Review

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The current management of cholangiocarcinoma: A comparison of current guidelines

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Summary **Cholangiocarcinoma (CC) accounts for about 3% of all gastrointestinal tumors and is the second most common primary liver tumor. Quality guidelines on CC are needed to guide hepatobiliary surgeons. Here, current guidelines on CC were reviewed to provide useful information and suggestions to help institutes and organizations all around the world to draft better guidelines on CC. Literature databases were electronically searched to identify guidelines or consensus statements regarding CC published from 2002-2016. Nine guidelines were included in this review. Comparison of the current guidelines revealed several inconsistencies. Signs of conflicting views indicated a lack of high level evidence. More studies need to be conducted in areas of contention to help update the guidelines. Organizations and medical societies need to be encouraged to use standard evaluation measures, to restrict tumors to CC or iCC, pCC, or dCC specifically, to give recommendations in accordance with the equipment that is available for diagnosis and treatment in different counties, and to use an appropriate and consistent structure when establishing and drafting guidelines for CC.**

Keywords: Cholangiocarcinoma, Klatskin's tumor, clinical guideline

1. Introduction

Cholangiocarcinoma (CC) is a malignant tumor arising from the epithelium of the bile ducts. CC accounts for about 3% of all gastrointestinal tumors and is the second most common primary liver tumor. Over 90% of these tumors are adenocarcinomas (*1*). Depending on the anatomical location, CC is divided into intrahepatic cholangiocarcinoma (iCC), perihilar cholangiocarcinoma (pCC), and distal cholangiocarcinoma (dCC). The pCC and dCC are also defined as extrahepatic cholangiocarcinoma. pCC is the most common type of CC, accounting for 50-60% of cases (*2*). Currently, the prognosis of CC is poor due to the difficult of early diagnosis and limited treatment methods, where patients associate with a median survival of 24 months after initial diagnosis (*3*).

Practice guideline is a useful source of advice, an educational tool, and could help to improve the quality of care. Guideline-adherent therapy has significant improved the efficacy rate of diagnosis and survival outcomes in ovarian cancer, breast cancer and so on (*4-6*). Thus, quality guidelines on CC are needed to guide hepatobiliary surgeons. There are 17 guidelines on hepatocellular carcinoma (HCC) worldwide (*7,8*), but guidelines on CC are more disparate and fewer in number for two main reasons. One is a lack of studies constituting a high level of evidence. The other is that iCC, pCC or dCC being different in incidence and management should be viewed as separate entities (*9*). Therefore, drafting comprehensive guidelines on CC is much more difficult.

Here, current guidelines on CC were reviewed and compared to provide useful information and suggestions to help institutes and organizations all around the world to draft better guidelines on CC.

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Table 1. Current guidelines on cholangiocarcinoma

Guidelines	Approach	Content	Tumor	Evaluation measures	*Ref.*
NCCN Guideline (*2016*)	Expert panel	D&T + E + F	CC, GBC, HCC	Consensus categories	(*14*)
SEOM Guideline (*2015*)	Literature analysis	D&T + E	CC, GBC	Evidence categories and recommendation grades	(*13*)
Japanese Guideline (*2014*)	Expert panel	D&T + E	CC, GBC, AC	Evidence categories and recommendation grades	(*18*)
Chinese Guideline 1 (*2014*)	Expert panel	D&T + E	CC	-	(*16*)
EASL Guideline (*2014*)	Expert panel	D&T + E	iCC	Evidence categories and recommendation grades	(*15*)
Asia-Pacific Guideline (*2013*)	Expert panel	D&T + E	pCC	Evidence categories and recommendation grades	(*19*)
Chinese Guideline 2 (*2013*)	Expert panel	D&T	pCC	Evidence categories and recommendation grades	(*17*)
BSG Guideline (*2012*)	Literature analysis	D&T + E + F	CC	Evidence categories and recommendation grades	(*11*)
Italian Guideline (*2010*)	Expert panel	D&T + E	CC	Evidence categories and recommendation grades	(*12*)

D&T, diagnosis and treatment; E, epidemiology; F, follow up. CC, cholangiocarcinoma; pCC, perihilar cholangiocarcinoma; iCC, intrahepatic cholangiocarcinoma; GBC, gallbladder carcinoma; AC, ampullary carcinoma; HCC, hepatocellular carcinoma.

