



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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ARTICLE INFO

Article history:

Received 1 April 2010

Accepted 11 June 2010

Available online 11 August 2010

Keywords:

Chemotherapy

Cholangiocellular carcinoma

Diagnosis

Radiotherapy

Risk factors

Standard of care

Surveillance

ABSTRACT

The incidence of Cholangiocellular carcinoma (CCA) is increasing, due to a sharp increase of the intra-hepatic form. Evidence-ascertained risk factors for CCA are primary sclerosing cholangitis, *Opisthorchis 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.

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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 extra-hepatic 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 needed.

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: intra-hepatic, perihilar, and distal or extrahepatic. Perihilar tumors, also known as Klatskin tumors [45], involve the hepatic duct bifurcation. Klatskin 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 intra-hepatic 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 U/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 improvement [69]. Combination regimens with 5FU increased objective response, but also increased toxicity. In a phase II trial, 5FU plus subcutaneous interferon (IFN)- α 2b 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 EBRT 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 intra-hepatic 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, carcinoembryonic 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- α 2b, 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.

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