Current Updates on Diagnosis and Management of Cholangiocarcinoma: from Surgery to Targeted Therapy

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ABSTRACT

Cholangiocarcinoma is commonly described as any malignancy arising from the lining of the bile duct and is recognized as one of the most common biliary malignancies. We conducted a literature review of current available evidences and guidelines.

Based on the anatomical location of the origin of the mass, cholangiocarcinoma can be divided into intrahepatic, perihilar, and distal cholangiocarcinoma. Each of these subtypes has their own risk factors, best treatment options, and prognosis. The most common risk factors for cholangiocarcinoma also differs based on geography and population backgrounds. Histopathological biopsy remained the gold standard for cholangiocarcinoma diagnosis, however various advances has been made in diagnostic procedure, including MRCP, EUS, ERCP, EBUS, and cholangioscopy. Surgical resection is still the best treatment modality for cholangiocarcinoma, but it can only be done in few patients considering most patients were diagnosed in the unresectable state. Other treatment options includes conventional chemotherapy, locoregional therapy, systemic targeted therapy, and palliative best supportive care. Cholangiocarcinoma has an abundance of molecular targets and advances in biomolecular technologies bring further hope for future curative treatment options. Treatment options should be chosen individually based on each patient's condition and setting.

Cholangiocarcinoma is still a major health problem in hepatobiliary malignancies. Multiple options are available for cholangiocarcinoma treatments.

***Keywords**. Cholangiocarcinoma, biliary malignancy, targeted therapy.*

INTRODUCTION

Cholangiocarcinoma is a group of malignancy that arises from cholangiocytes, the epithelial lining of the bile duct.[1-4] Although it accounts for <1% of all human malignancy, cholangiocarcinoma is the second most common (10-15%) primary liver cancer.[5] The incidence of cholangiocarcinoma varies widely between different geographic locations, with Asian countries tend to have higher incidence of cholangiocarcinoma compared to Western Countries. Incidence in some Asian countries may be as high as 85-113 per 100.000.[2,4,5]

Although the overall incidence of this condition is not that high, the mortality rate of cholangiocarcinoma were pretty high, mostly due to the late presentation and limited treatment options. [3] This disease was more prevalent among males compared to females and tend to be found in older patients. Anatomically, cholangiocarcinoma may be classified as intrahepatic origin or extrahepatic origin, the later might also be divided into perihilar and distal cholangiocarcinoma.[2,4]

A majority high cholangiocarcinoma were perihilar (60%), followed by distal (30%), while the rest were intrahepatic.[4] In rare instances, primary liver cancer can be comprised of combination of cholangiocarcinoma and hepatocellular carcinoma to form an aggressive kind of cancer. On the other hand, cancer arising from the ampulla of vater has distinct characteristics that combines the biliary and intestinal epithelial. Both of these malignancies have their own characteristics and treatments and are not classified as cholangiocarcinoma. However, carcinoma arising from the gallbladder has been classified as cholangiocarcinoma under most definitions.[5]

CLASSIFICATION AND EPIDEMIOLOGY

Cholangiocarcinoma is typically classified based on their anatomic origin. Various classification system has been proposed over the years, but the most accepted classification is comprised of 3 subtypes, intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, and distal cholangiocarcinoma. Intrahepatic cholangiocarcinoma arises within the hepatic parenchyma, starting from proximal to second-order bile ducts. Perihilar cholangiocarcinoma arises between second-order bile ducts and the cystic duct insertion, while distal cholangiocarcinoma arises from below the cystic duct insertion in the common bile duct (CBD).[1, 2, 5] Some earlier publications might group the perihilar cholangiocarcinoma together with either intrahepatic or distal cholangiocarcinoma instead of classifying it as a distinct subtype. Most guidelines recognized gallbladder cancer as its own entity but some group it together with distal cholangiocarcinoma.[1, 5]

The incidence of cholangiocarcinoma varied significantly across different populations. This difference is likely caused by difference occurrence of genetic or environmental risk factors in different populations. South East Asian countries were known to have the highest incidence of cholangiocarcinoma with the high rate of Age Standardized Incidence Rate (ASIR) per 100,000 population in Northern Thailand (ASIR of 100 among men). The number was high compared to ASIR 0.3-3.4 in the Western Countries. This high incidence was likely caused by endemicity of liver flukes in Northern Thailand which were a known risk factor for cholangiocarcinoma.[1] Intrahepatic cholangiocarcinoma is the second most common primary liver malignancy behind hepatocellular carcinoma and accounts for approximately 10% to 25% of all hepatobiliary malignancies.[4] There are recorded global increase in the prevalence and mortality of intrahepatic cholangiocarcinoma, while the prevalence and mortality rate of perihilar and distal cholangiocarcinoma have been decreasing.[1] Latest data suggested that the mortality rate of intrahepatic cholangiocarcinoma was 1.2-2.5/100,000, while the mortality of perihilar and distal cholangiocarcinoma were below 1.0/100,000.[6] Cholangiocarcinoma globally had a women vs men ratio of 1:1.2 to 1.5. it rarely occurs before age of 40 and typically presents in the seventh decade of life.[4]

