar, celiac axis and para-aortic lymph nodes to determine local and distant metastasis; FNAB of these lymph nodes is the most accurate method to diagnose CCA, simultaneously allowing for accurate staging. In 2004 Fritscher-Ravens et al. [52], in patients with hilar strictures and inconclusive diagnosis by ERCP, showed that EUS with FNAB revealed hilar CCA in 59% of the cases, with a high accuracy, inducing a change in tumor management in more than half of cases. These data were confirmed by Eloubeidi et al. [53]. By performing EUS with FNAB, before biliary decompression, in patients with indeterminate biliary strictures, surgical treatment could be tailored and most appropriate management decisions were made. Also high frequency intraductal ultrasound probes (IDUS) can be used in the diagnostic work-up of biliary strictures and, with this technique, the finding of an irregular wall thickening can be highly suggestive of malignancy. It must however be kept in mind that these procedures require well trained and experienced endoscopists and up-to-date equipment.

ERCP is useful in both the diagnosis and management of CCA. ERCP can delineate the anatomy of the biliary system and determine the extent of bile duct involvement, which is important in determining resectability and surgical management. Due to the risk of complications, ERCP is generally used when both a diagnostic and a treatment target is needed. ERCP-obtained brush cytology has a specificity of nearly 100%, even though sensitivity is much lower, ranging from 18% to 60% in various series.

From the therapeutic point of view, biliary stenting is the target in inoperable cases and can be achieved endoscopically or percutaneously. Endoscopic biliary stenting is the most common approach and the percutaneous approach is usually performed only for intra-hepatic peripheral stenosis or when the endoscopic drainage fails or cannot be performed. External stents have the disadvantage of stopping the enteric bile acid recycling and are associated with patient discomfort. Endoscopic stents used can either be self-expanding metallic or plastic (polyethylene). Metal stents are more expensive but have larger diameters and provide better patency rates. In inoperable malignant biliary obstruction, metal stents are cost-effective for patients with an expected sur-

Table 2
Gemcitabine in combination with other chemotherapeutic agents: response rate and median survival.

Combination therapy	Response rate (%)	Median survival (months)	PFS (months)	Author
GEM + CDDP	34.5	11	3	Kim [74]
GEM + CAPE	29	6.2	12.7	Reichelman [75]
GEM + DOC	67.4	11	UK	Kuhn [76]
GEM + CDDP	59.2	5.6	10	Park [77]
GEM + 5 FU	56	9	UK	Murad [78]
GEMOX fixed dose	62 (good PS)52 (poor PS)	15.4 (good PS)7.6 (poor PS)	5.7 (good PS)3.9 (poor PS)	Andre [79]
GEM + CAPE	73	14	7	Knox [80]

GEM: gemcitabine; CDDP: cis-diamminedichloroplatinum; CAPE: capecitabine; DOC: docetaxel; GEMOX: gemcitabine + oxaliplatin; PS: performance status; PFS: progression-free survival

vival of at least 4 months, since they require fewer interventions and shorter hospitalizations. A recent study showed that covered metallic stents in patients with unresectable distal biliary malignancies have a substantially higher patency time than uncovered stents [54].

Amongst other palliative methods, photodynamic therapy (PDT) is an emerging palliative strategy that has shown to improve quality of life, favouring biliary drainage, and prolonging survival in patients with advanced CCA. Intravenous administration of photosensitizing agents that preferentially accumulate in malignant cells is followed by delivering light at specific wavelengths, thus activating the sensitizer and causing tumor cell necrosis. Depth of tumor necrosis is between 4 and 6 mm. PDT is currently used in conjunction with biliary stenting for nonresectable CCA. A randomized controlled trial (RCT) comparing PDT plus endoscopic stenting with stenting alone in patients with unresectable CCA was terminated prematurely because PDT proved to be markedly superior to simple stenting [55].

5. Imaging and assessment of resectability

The major determinants of resectability include: the extent of tumor diffusion within the biliary tree, the amount of hepatic parenchyma involved, the presence of vascular invasion, of lobar hepatic atrophy and of metastatic disease [56]. Radiologic invasion of the main portal vein or vessels supplying the hepatic remnant are considered absolute contraindications to surgery. Sometimes however even CT and MRI lack sensitivity and under- or overestimate tumor diffusion, thus suggesting that the diagnostic and staging procedures should be managed by a "digestive cancer team" involving gastroenterologists, radiologists and surgeons, possibly with multidisciplinary meetings [57]. Promising results in staging are presently reported for positron emission tomography (PET) and CT/PET [58].

6. Liver resection and transplantation

Surgical treatment is the option of choice, if feasible, for CCA. Solitary intra-hepatic CCAs are approached by limited resection, such as segmentectomy, or, when larger, by lobectomy. Five-year survival rates are approximately 30%, depending on the presence of a negative resection margin and on the absence of nodal and vascular involvement [59–61]. Survival rates after surgical treatment have improved in the last few years, mainly due to an improved surgical technique and a more careful patient selection [62]. Resection is however indicated when a curative result is reasonably foreseen, given that no increase in survival is obtained with noncurative resection [63].

The problem remaining is that, overall, complete margin-negative (R0) resection rates do not exceed 50% of the cases. The efficacy and usefulness of neo-adjuvant and adjuvant treatment (radiation or chemoradiation) is still open to debate and cannot be routinely indicated.

The historical experience with liver transplantation for CCA was rather discouraging. The University of Pittsburgh was the first to report a disappointing 3-year survival of 20%, with very high recurrence rates; these data were confirmed by results deriving from the Cincinnati Transplant Tumor Registry [64].