2. Current guidelines on CC

The first guideline on CC was created by the British Association for the Study of the Liver (BASL) and the British Society of Gastroenterology (BSG) in 2002 (*10*). The BSG updated this guideline in 2012 (*11*). Literature databases were electronically searched to identify guidelines or consensus statements regarding CC published from 2002-2016. In addition, citations within the reference lists were searched manually to avoid missing eligible guidelines. The guidelines were required to meet the following criteria: (*i*) The guidelines should covered diagnosis and treatment of iCC, pCC, or dCC at a minimum; (*ii*) Credibility, guidelines were those drafted by medical societies with or without government support. Nine guidelines were included in this review (*11-19*) (Table 1). Only the latest versions of the guidelines were included in the table, but the old versions of guidelines may be discussed as sources of evidence. Most of the guidelines were written in English, but two guidelines were written in other languages (one was in Japanese and the other was in Chinese). All of the nine guidelines were drafted for clinicians and mainly intended for hepatobiliary surgeons. Although the specific contents are different, the form of evidence categories and recommendation grades are the mainstay of guidelines evaluation measures. Seven of these guidelines used such an approach. NCCN guidelines use consensus categories, which was named NCCN categories of evidence and consensus. Only Chinese guideline 1 did not mention evaluation measures. CC belongs to biliary tract cancer, so gallbladder carcinoma (GBC) was included in a few of the guidelines (2 guidelines). The NCCN guideline applied to hepatobiliary cancers, which include HCC, GBC, and CC. Chinese guideline 2 and the Asia-Pacific guideline were created exclusively for pCC. The EASL guideline was created solely for iCC. Most of the guidelines included epidemiology, diagnosis, and treatment. Follow-up was only mentioned in two guidelines, and little information was presented. This is because there are few studies about follow-up and little evidence of its effectiveness. The EASL guideline stated that the terms "Klatskin" and "extrahepatic" should be discouraged. Accordingly, future studies should use the classification iCC, pCC, and dCC. Overall, most of the recommendations in the current guidelines were of a low grade. For example, nine recommendations were given by the SEOM guideline, which used the Oxford Center for Evidence-based Medicine level (Grades A to D, with A representing studies that constitute the highest level of evidence). Up to 67% of the recommendations in the SEOM guideline were grade C or D. This means that a high level of evidence for CC is still lacking, so this review has identified areas where further study is urgently needed.

3. Epidemiology and risk factors

CC has a prevalence that differs depending on regions, ethnic group, sex, and tumor location (*20,21*). Over the past 30 years, there is a steady increasing of mortality in iCC, meanwhile a stable or slightly decreasing in pCC and dCC (*22*). In general, the incidence of all forms of CC seems to be increasing (*23*). These trends suggest that CC needs to be watched closer than before. A misclassification of CC based on epidemiological data has recently been addressed. The tumor coding in the 2nd edition of the ICD-0 misclassified Klatskin's tumor (pCC) as iCC, resulting in an overestimated incidence of iCC in several studies (*23,24*). Further studies should pay closer attention to data on the incidence of iCC to avoid misclassification. The reason for the changes in the incidence of CC is still unclear, thus a better explain is anticipated in the coming research.

Although several risk factors have been identified, over 70% of patients diagnosed as CC without predisposing factors in fact (*25*). The BSG guideline and the SEOM guideline summarized the risk factors in table form, and the other guidelines did so in a description. In summary, established risk factors include primary sclerosing cholangitis (PSC), bile duct cysts, parasitic infections, hepatolithiasis (intrahepatic stones), toxins, and HBV and HCV infection. Moreover, some evidence has indicated that potential risk factors include alcohol consumption, smoking, diabetes, inflammatory bowel disease, and genetic polymorphisms. The role

of surveillance is to monitor disease in the at-risk population to detect tumors early. This is crucial for CC since early diagnosis means a higher chance of curative treatment and a better prognosis. Guidelines on HCC suggest a surveillance interval of 6 months for high-risk patients, they also recommend imaging modalities and tumor markers (*26,27*). However, for CC, there is no such recommendation of surveillance in any of current guidelines. Among the risk factors, the reported prevalence of CC in PSC is thought to be the highest varying from 5% to 36% (*28*). In fact, Razumilava *et al*. suggested a process for surveillance of CC in PSC in 2011 (*29*). However, there is a lack of related evidenced-based studies and an analysis of the cost-effectiveness of that approach. Only the BSG guideline features a recommendation regarding surveillance in PSC. Another key risk factor is congenital choledochal cysts. This disease is associated with pancreaticobiliary maljunction (PBM), which is now recognized as an independent disease. Cases registered with the Japanese Study Group on Pancreaticobiliary Maljunction (JSPBM) over the last 10 years have indicated that the incidence of CC is 7.0% (gallbladder cancer: 13.4%) in cases of a PBM with dilated bile ducts (*30*). Therefore, the Japanese guideline recommends excision of extrahepatic biliary tracts and the gallbladder in patients with PBM with dilated bile ducts (choledochal cysts) to prevent cancer. Because of the rare rate of choledochal cysts in the West (*31*), this recommendation is not mentioned in other guidelines. In addition to PSC and PBM, iCC involves many of the same risk factors as HCC does, such as HBV, HCV, and cirrhosis, thus these population were luckily monitored by the surveillance method of HCC. Complete surveillance of HCC may be another reason for the increasing incidence of iCC. Unfortunately, there are few studies of surveillance of populations with other risk factors for CC. Future guidelines should pay close attention to the latest studies of surveillance. Further study of surveillance should be encouraged to improve the early detection of CC.