There are various known risk factors for cholangiocarcinoma, some accounts only for a specific type while others are associated with all types of cholangiocarcinoma. Cirrhosis, viral

hepatitis, and hepatolithiasis are associated with increased risk of intrahepatic cholangiocarcinoma, while choledocolithiasis is associated with perihilar and distal cholangiocarcinoma.[1] Recent meta-analysis showed that risk factors for intrahepatic cholangiocarcinoma in general included cirrhosis with odd ratio (OR) of 22.92 (95% confidence interval (CI) 18.24-28.79), followed by hepatitis B virus with OR of 5.10 (95% CI 2.91-8.95), and Hepatitis C virus with OR of 4.84 (95% CI 2.41-9.71) for hepatitis C virus (HCV).[7] Diabetes, obesity, and the use of hormonal contraception have also been proven to be related to increased risk of intrahepatic cholangiocarcinoma.[5] Caroli's disease, choledochal cysts, primary sclerosing cholangitis (PSC), and liver flukes are known risk factors of all kinds of cholangiocarcinoma.[1] As for, gallbladder cancer, increased risk of cholecystitis such as the presence of gallbladder and oler age will also increase risk of gallbladder cancer.[5]

As mentioned above, liver flukes are responsible for most cases of cholangiocarcinoma in Asia, while PSC is the main cause of cholangiocarcinoma in the West. Other known and possible risk factors of cholangiocarcinoma include toxic agents, alcohol, diabetes, smoking, and obesity.[1, 8, 9] In general, increased and prolonged inflammations of the biliary epithelial is the key risk factor for cholangiocarcinoma, be it PSC in the west or liver flukes in the East.[5]

DIAGNOSIS

Most cases of intrahepatic cholangiocarcinoma are asymptomatic and found incidentally on medical check-ups as liver nodules. Such nodules can also be caused by hepatocellular carcinoma (HCC) or metastatic cancer to the liver, therefore common symptoms of intrahepatic cholangiocarcinoma is also similar to HCC such as abdominal discomfort, jaundice, or even impaired liver function. On the other hand, painless jaundice is the most common clinical presentation of both perihilar and distal cholangiocarcinoma.[1]

The role of biliary imaging modalities in the management of cholangiocarcinoma comprised of two major roles: distinguishing the major anatomical subtypes of cholangiocarcinoma (intrahepatic, perihilar, distal, and gallbladder), and acquiring samples for histopathological examination to actually ascertain malignancy. Non-invasive modalities such as CT scan or MRCP are typically enough to cover the first role.[1, 5] MRCP and MRI are more superior in assessing the mass itself and the anatomy of the biliary tree. For perihilar and distal cases, MRCP can be used to differentiate between benign and malignant lesions with sensitivity of 87% and specificity of 85%.[10] CT scan, on the other hand, is more superior in assessing vascular involvement and therefore resectability of the disease. Multiphase CT-Scan is also very sensitive in assessing intrahepatic cholangiocarcinoma. Typical imaging feature of intrahepatic cholangiocarcinoma is initial rim or peripheral enhancement in the arterial phase followed by progressive homogenous enhancement of the tumor in the delayed phases.[1, 11] These patterns are remarkably different from those found in hepatocellular carcinoma or metastatic nodule of the liver. Other radiologic modalities for cholangiocarcinoma includes contrast enhanced ultrasound or PET scan (especially good in assessing lymph nodes involvement, distant metastasis, and disease recurrence).[1, 5] Differentiating between intrahepatic and extrahepatic cholangiocarcinoma is also important to asses prognosis, with one study in particular showed that patients with intrahepatic cholangiocarcinoma had increased overall survival (median 4 months) compared to their extrahepatic counterparts in non-metastatic setting.[12]

Definitive diagnosis of cholangiocarcinoma requires histopathological evaluation of biopsy specimens. For intrahepatic cholangiocarcinoma, biopsy samples can be obtained percutaneously or using endoscopic ultrasound (EUS). Perihilar and distal cholangiocarcinoma typically require more advanced method of biopsy, such as cytobrushing using ERCP, fine needle biopsy using EUS, or even direct biopsy using cholangioscopy.[1] Biopsy is generally preferred over biliary brush cytology and should be carried out whenever possible not only for diagnostic purpose, but also for molecular profiling of the suspected malignancy.[5]

ERCP is currently the most common technique since it can also be used to assess the biliary anatomy and to perform invasive therapeutic procedure as well. Biliary brushing obtained using ERCP can then be used for cytology examination or even FISH.[1] Percutaneous transhepatic cholangiography might also be used to obtained biopsy samples.[5] EUS combined with Fine Needle Aspiration is effective especially for distal cholangiocarcinoma. EUS-FNA can also be used to assess lymph node involvement around the biliary tree.[1, 5]