In 2005, Rea et al. [65] published a follow-up of two earlier studies examining the results of an innovative treatment protocol for patients with stage I and II hilar CCAs [66,67], in which liver transplantation was performed following neo-adjuvant chemoradiation. This protocol resulted in a 1-, 3-, and 5-year survival rate of 92%, 82% and 82%, respectively. The results of this study, as well as of a few additional promising reports, are however to be interpreted with caution: the data were retrospectively collected, the selection criteria were quite strict, some patients died on the waiting list and some were still on the list when the paper was published; these data have not been yet replicated.

Overall, the general feeling is that there might be room for liver transplantation in patients with CCA, that neo-adjuvant treatment is mandatory, that selection criteria must be maintained strict and that we need prospective data confirming these preliminary results. The procedure should be at this point performed only in an experimental setting.

7. Chemotherapy

In unresectable or metastatic CCA, the primary aim of treatment is not only to prolong survival but also to maintain quality of life. Systemic chemotherapy should be the treatment of choice for patients with a good performance status who cannot benefit from loco-regional treatment.

The role, if any, of chemotherapy in the adjuvant treatment of CCA has been indeed debated for a long time. Some phase II studies showed better outcomes for certain groups of patients treated with adjuvant chemotherapy compared to surgery alone, but other retrospective series failed to demonstrate the same benefit [68]. In patients with stage I or II CCA, Rea et al. [65] reported a 1-, 3-, and 5-year survival of 82%, 48%, and 21% after neo-adjuvant radiotherapy, chemosensitization and resection, with a 25% recurrence rate. The results obtained with this treatment approach require further confirmation. As a consequence, the role of neo-adjuvant therapy remains investigational.

The evidence of benefit of systemic chemotherapy in CCA is limited because it is essentially based on small phase II and, recently, few phase III trials. All these studies evaluated the role of systemic chemotherapy generally in biliary tract cancer, peri-ampullary and pancreatic cancer, this being an additional limitation.

5-Fluorouracil (5FU) alone or combined with leucovorin (LV) was shown to achieve response rates of up to 10%, but median survival was in the range of 6 months and the weekly application of high-dose 5FU/LV only resulted in a modest improval [69]. Combination regimens with 5FU increased objective response, but also increased toxicity. In a phase II trial, 5FU plus subcutaneous interferon (IFN)-α2b produced a median survival of 12 months [70],

whilst polychemotherapy with the ECF regimen (epirubicin, cisplatin, 5FU) produced a response rate of 40% with a median survival of 11 months [71]. Moderate single-agent activity was also shown for capecitabine with a response rate of 6% and a median survival of 8.1 months observed in 18 patients [72], whilst in phase II trials the drug achieved a 30–36% RR, with a median survival ranging from 30 to 56 weeks, with only mild and manageable side effects [73]. The results from phase II trials depicting the role of combination Gemcitabine-based chemotherapy are summarized in Table 2 [74–80].

The pooled analysis published in 2007, including 104 trials and involving 2810 patients pointed towards gemcitabine as the most active agent [81] and demonstrated a correlation between response rate, disease control rate and overall survival. In this analysis, including all biliary tract cancers, median time to progression was 4.1 months and overall survival 8.2 months. Subgroup analysis conducted in CCA versus gallbladder carcinoma demonstrated a longer overall survival, but lower response rates in CCA patients versus gallbladder cancer patients (9.3 months versus 7.2 months and 18% versus 36%, respectively). Gemcitabine and platinum-containing regimens produced highest response rates and longer tumor control rate in CCA compared to other type of therapies; this was confirmed in a Japanese retrospective analysis [82], suggesting gemcitabine-based chemotherapy as a clinical standard and a possible benefit with the combination of gemcitabine and platinum.

At the 2009 Conference of the American Society for Clinical Oncology (ASCO), Valle et al. presented the results of a phase III trial of GEM-CDDP combination demonstrating an increased median survival (11.7 versus 8.3 months, $p = 0.002$) with a 30% reduction in death hazard ratio, a significant improvement in progression-free survival and reduction in disease progression [83].

There is instead no proven benefit for second-line therapy, and in this setting, designing and implementation of phase I/II studies would be appropriate.

In conclusion, gemcitabine-based chemotherapy is routinely used in clinical practice in biliary tract cancer and the benefit of gemcitabine-platinum combination has been confirmed. Therefore, depending on performance status, liver function, and motivation of the patient, gemcitabine single agent or gemcitabine and platinum-containing regimens may be selected as optimal treatment strategy. Attention should be paid on patients' age and comorbidities [84,85].

Recent studies reported a moderate activity of biological therapies. Several clinical trials are ongoing evaluating target therapies (COX-2 inhibitors, small molecules or monoclonal antibodies) alone or in combination with other agents (Celecoxib, Sorafenib, Erlotinib, Lapatinib, Herceptin and Bevacizumab). The reasons behind this novel approach to treatment with sorafenib or other kinase- or vascular endothelial growth factor inhibitors, lie in some interesting preclinical results, which however have not been translated so far in similarly exciting clinical data [86,87].

8. Radiotherapy

Surgery is the only curative treatment for bile duct cancer, and the number of radical resections has increased recently, but improvement in long-term survival rate is limited [88–92] and usually the tumor-related cause of death after radical surgery is loco-regional persistence of disease [90].