4. Diagnosis

The initial common symptoms of CC are jaundice (84-90%), weight loss (35%), abdominal pain (30%), nausea and vomiting (12-25%), and fever (10%) according to current evidence (*32,33*). Compared to patients with pCC and dCC, patients with iCC are more likely to present with abdominal pain. However, most cholangiocarcinomas are usually not diagnosed in an early stage since patients are asymptomatic. In order to diagnose CC as early as possible, at-risk populations should undergo aggressive examinations if they have nonspecific symptoms. Those nonspecific symptoms include tiny abnormal serum levels of alkaline phosphatase and gamma glutamyl transpeptidase or a common hepatic duct more than 8 mm in diameter on abdominal ultrasound (US) because of unknown reasons. In some patients with early iCC, a solitary mass is incidentally detected during imaging. Although there are no specific tumor markers, CA19-9 and CEA can support a diagnosis of CC. In Japan, CA19-9 was elevated 69% and CEA was elevated 18% in registered patients with CC (*18*). However, elevated CA19-9 is also evident in non-malignant obstructive jaundice. Thus after decompression, the persistently high level of CA19-9 prompted carcinoma (*34*). In addition, the levels of CA19-9 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 CC compared to 28% of unresectable tumors (*35*). Descriptions of these aspects of diagnosis are almost the same in the current guidelines.

Abdominal Ultrasound (US) is frequently the initial modality used to evaluate populations suspected of having CC. Abdominal US can demonstrate the dilation of bile duct and indentify the site of obstruction especially in pCC and dCC. However, US lacks specific features to distinguish iCC from other solidary intrahepatic mass lesions (*36*). Moreover, US is more popular in Asia, and the sensitivity and specificity of US differs depending on the tumor type, the quality of the equipment, and experience of the operator (*37*). Thus, only the Japanese guideline and the 2002 edition of the BSG guideline recommended US for initial examination included in diagnostic algorithms. Although staging workup should rely on other imaging modalities, we believe that the US, as a noninvasive and convenient technique, should be performed initially for suspected CC.

Multidetector Computed Tomography (MDCT) and Magnetic Resonance Cholangiopancreatography (MRCP) are definitely the main imaging modalities for diagnosis and staging of CC. On dynamic CT, iCC is characterized by a progressing contrast uptake from the arterial to the venous and especially in the delayed phase. This can help distinguish between iCC and HCC (*38*). MRI and CT are very useful at determining tumor resectability by showing the primary tumor, its relationship to nearby major vessels and the biliary tree, and metastasis and lymph node involvement (*39*). MRCP is gradually replacing ERCP for the diagnosis of CC. MRCP has a higher level of sensitivity (96%), specificity (85%), and accuracy (91%) compared to ERCP when differentiating between CC and benign masses (*40*). All the current guidelines agreed on performing MRI/MRCP or MDCT with the highest grade of recommendation.

However, not like HCC (*41*), the radiological criteria of CT or MRI are insensitive for the diagnosis of CC. Thus, pathological diagnosis is required for a definitive diagnosis of CC. Moreover, CT/MRI may miss small lesions (*38,42*). Therefore, in order to make a proper