Several recent reports suggest that radiotherapy, both as primary treatment as well as after resection to eradicate microscopic residue, may improve survival; this has led to a reappraisal of the technique, with several recently developed advanced irradiation modalities, in an attempt to improve the prognosis of patients with advanced CCA.

These advanced techniques include:

1. Conformal irradiation, in which improved imaging techniques have rendered tumor/target definition more precise for the delivery of sophisticated high-dose external beam radiotherapy (EBRT) with the aid of 3D treatment planning, with acceptable morbidity.
2. Improvement of local control by adding specialized boost techniques such as conformal EBRT, brachytherapy via transhepatic catheters or an endoscopic stent.
3. Intra-operative irradiation with electrons (IOERT).

Several data support the above approaches. For instance, in patients with unresectable CCA, data collected in non-randomized studies show a trend towards an improved survival in patients treated by ERBT compared with those receiving palliative treatment alone [91,92], particularly in patients without distant metastasis. EBRT however, at doses higher than 40–45 Gy, has rarely been delivered with acceptable morbidity, because of the presence in the field of irradiation, of multiple dose-limiting organs, including liver, stomach, duodenum, kidneys, colon, and spinal cord. Recently, though, improved imaging techniques have rendered the tumor/target definition precise enough to allow for the delivery of sophisticated high-dose EBRT with the aid of 3D treatment planning (conformal irradiation), with acceptable morbidity.

Newly developed radiation techniques [93] using charged particles of helium and neon, showed significant prolongation of survival for patients with unresectable CCA in comparison with conventional radiotherapy using photons. These techniques attempt to take advantage of the excellent dose-localization properties offered by helium or neon ions, as well as of the increased biological effectiveness of neon.

Brachytherapy using iridium wire via transhepatic catheters or a retrograde endoscopic stent was long ago introduced as a therapeutic modality [94]. The temporary insertion of sealed radioactive sources can deliver localized high-dose irradiation. Thus, this modality is frequently used as a supplemental boost dose to EBRT to improve local control; several authors [95] have shown that the higher the irradiation doses the higher the survival rate.

Intra-operative irradiation with electrons (IOERT) is a technique that enables the delivery of high-dose radiation to the exact area of the tumor, whilst adjacent radiosensitive structures are retracted from the field, and radiation damage of normal tissue behind the cancerous tissue can be avoided by selecting appropriate electron beam energy. In early studies, a single high dose of 25–35 Gy was given during surgery for unresectable cases. Improved survival data were however reported by Mayo Clinic investigators in patients treated by combination of IOERT (20 Gy) and EBRT (45–50 Gy) with a median survival of 18 months [96].

There is also probably room for a combination of radio- and chemotherapy. A possible important role of the simultaneous administration of 5FU with EBRT was suggested by Foo et al. [97]. They reported a higher 5-year survival rate (22%) in the group treated by adding 5FU to EBRT (45–50.4 Gy) plus brachytherapy (20–25 Gy) compared to the group treated without 5FU (8%).

The efficacy of adjuvant radiotherapy following surgery is debatable, particularly in the treatment of patients with locally advanced CCA. Recent data however demonstrated beneficial results in combining IOERT plus EBRT with resection for patients with stage IV hilar CCA and increased the 5-year survival rate to about 40%, even though not in a randomized study [98]. Many other studies have also suggested that the combination of resection and radiotherapy may be more advantageous for improving survival in the treatment of patients with locally advanced bile duct carcinoma than either procedure alone [99,100] with acceptable morbidity and mortality.

Even more limited are the data on neo-adjuvant treatment, although preoperative radiotherapy could increase the possibility of achieving radical resection margins. Only three reports regarding preoperative radiotherapy have been published. In the first preliminary experience [101] patients with locally advanced CCA underwent preoperative EBRT (15–60 Gy) that induced the regression of a portal neoplastic invasion thus allowing resection. A second experience [102] reported that three of nine patients who underwent chemoradiation (30–50.4 Gy + 5FU) prior to resection had a histological complete response, and the rate of margin-negative resection was 100% without intra-abdominal complications. Recently, Nelson [103] suggested that a treatment strategy that includes preoperative chemo-radiotherapy might result in improved tumor resectability with similar surgical morbidity compared with patients treated postoperatively, as well as potentially improved survival outcomes.

Because of disappointing results, the indication for liver transplantation in proximal CCA has been controversial during the past several years [104,105]. Reports from the Mayo Clinic and the University of Pittsburgh have demonstrated surprisingly improved 5-year survival rates after combining preoperative EBRT with concomitant 5FU plus brachytherapy for patients with locally advanced proximal CCA. The 5-year survival rate after transplantation improved significantly in patients without lymph node metastasis when compared with that of patients who underwent resection alone (65% vs 0%, respectively). The cases treated were few but all patients with primary unresectable lesions by standard surgical criteria remained alive and achieved a 100% cumulative 5-year survival rate after a combination of EBRT plus concomitant 5- FU and brachytherapy prior to staging laparotomy, and a subsequent liver transplantation [106,107].

In summary, even though promising results have been obtained in specific settings, the experience in radiation therapy of CCA is not sufficient, and there has not been any report of controlled randomized trials including a reasonable sample size. Therefore, amongst other factors, the radiation method, the optimal dose, and the method to be used in combination with surgical resection, including transplantation, must be studied further to assess the effectiveness of combination modalities, as recently underlined [108].

9. Statements and recommendations

1. The incidence of CCA is increasing and the tumor should not be considered a rare entity; this is particularly true for the intrahepatic form, probably associated with environmental, genetic and viral risk factors, whose roles are emerging.
2. Evidence-ascertained risk factors for CCA are: PSC, *O. viverrini* infection, Caroli disease, congenital choledocal cyst, Vater ampulla adenoma, bile duct adenoma and intra-hepatic lithiasis. In contrast, obesity, diabetes, smoking, abnormal biliary-pancreatic junction and bilio-enteric surgical drainage need confirmation by additional studies. HCV, HBV and viral cirrhosis are emerging risk factors, recently considered the reason for the increasing incidence of intra-hepatic-CCA; definitive confirmation, however, needs longitudinal prospective studies.
3. Patients with primary sclerosing cholangitis should undergo careful surveillance for CCA development, even though surveillance programs have not been validated yet and a survival benefit has not been assessed. Most cases are diagnosed within the first 2 years, thus suggesting particular attention in that period (Level II-3 and III, recommendation C).
4. CCA is most often diagnosed in an advanced stage, when therapeutic options are limited to palliation, and the diagnosis of the tumor is often difficult. Cholangio-MRI and EUS are the main diagnostic tools, but all the available techniques (CT, ERCP, PET, PET/CT) should be used, particularly for staging (Level IV, recommendation C).
5. Surgery is the standard of care for resectable CCA with a curative intent, whilst liver transplantation should be considered only in an experimental setting, probably preceded by neo-adjuvant treatments (Level II, recommendation B).
6. Metal stenting is the standard of care in inoperable patients who are expected to survive at least 4 months (Level I, recommendation A).
7. Gemcitabine or platinum analogues are recommended as a worldwide standard of care and represent the backbone for further studies in advanced and metastatic CCA. Presently there are no validated neo-adjuvant treatments or second-line chemotherapies. Particular attention must be given to performance status, co-morbidities and multidimensional geriatric evaluations (Level I, recommendation A).
8. Even though promising results have been obtained in CCA treatment with radiotherapy, particularly in specific settings, the present experience is not conclusive and further RCTs, including sufficiently large series of patients are needed (Level IV, recommendation C).

Conflict of interest statement
None declared.

List of abbreviations

SIGE, Italian Society of Gastroenterology; AIGO, Italian Association of Hospital Gastroenterology; AIOM, Italian Association of Medical Oncology; AIRO, Italian Association of Oncological Radiotherapy; CCA, Cholangiocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; Cholangio-NMR, cholangio-nuclear magnetic resonance; EUS, endoscopic ultrasound; RCTs, randomized controlled trials; HCC, hepatocellular carcinoma; IH-CCA, intra-hepatic cholangiocellular carcinoma; EH-CCA, extra-hepatic cholangiocellular carcinoma; PSC, primary sclerosing cholangitis; Ca 19-9, carbohydrate antigen 19-9; CEA, carcinoembrionary antigen; UI, international units; US, ultrasound tomography; CT, computed tomography; NRM, nuclear magnetic resonance; ERCP, endoscopic retrograde cholangio-pancreatography; HCV RNA, hepatitis C virus ribonucleotide acid; IGF-I, insulin-like growth factor-1; FNAB, fine needle aspiration biopsy; IDUS, intraductal ultrasound; PDT, photodynamic therapy; PET, positron emission tomography; CT/PET, computed tomography/positron emission tomography scanning; RO resection, complete margin-negative resection; 5FU, 5-fluorouracil; LV, leucovorin; IFN-α2b, interferon-alpha2b; ECF regimen, Epirubicin + Cisplatin + 5FU; RR, response rate; PFS, ECOG performance status; TTP, time to progression; OS, overall survival; ASCO, American Society for Clinical Oncology; COX-2, cyclo-oxygenase inhibitor-2; EBRT, external beam radio-therapy; IOERT, intraoperative irradiation with electrons; Gy, Gray.

References

[1] Eddy DM. Manual for assessing health practices and designing practice guidelines. Philadelphia, PA: American College of Physicians; 1996.
[2] Shaib YH, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? J Hepatol 2004;40:472–7.
[3] Blendis L, Halpern Z. An increasing incidence of cholangiocarcinoma: why? Gastroenterology 2004;127:1008–9.
[4] Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. Semin Liver Dis 2004;24:115–25. Review.
[5] Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001;33:1353–7.