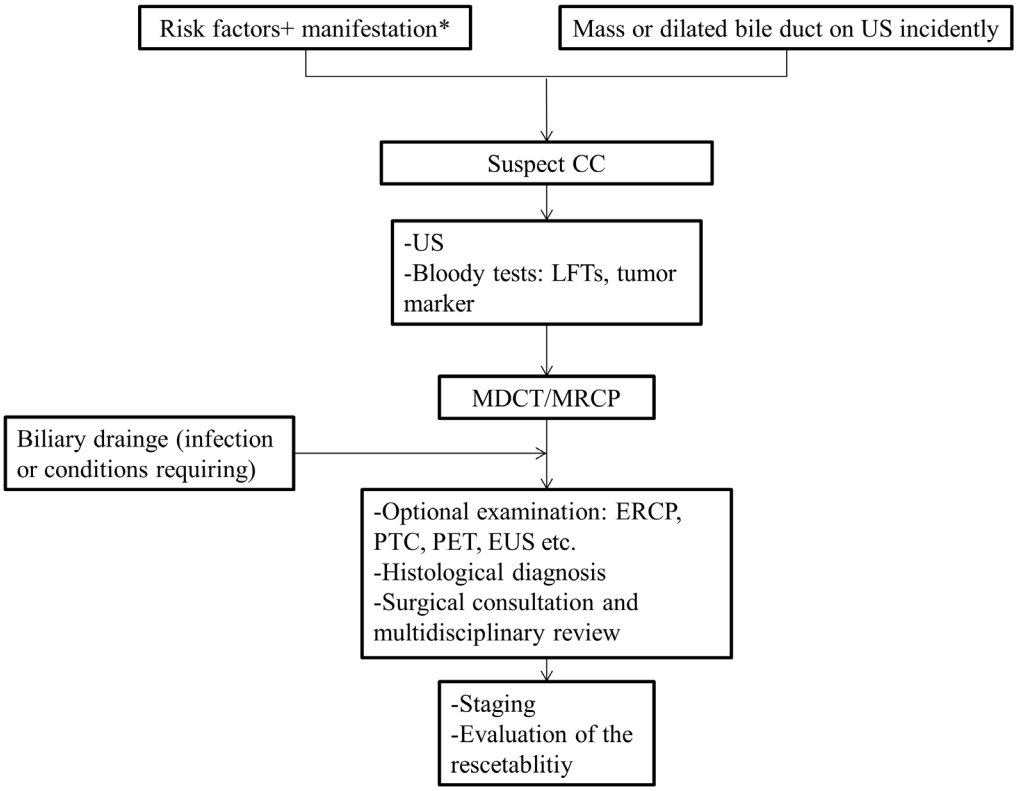

Figure 1. The diagnostic algorithm in current guidelines for cholangiocarcinoma. *Common symptoms and nonspecific symptoms. CC, cholangiocarcinoma; US, ultrasound; LFTs, liver function tests; MDCT, multidetector computed tomography; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; PTC, percutaneous transhepatic cholangiography; PET, positron emission tomography; EUS, endoscopic ultrasound.

diagnosis, further optional examinations are needed to obtain pathological diagnosis and correct staging of disease at the same time.

Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) allow bile sampling for cytology and stent insertion for relief of a biliary obstruction. These two modalities are generally used both a diagnosis and a treatment target is needed in patients who need biliary drainage for cholangitis or other conditions. ERCP has the advantage of showing a biliary stricture with cholangiography, and ERCP allows correct differentiation of malignant from benign lesions (*43*). Through cytology by brushings and biopsy, the positive rate is 40-70% (*44*). More importantly, ERCP and PTC can delineate the anatomy of the biliary system and determine the extent of bile duct involvement, which allows determination of resectability and surgical management. But catheter tract implantation metastasis is not a rare complication following PTC or PTCD (*45*), Thus, Chinese guideline 1 did not suggest a puncture biopsy. Endoscopic ultrasound (EUS) can detect small lesions that were missed by other modalities. EUS and EUS-FNA are sensitive enough to diagnose CC and very specific in predicting unresectability (*46*). EUS-FNA has a sensitivity of 84% and a specificity of 100%. The rates of tumor seeding after EUS-FNA are very low (between 1:10000 and 1:40000) (*47*). Emission Tomography (PET) is usually used to detect regional lymph metastases and distant metastases. Using PET to diagnose CC has yet to be substantiated (*48*).

The surgical treatment of CC usually involves a major operation, such as a pancreaticoduodenectomy or an extended right hepatectomy, so careful evaluation and complete staging must be achieved through a surgical consultation. The NCCN guideline emphasizes that a multidisciplinary team of experts including experienced radiologists and surgeons needs to review examination results in order to stage the disease and determine potential treatment options. The Italian guideline also suggested that "a digestive cancer team" with multidisciplinary meetings should be involved in diagnosis and staging.