[6] Patel T. Worldwide trends in mortality from biliary tract malignancies. BMC Cancer 2002;2:10.
[7] West J, Wood H, Logan RF, Quinn M, Aithal GP. Trends in the incidence of primary liver and biliary tract cancers in England and Wales 1971–2001. Br J Cancer 2006;94:1751–8.
[8] McLean L, Patel T. Racial and ethnic variations in the epidemiology of intrahepatic cholangiocarcinoma in the United States. Liver Int 2006;26:1047–53.
[9] Sorensen HT, Friis S, Olsen JH, Thulstrup AM, Mellemkjaer L, Linet M, Trichopoulos D, Vilstrup H, Olsen J. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. Hepatology 1998;28:921–5.
[10] Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. Am J Gastroenterol 2004;99:523–6.
[11] Jepsen P, Vilstrup H, Tarone RE, Friis S, Sørensen HT. Incidence rates of intra- and extrahepatic cholangiocarcinomas in Denmark from 1978 through 2002. J Natl Cancer Inst 2007;99:895–7.
[12] Welzel TM, McGlynn KA, Hsing AW, O'Brien TR, Pfeiffer RM. Impact of classification of hilar cholangiocarcinomas (Klatskin tumors) on the incidence of intra- and extrahepatic cholangiocarcinoma in the United States. J Natl Cancer Inst 2006;98:873–5.
[13] Commissione AISF 2009. Il Colangiocarcinoma. Web site: webaisf.com.
[14] Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. Lancet 2005;366:1303–14.
[15] Blechacz B, Gores GJ. Cholangiocarcinoma: advances in pathogenesis, diagnosis, and treatment. Hepatology 2008;48:308–21.
[16] Angulo P, Lindor KD. Primary sclerosing cholangitis. Hepatology 1999;30:325–32.
[17] Boberg KM, Bergquist A, Mitchell S, Pares A, Rosina F, Broomé U, Chapman R, Fausa O, Egeland T, Rocca G, Schrumpf E. Cholangiocarcinoma in primary sclerosing cholangitis: risk factors and clinical presentation. Scand J Gastroenterol 2002;37:1205–11.
[18] Bergquist A, Ekbom A, Olsson R, Kornfeldt D, Lööf L, Danielsson A, Hultcrantz R, Lindgren S, Prytz H, Sandberg-Gertzén H, Almer S, Granath F, Broomé U. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. J Hepatol 2002;36:321–7.
[19] Charatcharoenwitthaya P, Enders FB, Halling KC, Lindor KD. Utility of serum tumor markers, imaging, and biliary cytology for detecting cholangiocarcinoma in primary sclerosing cholangitis. Hepatology 2008;48:1106–17.
[20] Shin HR, Lee CU, Park HJ, Seol SY, Chung JM, Choi HC, Ahn YO, Shigemastu T. Hepatitis B and C virus, *Clonorchis sinensis* for the risk of liver cancer: a case-control study in Pusan, Korea. Int J Epidemiol 1996;25:933–40.
[21] Andoh H, Yasui O, Kurokawa T, Sato T. Cholangiocarcinoma coincident with schistosomiasis japonica. J Gastroenterol 2004;39:64–8.
[22] Honjo S, Srivatanakul P, Sriplung H, Kikukawa H, Hanai S, Uchida K, Todoroki T, Jedpiyawongse A, Kittiwatanachot P, Sripa B, Deerasamee S, Miwa M. Genetic and environmental determinants of risk for cholangiocarcinoma via *Opisthorchis viverrini* in a densely infested area in Nakhon Phanom, northeast Thailand. Int J Cancer 2005;117:854–60.
[23] Rota AN, Weindling HK, Goodman PG. Cholangiocarcinoma associated with thorium dioxide (thorotrast): report of a case. Mich Med 1971;70:911–5.
[24] Ito Y, Kojiro M, Nakashima T, Mori T. Pathomorphologic characteristics of 102 cases of thorotrast-related hepatocellular carcinoma, cholangiocarcinoma, and hepatic angiosarcoma. Cancer 1988;62:1153–62.
[25] National Toxicology Program. NTP toxicology and carcinogenesis studies of a mixture of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (CAS No. 1746-01-6), 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) (CAS No. 57117-31-4), and 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126) (CAS No. 57465-28-8) in female Harlan Sprague–Dawley rats (Gavage Studies). Natl Toxicol Program Tech Rep Ser 2006;526:1–180.
[26] Robertson JF, Raine PA. Choledochal cyst: a 33-year review. Br J Surg 1988;75:799–801.
[27] De Vries JS, de Vries S, Aronson DC, Bosman DK, Rauws EA, Bosma A, Heij HA, Gouma DJ, van Gulik TM. Choledochal cysts: age of presentation, symptoms, and late complications related to Todani's classification. J Pediatr Surg 2002;37:1568–73.
[28] Pisano G, Donlon JB, Platell C, Hall JC. Cholangiocarcinoma in a type III choledochal cyst. Aust N Z J Surg 1991;61:855–7.
[29] Voyles CR, Smadja C, Shands WC, Blumgart LH. Carcinoma in choledochal cysts. Age-related incidence. Arch Surg 1983;118:986–8.
[30] Su CH, Shyr YM, Lui WY, P'Eng FK. Hepatolithiasis associated with cholangiocarcinoma. Br J Surg 1997;84:969–73.
[31] Ishiguro S, Inoue M, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Risk factors of biliary tract cancer in a large-scale population-based cohort study in Japan (JPHC study); with special focus on cholelithiasis, body mass index, and their effect modification. Cancer Causes Control 2008;19:33–41.
[32] Hsing AW, Gao YT, Han TQ, Rashid A, Sakoda LC, Wang BS, Shen MC, Zhang BH, Niwa S, Chen J, Fraumeni Jr JF. Gallstones and the risk of biliary tract cancer: a population-based study in China. Br J Cancer 2007;97:1577–82.
[33] Roukounakis NE, Kuhn JA, McCarty TM. Association of an abnormal pancreaticobiliary junction with biliary tract cancers. Proc (Bayl Univ Med Cent) 2000;13:11–3.
[34] Gwak GY, Yoon JH, Lee SH, Lee SM, Lee HS, Gores GJ. Lysophosphatidylcholine suppresses apoptotic cell death by inducing cyclooxygenase-2 expression via a Raf-1 dependent mechanism in human cholangiocytes. J Cancer Res Clin Oncol 2006;132:771–9.