The diagnostic algorithm in current guidelines is summarized in Figure 1. In general, the main inconsistencies regarding diagnosis are (*i*) the selection of further examinations (after CT/MRI) and (*ii*) whether a preoperative biopsy is needed before proceeding to a definitive resection. Regarding the former one, the current guidelines mainly discussed the selection of further examinations without offering recommendations. Further guidelines or studies have better separate CC as iCC, pCC, dCC in this part to give a recommendation or do relative researches. ERCP, PTC, and EUS have

differing levels of sensitivity and specificity depending on the tumor location, and these modalities also have their own indications and contraindications. More specific recommendations should be provided in coming guidelines. The later one, towards patients with suspected iCC, the NCCN guideline and the EASL guideline emphasized that a preoperative biopsy is not always necessary before proceeding with a definitive, potentially curative resection. A presumed radiographic diagnosis is sufficient in non-cirrhotic patients. Regarding pCC and dCC, Japanese guideline strongly recommended that obtain the pathological diagnosis via a biopsy or cytology before surgery. After all, Nakayami *et al*. reported that 10% of suspected and resectable CC were benign cases (*49*). The BSG guideline only suggests that the surgical assessment of resectability should be established prior to biopsy attempted. The NCCN guideline states that a pathologic workup can be suggestive of CC but that it is not definitive. The remaining guidelines do not give recommendations regarding preoperative biopsy. Further studies of these controversial topics are needed. In addition, the techniques mentioned above are not all available in many countries or hospitals. Thus, future guidelines should discuss or give recommendations in light of what equipment is available in their countries or institutions.

5. Staging

In the past, pCC and dCC were grouped together as extrahepatic cholangiocarcinoma sharing a same staging system, and iCC was staged identically to HCC. Currently, iCC, pCC and dCC are recognized as a separate entity with individual staging system. The 7th edition of the AJCC staging system is the most common staging system used, and it is also recommended by most of the current guidelines. However, the AJCC staging system still has many limitations. A new staging system for iCC was proposed by the Liver Cancer Group of Japan in 2015 (*50*). This new system, which specifically includes a tumor cutoff size of 2 cm and major biliary invasion, has provided good stratification of overall patient survival depending on the stage of disease. It would be useful in terms of assigning patients to surgery. The classical modified Bismuth-Corlette staging system (*51*), which divides pCC into 4 types depend on the extent of biliary duct involvement, is still recommended by the HBG guideline and Chinese guideline 2. Another one, the Blumgart staging system (*52*) can more clearly predict the resectability and metastasis and survival for pCC. However, no guidelines recommended this staging system for pCC. In order to achieve a correct staging, sometime a staging laparoscopy is used to exclude local metastatic disease in those considered resectable on imaging. However, with the developing in imaging techniques, the overall yield and accuracy of staging laparoscopy has been reported decreased (*53*). A grade A of recommendation in Asia-Pacific guideline suggested staging laparoscopy should be considered before attempting a curative resection to avoid unnecessary laparotomy, and the BSG guideline offers the same suggestion with a grade B recommendation. In addition, the NCCN guideline states that gastroscopy and colonscopy are needed for iCC patients to rule out metastatic disease. In summary, most of the guidelines use the 7th AJCC/TNM staging system, but this system needs further validation in future studies. Other staging systems should also be considered. Updated guidelines had better minutely explain the selection of the staging system for iCC, pCC, dCC separately.

6. Treatment

The treatment algorithm of CC is divided into resectable one and unresectable one (Figure 2). This format is used by most of the current guidelines. EASL guideline solely adopted TNM staging to establish the algorithm of treatment.

6.1. *Resectable*

According to current evidence, surgical resection is the only curative treatment method which is approved by all the guidelines. This is the main reason why patients who were suspected or diagnosed as CC need relatively complex preoperative examinations for correct staging to predict resectable as much as possible. R0 resection or curative resections with free margins is the ultimate goal of surgery, and it is associated with significant higher survival rates and lower recurrence rates (*54,55*). In summary, the main selection of surgical procedures is: (*i*) iCC, segment or lobe resection. Extensive hepatic resections are usually needed to confirm R0 resection; (*ii*) pCC, extended right or left heptectomy combine with caudate lobectomy. The extent of the involed biliary tract determines the range of heptectomy. (*iii*) pCC, pancreatoduodenectomy is performed generally. Few patients with CC in the middle part of the extrahepatic bile duct are cured with isolated resection of the bile duct. Regarding the lymph node dissection (LND), there is no sufficient data to support a routine LND in patients with CC to improve prognosis (*56*), but the NCCN guideline suggested LND which provides staging information could be considered at operation due to lymph node metastases is an important prognostic indicator of survive. A recent expert consensus statement also stated regional lymphadenectomy should be considered a standard part of surgical therapy for ICC (*57*). Li *et al.* added that lymph node metastases may not benefit from aggressive lymphadenectomy (*58*). A systematic analysis has suggested that a lymph node count greater than or equal to 7 is adequate for prognostic staging of pCC (*59*). In conclusion, routine LNC is suggested to be recommended in the future