[35] Costamagna G, Tringali A, Shah SK, Mutignani M, Zuccalà G, Perri V. Long-term follow-up of patients after endoscopic sphincterotomy for choledocholithiasis, and risk factors for recurrence. Endoscopy 2002;34:273–9.
[36] Strömberg C, Luo J, Enochsson L, Arnelo U, Nilsson M. Endoscopic sphincterotomy and risk of malignancy in the bile ducts, liver, and pancreas. Clin Gastroenterol Hepatol 2008;6:1049–53.
[37] Mortensen FV, Jepsen P, Tarone RE, Funch-Jensen P, Jensen LS, Sørensen HT. Endoscopic sphincterotomy and long-term risk of cholangiocarcinoma: a population-based follow-up study. J Natl Cancer Inst 2008;100:745–50.
[38] Donato F, Gelatti U, Tagger A, Favret M, Ribero ML, Callea F, Martelli C, Savio A, Trevisi P, Nardi G. Intrahepatic cholangiocarcinoma and hepatitis C and B virus infection, alcohol intake, and hepatolithiasis: a case–control study in Italy. Cancer Causes Control 2001;12:959–64.
[39] Yamamoto S, Kubo S, Hai S, Uenishi T, Yamamoto T, Shuto T, Takemura S, Tanaka H, Yamazaki O, Hirohashi K, Tanaka T. Hepatitis C virus infection as a likely etiology of intrahepatic cholangiocarcinoma. Cancer Sci 2004;95:592–5.
[40] Lu H, Ye MQ, Thung SN, Dash S, Gerber MA. Detection of hepatitis C virus RNA sequences in cholangiocarcinomas in Chinese and American patients. Chin Med J (Engl) 2000;113:1138–41.
[41] Kobayashi M, Ikeda K, Saitoh S, Suzuki F, Tsubota A, Suzuki Y, Arase Y, Murashima N, Chayama K, Kumada H. Incidence of primary cholangiocellular carcinoma of the liver in Japanese patients with hepatitis C virus-related cirrhosis. Cancer 2000;88:2471–7.
[42] Perumal V, Wang J, Thuluvath P, Choti M, Torbenson M. Hepatitis C and hepatitis B nucleic acids are present in intrahepatic cholangiocarcinomas from the United States. Hum Pathol 2006;37:1211–6.
[43] Welzel TM, Graubard BI, El-Serag HB, Shaib YH, Hsing AW, Davila JA, McGlynn KA. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. Clin Gastroenterol Hepatol 2007;5:1221–8.
[44] Ahrens W, Timmer A, Vyberg M, Fletcher T, Guénel P, Merler E, Merletti F, Morales M, Olsson H, Olsen J, Hardell L, Kaerlev L, Raverdy N, Lynge E. Risk factors for extrahepatic biliary tract carcinoma in men: medical conditions and lifestyle: results from a European multicentre case-control study. Eur J Gastroenterol Hepatol 2007;19:623–30.
[45] Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. An unusual tumor with distinctive clinical and pathological features. Am J Med 1965;38:241–56.
[46] Aljiffry M, Abdulelah A, Walsh M, Peltekian M, Alwayn I, Molinari M. Evidence-based approach to cholangiocarcinoma: a systematic review of the current literature. J Am Coll Surg 2009;208:134–47.
[47] Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. Surg Gynecol Obstet 1975;140:170–6.
[48] Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer 1995;75:171–90.
[49] Chen CY, Shiesh SC, Tsao HC, Lin XZ. The assessment of biliary CA 125, CA 19-9 and CEA in diagnosing cholangiocarcinoma—the influence of sampling time and hepatolithiasis. Hepatogastroenterology 2002;49:616–20.
[50] Alvaro D, Macarri G, Mancino MG, Marzioni M, Bragazzi M, Onori P, Corradini SG, Invernizzi P, Franchitto A, Attili AF, Gaudio E, Benedetti A. Serum and biliary insulin-like growth factor I and vascular endothelial growth factor in determining the cause of obstructive cholestasis. Ann Intern Med 2007;147:451–9.
[51] Alvaro D. Serum and bile biomarkers for cholangiocarcinoma. Curr Opin Gastroenterol 2009;25:279–84.
[52] Fritscher-Ravens A, Broering DC, Knoefel WT, Rogiers X, Swain P, Thonke F, Bobrowski C, Topalidis T, Soehendra N. EUS-guided fine-needle aspiration of suspected hilar cholangiocarcinoma in potentially operable patients with negative brush cytology. Am J Gastroenterol 2004;99:45–51.
[53] Eloubeidi MA, Chen VK, Jhala NC, Eltoum IE, Jhala D, Chhieng DC, Syed SA, Vickers SM, Mel Wilcox C. Endoscopic ultrasound-guided fine needle aspiration biopsy of suspected cholangiocarcinoma. Clin Gastroenterol Hepatol 2004;2:209–13.
[54] Levy MJ, Baron TH, Gostout CJ, et al. Palliation of malignant extrahepatic biliary obstruction with plastic versus expandable metal stents: an evidence-based approach. Clin Gastroenterol Hepatol 2004;2:273–85.
[55] Ortner ME, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology 2003;125:1355–63.
[56] Anderson CD, Pinson CW, Berlin J, Chari RS. Diagnosis and treatment of cholangiocarcinoma. Oncologist 2004;9:43–57.
[57] Winawer SJ. The role of the gastroenterologist in the management of patients with digestive cancers. World Gastroenterology News 2004;9:36–7.
[58] He YX, Guo QY. Clinical applications and advances of positron emission tomography with fluorine-18-fluorodeoxyglucose (18F-FDG) in the diagnosis of liver neoplasms. Postgrad Med J 2008;84(991):246–51.
[59] Lieser MJ, Barry MK, Rowland C, Ilstrup DM, Nagorney DM. Surgical management of intrahepatic cholangiocarcinoma: a 31-year experience. J Hepatobiliary Pancreat Surg 1998;5:41–7.
[60] Madariaga JR, Iwatsuki S, Todo S, Lee RG, Irish W, Starzl TE. Liver resection for hilar and peripheral cholangiocarcinomas: a study of 62 cases. Ann Surg 1998;227:70–9.