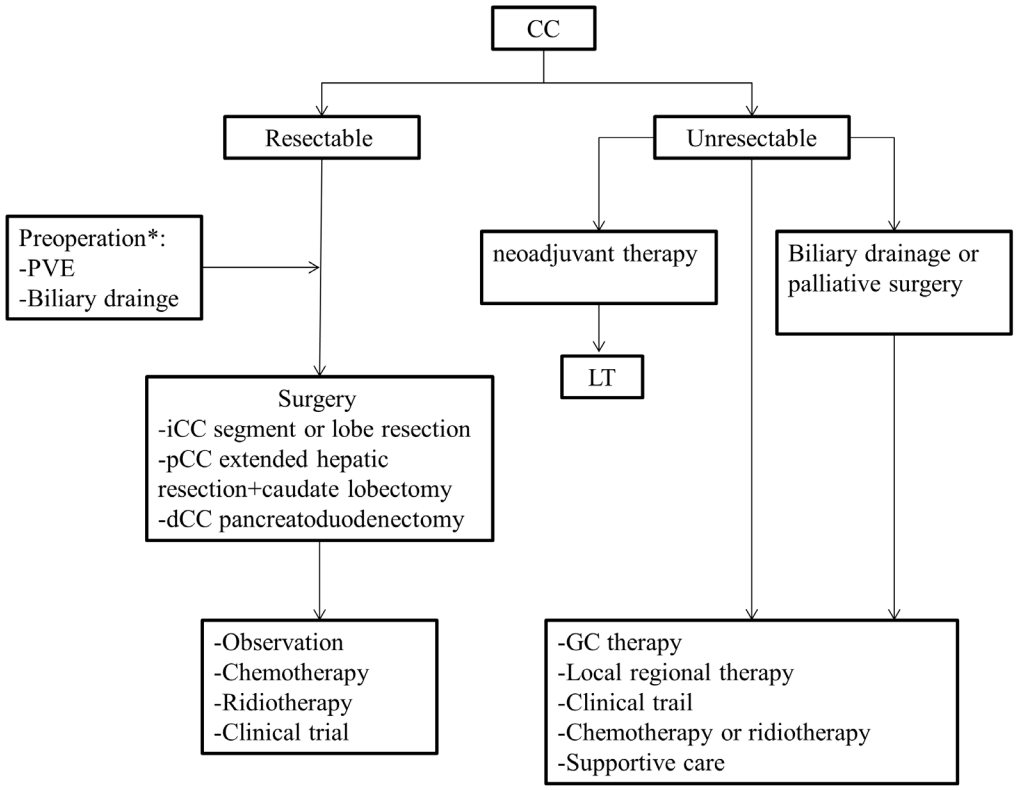

Figure 2. The treatment algorithm in current guidelines for cholangiocarcinoma. *Major hepatectomy with small FLR volume or insufficient liver function. PVE, portal vein embolization; LT, liver transplantation; GC, Gemcitabine/cisplatin combination.

guidelines.

Postoperative liver failure (PLF) remains the most common cause of mortality after extended hepatectomy (*60*). The liver function of patients with pCC or iCC may be influenced by jaundice, and those patients usually undergo a major hepatectomy to achieve R0 resection. Therefore, PVE and biliary drainage before operation are common selective options to avoid PLF. Definitely biliary drainage should be indicated in a CC patient with acute cholangitis, but the routine use of biliary drainage is controversial. Chinese guideline 1 and the BSG guideline stated that routine biliary drainage preoperatively should be avoided except cholangitis. This is based on the only one RCT showing the rates of infectious complications were 39% in the early surgery group and 74% in the biliary drainage group (*61*). However, the evidence is indicated in obstructive jaundice for pancreatic carcinomas other than CC. The Japanese guideline advised surgeons to perform biliary drainage if the patient was a candidate for a major hepatectomy, but the level of evidence is low. In fact, many institutions in Japan routinely perform ERCP for patients suspected CC, at that time ENBD was common performed for biliary drainage. The Asia-Pacific guideline stated that preoperative biliary drainage should be performed in selected patients with pCC, giving that recommendation a grade of B. However, there is no specific explain about the criteria. Chinese guideline 2 recommended preoperative biliary drainage for patients with pCC: (*i*) a major hepatectomy (> 60% of total liver volume) with total bilirubin index > 200 μmol/L; (*ii*) cholangitis; (*iii*) PVE; (*iv*) malnutrition. In spite of the controversy over whether to perform biliary drainage, PVE which induces the hypertrophy of future liver remnant (FLR), remain the first choice for insufficient FLR with consensus on current guidelines. Other techniques like two-staged hepatectomy and ALPPS (*62,63*) have many limitations and only top hospitals can perform these new techniques. Moreover, ALPPS and TSH still have high rates of morbidity and mortality. In general, the main controversy is whether to perform preoperative biliary drainage in patients with obstructive jaundice. Thus, we suggest hepatobiliary surgeons could design studies about this field in the future.

The states of post resection are commonly classified as R0, R1 and R2. An R0 resection is referred to as curative resection while an R1/R2 resection is referred to as non-curative resection. Following the operation, patients were assigned to observation, chemotherapy, radiotherapy or clinical trial usually depends on the experiences coming from the institutions. None of these arrangements has enough evidences to be supported currently.

The role of adjuvant chemotherapy has yet to be decided. The purpose of adjuvant chemotherapy is

to improve the poor prognosis of CC after complete resection, which is reported that 1-year disease-free survival (DFS) rate is reported to be 48-65%, and the 3-year DFS rate declines to 23-35% without adjuvant chemotherapy (*64,65*). Up till now, most of the studies are retrospective studies due to the low incidence of CC. And a systematic review and meta-analysis reported that adjuvant chemotherapy showed a benefit impact among CC patients compared with surgery alone, but it's non-significant (*66*). Fortunately, several randomized, controlled phase III trials including the ACTICCA-1 trial (*67*), the French PRODIGE-12 study, and the British BILCAP study are currently underway. These trials should yield persuasive evidence indicating what role adjuvant chemotherapy can play. Future guidelines need to update their recommendations in conjunction with the results of those trials. The NCCN guideline encourages patients to participate in a clinical trial, like those mentioned, due to the lack of a standard regimen.

The efficacy of adjuvant radiotherapy and chemoradiation is also debatable. A non-randomized study indicated that combining IOERT and EBRT with resection for patients with stage IV pCC increased their 5-year survival rate (*68*). Cheng *et al*. reported that radiotherapy conferred a highly significant benefit in survival, and the difference in survival was especially significant after R1/R2 resection and in patients with Bismuth type III or IV tumors (*69*). However, the level of evidence is very low in these studies. The Italian guideline recommended radiotherapy with a grade C recommendation and clearly stated that the present experience is not conclusive and future RCTs including sufficient large series of patients are needed.

The recommendations are better indicated to R0/R1/R0 resection separately. Only NCCN guideline used this pattern. In fact, there are not enough evidences to help establishing this type of recommendations. We suggested the coming studies could analysis the data more specifically including the states of surgical margin.

6.2. *Unresectable*

Generally speaking, locally advanced or metastatic disease is defined as unresectable CC. The EASL guideline used the AJCC/TNM staging system, and stage III or VI disease is classified as unresectable iCC (*15*). In regard to pCC, through reconstruction of portal vein and hepatic artery, part of T4 diseases could be resected in some institutions which were previously considered unresectable. However, there is insufficient evidence to indicate that resection of locally advanced pCC improves prognosis. Only the Japanese guideline recommends resection combined with portal vein resection since several researches showing a chance of curative resection and better prognosis compared with unresectable one (*70,71*).

The median survival for patients with advanced unresectable CC is dismal. A large-scale observational study reported that the overall survival time was a median of 3.9 months for patients who did not undergo surgery, chemotherapy, or radiotherapy (*72*). Thus, in order to improve the poor nature history of advanced CC, several opitions of treatment have been established.

Liver transplantation as a curative treatment for HCC and other liver diseases (*73-75*), was also considered to apply to iCC or pCC. In the past, a liver transplantation was not recommended because of the high rate of tumor recurrence and the lack of positive prognostic variables (*76*). Recent studies have yielded encouraged results contradicting this view. A multicenter study found the patients with pCC who were treated with neoadjuvant therapy followed by LT had a 65% 5-year DFS and the intention-to-treat 5-year survival rate was 53%. Twenty percent of those patients developed recurrence after LT, but the figure is very low compared to that in patients who did not undergo neoadjuvant therapy. The BSG guideline approved this approach and stated that LT can be successful in treating rigorously selected patients undergoing neoadjuvant therapy at highly specialised centers. The NCCN guideline also recommended the combination of LT and neoadjuvant chemoradiation only for select patients. Chinese guideline 2 emphasized two instances where LT would be considered for patients with pCC: (*i*) the tumor was limited to the liver parenchyma with PSD or decompensation of liver function; (*ii*) no lymph node metastasis, no perineural invasion, and no metastasis outside the liver (grade C recommendation). Regarding iCC, EASL guideline summaried LT is not recommended for iCC or mixed HCC-iCC due to the limited data (grade B recommendation). Recent data have indicated that LT for patients with "early" or "very early" iCC (tumors $\leq$ 2 cm) with cirrhosis achieved excellent 5-year survival rate (*77*). The neoadjuvant therapy also shoud be considered for iCC in the same manner as for pCC. In summary, three guidelines encouraged further research in this area.