[61] Valverde A, Bonhomme N, Farges O, Sauvanet A, Flejou JF, Belghiti J. Resection of intrahepatic cholangiocarcinoma: a Western experience. J Hepatobiliary Pancreat Surg 1999;6:122–7.
[62] Nathan H, Pawlik TM, Wolfgang CL, Choti MA, Cameron JL, Schulick RD. Trends in survival after surgery for cholangiocarcinoma: a 30-year population-based SEER database analysis. J Gastrointest Surg 2007;11:1488–96 [discussion: 1496-1487].
[63] Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507–17 [discussion: 517-509].
[64] Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. Transplantation 2000;69:1633–7.
[65] Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, Gores GJ, Nagorney DM. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg 2005;242:451–8, discussion 458-61.
[66] Kosuge T, Yamamoto J, Shimada K, et al. Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. Ann Surg 1999;230:663–71.
[67] Iwatsuki S, Todo S, Marsh JW, et al. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. J Am Coll Surg 1998;187:358–64.
[68] Figueras J, Llado L, Valls C, Serrano T, Ramos E, Fabregat J, Rafecas A, Torras J, Jaurrieta E. Changing strategies in diagnosis and management of hilar cholangiocarcinoma. Liver Transpl 2000;6:786–94.
[69] Chen JS, Jan YY, Lin YC, Wang HM, Chang WC, Liau CT. Weekly 24 h infusion of high-dose 5-fluorouracil and leucovorin in patients with biliary tract carcinomas. Anticancer Drugs 1998;9:393–7.
[70] Patt YZ, Jones Jr DV, Hoque A, et al. Phase II trial of intravenous flourouracil and subcutaneous interferon alfa-2b for biliary tract cancer. J Clin Oncol 1996;14:2311–5.
[71] Ellis PA, Norman A, Hill A, et al. Epirubicin, cisplatin and infusional 5-fluorouracil (5-FU) (ECF) in hepatobiliary tumours. Eur J Cancer 1995;31A:1594–8.
[72] Patt YZ, Hassan MM, Aguayo A, et al. Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer 2004;101:578–86.
[73] Kubicka S, Rudolph KL, Tietze MK, Lorenz M, Manns M. Phase II study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. Hepatogastroenterology 2001;48:783–9.
[74] Kim ST, Park JO, Lee J, Lee KT, Lee JK, Choi SH, Heo JS, Park YS, Kang WK, Park K. A Phase II study of gemcitabine and cisplatin in advanced biliary tract cancer. Cancer 2006;106:1339–46.
[75] Riechelmann RP, Townsley CA, Chin SN, Pond GR, Knox JJ. Expanded phase II trial of gemcitabine and capecitabine for advanced biliary cancer. Cancer 2007;110:1307–12.
[76] Kuhn R, Hribaschek A, Eichelmann K, Rudolph S, Fahlke J, Ridwelski K. Outpatient therapy with gemcitabine and docetaxel for gallbladder, biliary, and cholangio-carcinomas. Invest New Drugs 2002;20:351–6.
[77] Park BK, Kim YJ, Park JY, Bang S, Park SW, Chung JB, Kim KS, Choi JS, Lee WJ, Song SY. Phase II study of gemcitabine and cisplatin in advanced biliary tract cancer. J Gastroenterol Hepatol 2006;21:999–1003.
[78] Murad AM, Guimarães RC, Aragão BC, Rodrigues VH, Scalabrini-Neto AO, Padua CA, Moore FC. Phase II trial of the use of gemcitabine and 5-fluorouracil in the treatment of advanced pancreatic and biliary tract cancer. Am J Clin Oncol 2003;26:151–4.
[79] André T, Tournigand C, Rosmorduc O, Provent S, Maindrault-Goebel F, Avenin D, Selle F, Paye F, Hannoun L, Houry S, Gayet B, Lotz JP, de Gramont A, Louvet C, GERCOR Group. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. Ann Oncol 2004;15:1339–43.
[80] Knox JJ, Hedley D, Oza A, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. J Clin Oncol 2005;23:2332–8.
[81] Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 2007;26:896–902.
[82] Yonemoto N, Furuse J, Okusaka T, et al. A multi-center retrospective analysis of survival benefits of chemotherapy for unresectable biliary tract cancer. Jpn J Clin Oncol 2007;37:843–51.
[83] Valle JW, Wasan H, Johnson P, Jones E, Dixon L, Swindell R, Baka S, Maraveyas A, Corrie P, Falk S, Gollins S, Lofts F, Evans L, Meyer T, Anthoney A, Iveson T, Highley M, Osborne R, Bridgewater J. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study—The UK ABC-01 Study. Br J Cancer 2009;101:621–7.
[84] Sasaki T, Isayama H, Nakai Y, Togawa O, Kogure H, Ito Y, Yamamoto K, Mizuno S, Yagioka H, Yashima Y, Kawakubo K, Arizumi T, Matsubara S, Sasahira N, Hirano K, Tsujino T, Toda N, Tada M, Omata M, Koike K. Prognostic factors in patients with advanced biliary tract cancer receiving chemotherapy. Cancer Chemother Pharmacol 2010.
[85] Fernández-Ruiz M, Guerra-Vales JM, Colina-Ruizdelgado F. Comorbidity negatively influences prognosis in patients with extrahepatic cholangiocarcinoma. World J Gastroenterol 2009;15(42):5279–86.