Biliary drainage is considered for obstructive jaundice patients with unresectable or metastatic CC. Few studies have compared biliary drainage to no drainage in patients with unresectable disease, but biliary drainage can deal with pruritus, liver and renal dysfunction, and a poor quality of life caused by persistent jaundice (*78*). The methods of palliative drainage include ERCP, PTC and surgical bypass, and the non-surgical stenting is regarded as the first choice (*79*). The Japanese guideline, the BSG guideline, the Italian guideline, and the Asia-Pacific guideline are consistent in their recommendations regarding the choice of stenting. Moreover, the BSG guideline and the Chinese guideline 2 state that surgical bypass should only be reconsidered in patients with a good estimated life expectancy if endoscopic and/

or percutaneous stenting has failed. The Asia-Pacific guideline added one more condition when laparotomy that aimed for R0 discovers an unresectable locally advanced tumor. As for palliative resection, among patients with pCC, R1 resection was reported to offer long-time survive (*52,80*). However, only Chinese guideline 2 mentioned it and gave the recommendation (grade C) of palliative resection for pCC when a R1 resection can be obtained. More evidence is needed to resolve this area of contention, and this topic should be addressed in future guidelines.

The combination of gemcitabine and cisplatin (GC) chemotherapy is recommended as standard first-line treatment for advanced and metastatic CC. Persuasive evidence has come from the randomized, controlled, phase III ABC-02 study, which indicated that GC chemotherapy improved OS and PFS by 30% over gemcitabine alone (*81*). In Japan, similar findings were reported in a phase II randomized study (*82*). GC chemotherapy was given the highest grade of recommendation by the Japanese guideline, the BSG guideline, and the SEOM guideline, but the EASL guideline only gave GC chemotherapy a grade recommendation B. The Italian guideline came out before this evidence came to light and the remaining guidelines did not mention GC chemotherapy. In addition, the SEOM guideline and the EASL guideline emphasized that this recommendation should apply to patients with an ECOG Performance Status of 0-2. If patients score poorly in terms of their performance status (ECOG Performance Status > 2), only the best supportive care is indicated. Regarding the second-line chemotherapy, the Japanese and the SEOM guideline hold the same idea that currently couldn't give a recommendation due to insufficient data. Although local regional therapy is an important role in the management of HCC, its effectiveness in iCC is debatable. In the NCCN guideline, the recommendation for regional therapy is category 2B. The algorithm in the SEOM guideline recommends ablation of a locally advanced tumor ≤ 3 cm. The EASL guideline states that RCTs should be conducted to establish first-line local-regional treatment options for patients with unresectable iCC. Photodynamic therapy (PDT) is a new ablative therapy for patients with pCC or dCC. Two RCTs have revealed that a combination of PDT and stenting improved the OS of patients with unresectable disease (*83,84*). However, only the Asia-Pacific guideline recommended this approach (grade A recommendation) for patients with inoperable pCC. The Japanese guideline and the NCCN guideline mentioned this new therapy but offered no recommendations. Although PDT can be considered as an option, studies comparing it to chemotherapy are needed in order to indicate its clinical effectiveness. The remaining therapies include radiotherapy, chemoradiation, biological therapies etc. Current guidelines discussed these therapies and summarized relevant studies, but few offered recommendations because of limited evidence. Ongoing studies may change attitudes towards different therapies and they may be reflected in future guidelines.

7. Limitations

There are several limitations to this review. First, the contents in this article did not cover all the aspects of cholangiocarcinoma, such as pathology, genetic and molecular researches. This is because the guidelines differed in the extent to which they discussed the aspects of cholangiocarcinoma, and many only touched on some of those aspects. Second, the number of included guidelines is small. Two of those guidelines were limited to pCC and one was limited to iCC. Third, the algorithms of diagnosis and treatment (Figure 1 and 2) were not completed, it could not represent all the opinions from all the included guidelines.

8. Conclusion

It has been 14 years since the first guideline on CC was published. The management of CC requires varied techniques and cancer teams with experiences and skills. In order to improve the unsatisfied prognosis of CC around the world, well-established practice guidelines are very important. Comparison of the current guidelines revealed several inconsistencies. Signs of conflicting views indicated a lack of evidence of a sufficiently high level, which is the biggest problem in the management of CC. Large-scale studies need to be conducted in areas of contention to help update the guidelines. Organizations and medical societies need to be encouraged to use standard evaluation measures, to restrict tumors to CC or iCC, pCC, or dCC specifically, to give recommendations in accordance with the equipment that is available for diagnosis and treatment in different counties, and to use an appropriate and consistent structure when establishing and drafting guidelines for CC.

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