[86] Blechacz BR, Smoot RL, Bronk SF, Werneburg NW, Sirica AE, Gores GJ. Sorafenib inhibits signal transducer and activator of transcription-3 signaling in cholangiocarcinoma cells by activating the phosphatase shatterproof 2. Hepatology 2009;50:1861–70.
[87] Bengala C, Bertolini F, Malavasi N, et al. Sorafenib in patients with advanced biliary tract carcinoma: a phase II trial. Br J Cancer 2010;102:68–72 [Epub 2009 Nov 24].
[88] Klempnauer J, Ridder GJ, Werner M, Weimann A, Pichlmayr R. What constitutes long term survival after surgery for hilar cholangiocarcinoma? Cancer 1997;79:26–32.
[89] Todoroki T, Kawamoto T, Koike N, Takahashi H, Yoshida S, Kashiwagi H, Takada Y, Otsuka M, Fukao K. Radical resection of hilar bile duct carcinoma and predictors of survival [In Process Citation]. Br J Surg 2000;87:306–13.
[90] Jarnagin WR, Ruo L, Little SA, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implication for adjuvant therapeutic strategies. Cancer 2003;98:1689–700.
[91] Takamura A, Saito H, Kamada T, et al. Intraluminal low-dose rate 192 Ir brachiterapy combined with external beam radiotherapy and biliary stenting for unresectable extraepatic bile duct carcinoma. Int J Radiat Oncol Biol Phys 2003;57:1357–65.
[92] Qian XJ, Zhai RY, Dai DK, et al. Treatment of malignant biliary obstruction by combined percutaneus transhepatic biliary drainage with local tumor treatment. World J Gastroenterol 2006;12:331–5.
[93] Schoenthaler R, Castro JR, Halberg FE, Phillips TL. Definitive postoperative irradiation of bile duct carcinoma with charged particles and/or photons. Int J Radiat Oncol Biol Phys 1993;27:75–82.
[94] Lu JJ, Bains YS, Abdel-Wahab M, et al. High dose rate remote after loading intracavitary brachiterapy for the treatment of extrahepatic biliary duct carcinoma. Cancer J 2002;8:74–8.
[95] Alden ME, Mohiuddin M. The impact of radiation dose in combined external beam and intraluminal Ir-192 brachytherapy for bile duct cancer. Int J Radiat Oncol Biol Phys 1994;28:945–51.
[96] Todoroki T, Ohara K, Kawamoto T, Koike N, Yoshida S, Kashiwagi H, Otsuka M, Fukao K. Benefits of adjuvant radiotherapy after radical resection of locally advanced main hepatic duct carcinoma [see comments]. Int J Radiat Oncol Biol Phys 2000;46:581–7.
[97] Foo ML, Gunderson LL, Bender CE, Buskirk SJ. External radiation therapy and transcatheter iridium in the treatment of extrahepatic bile duct carcinoma. Int J Radiat Oncol Biol Phys 1997;39:929–35.
[98] Gonzalez Gonzalez D, Gerard JP, Maners AW, De la Lande-Guyaux B, Van Dijk-Milatz A, Meerwaldt JH, Bosset JF, Van Dijk JD. Results of radiation therapy in carcinoma of the proximal bile duct (Klatskin tumor). Semin Liver Dis 1990;10:131–41.
[99] Shinohara ET, Mitra N, Guo M, et al. Radiotherapy is associated with improved survival in adjuvant and palliative treatment of extrahepatic cholangiocarcinomas. Int J Radiat Oncol Biol Phys 2009;74:1191–8.
[100] Cheng Q, Luo X, Zhang B, et al. Predictive factors for prognosis of hilar cholangiocarcinoma: postresection radiotherapy improves survival. Eur J Surg Oncol 2007;33:202–7.
[101] Sunakawa Y, Mizunuma K, Mochizuki S. Preoperative irradiation of biliary tract malignancy. Jikei Med J 1994;41:63–80.
[102] McMasters KM, Tuttle TM, Leach SD, Rich T, Cleary KR, Evans DB, Curley SA. Neoadjuvant chemoradiation for extrahepatic cholangiocarcinoma. Am J Surg 1997;174:605–8, discussion, 608–609.
[103] Nelson JW, Ghafoori AP, Willett CG, et al. Concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys 2009;73:148–53.
[104] Altaee MY, Johnson PJ, Farrant JM, Williams R. Etiologic and clinical characteristics of peripheral and hilar cholangiocarcinoma. Cancer 1991;68:2051–5.
[105] Pichlmayr R, Weimann A, Klempnauer J, Oldhafer J, Maschek H, Tusch G, Ringe B. Surgical treatment in proximal bile duct cancer. A single-center experience. Ann Surg 1996;224:628–38.
[106] Gunderson LL, Haddock MG, Burch P, Nagorney D, Foo ML, Todoroki T. Future role of radiotherapy as a component of treatment in biliopancreatic cancers. Ann Oncol 1999;10(Suppl. 4):291–5.
[107] Rea David J, Rosen Charles B, Nagorney David, et al. Transplantation for Cholangiocarcinoma: When and Whom? Surg Oncol Clin N Am 2009;18:325–37.
[108] Aljiffry M, Walsh MJ, Molinari M. Advances in diagnosis, treatment and palliation of cholangiocarcinoma: 1990–2009. World J Gastroenterol 2009;15:4240–62.