Another application of advanced ultrasonography in biliary malignancy is the insertion of intraductal ultrasound (IDUS) using ERCP technique. Unlike EUS, IDUS can be performed in the same session as ERCP and is excellent in acquiring detailed images of the bile duct and periductal structures. IDUS is especially excellent in assessing the longitudinal extent of bile duct mass. Reported sensitivity, specificity, and accuracy of the assessment of the longitudinal extent of cancer on the hepatic and duodenal side by IDUS were 82%, 70%, 78% and 85%, 43%, 70%, respectively.[13, 14] IDUS can also be used to guide trans-papillary biopsy and with significantly higher accuracy than conventional trans-papillary biopsy (90.8% vs 76.9%).[13]

Cholangioscopy is a method of using a specific scope to directly visualize and manipulate the biliary ductal system. Recent studies have shown that cholangioscopy might be superior to both ERCP and EUS in determining the malignancy of bile duct lesions.[5, 15, 16] Per-oral cholangioscopy techniques can be divided into 3 main techniques, "Mother-Baby" dual operator cholangioscopy, single operator cholangioscopy using SpyGlass™ system, and direct per-oral cholangioscopy. The "Mother-Baby" dual operator cholangioscopy was caried out by inserting a smaller "Baby" cholangioscope through the working channel of a "Mother" duodenoscope. This procedure requires two operators with two sets of towers. It is technically challenging but might yields good image quality with enabled Narrow Band Imaging (NBI). The direct per-oral cholangioscopy was done using guidewires to directly insert an ultraslim cholangioscope to the biliary tract. This resulted in a very excellent image quality and can be performed by only a single operator and a single set of towers. The procedure, however, is technically challenging. The SpyGlass™ method still requires the presence of guiding "Mother" duodenoscope, but the role of the "Baby" cholangioscope is replaced by a smaller, more flexible scope that is introduced to the bile duct using a delivery catheter. The cholangioscope in this technique is smaller but has a four way tip deflection and has its own dedicated irrigation channel. This advantages, however, comes with the disadvantages that the image quality of the SpyGlass™ is more limited than the two previous methods. The advancement of the scope, using digital enhancement technology (The SpyGlass™ DS series) has in some ways lessen this disadvantage to some degree.[15, 16] The most common cytology findings for cholangiocarcinoma is adenocarcinoma.[1]

The role of tumor marker for the diagnosis of cholangiocarcinoma is limited due to its low specificity. Serum carbohydrate antigen (Ca) 19-9, the most used tumor marker for biliary malignancy, is a nonspecific marker which can be elevated in patients with biliary and other gastrointestinal malignancies, as well as in benign biliary obstruction.[5] However, Ca 19-9 value above 1000 U/mL may indicate metastatic cholangiocarcinoma.[17] Current guidelines stated that Ca 19-9 use is still recommended for prognosis and response monitoring purposes.[1, 2, 5] Staging for the severity of cholangiocarcinoma is divided according to anatomical classifications. The TNM system is still considered to be the most appropriate system for the staging and the 8th edition of the Union for International Cancer Control (UICC) system is commonly recommended to be used clinically. The Bismuth-Corlette classification is also used for perihilar cholangiocarcinoma to further describe their anatomical location.[4, 5]

TREATMENT

Surgery

Treatment options for cholangiocarcinoma includes resection, chemotherapy, or best supportive care (BSC). In general, resection

is always the best option for resectable cases. In intrahepatic cholangiocarcinoma, the presence of lymph node involvement beyond the hepatoduodenal and gastrohepatic ligament means that the tumor is unresectable. For intrahepatic cholangiocarcinoma, the resection procedure of choice is hepatectomy, while the most typically applied surgical procedure for perihilar and distal cholangiocarcinoma is pancreatoduodenectomy. Hepatectomy can even be performed using laparoscopic technique and embolization of either portal vein alone or both portal and hepatic vein might be required. Lymphadenectomy at the level of the hepatoduodenal ligament during surgery is recommended for all hepatectomy in intrahepatic cholangiocarcinoma cases.[1, 4, 5] Available data reported that the 5-year survival rate of intrahepatic cholangiocarcinoma cases after resection is between 25-70%, with median overall survival around 40 months after resection. Risk of recurrence is reported to be between 50%– 70%, with a median time to recurrence of 2 years.[18, 19] In the case of suitable intrahepatic cholangiocarcinoma, liver transplant is considered to be a good option if the nodule was solitary with diameter of 2 cm or less.[1]

Although pancreatoduodenectomy is regarded as the best surgical option of perihilar cholangiocarcinoma, its morbidity and mortality are still reported to be high, even in experienced centers. Several methods have been proposed to improve the morbidity of this procedure, including preoperative biliary drainage, which can be conducted percutaneously. Besides the aforementioned extrahepatic lymph node involvements, other criteria for unresectability of perihilar cholangiocarcinoma is the involvement of both distal and proximal common bile duct.[1, 5] Experts form Americas Hepato-Pancreato-Biliary Association hilar CCA consensus meeting agreed that unresectable hilar cholangiocarcinoma is if the case meet any of the following criteria: bilateral segmental ductal extension, unilateral atrophy with either contralateral segmental ductal or vascular inflow involvement, or unilateral segmental ductal extension with contralateral vascular inflow involvement.[4]

Pancreaticoduodenectomy (also called Whipple's procedure) itself is a very radical approach that involves resection of the bile duct and gallbladder, head of the pancreas and first part of the duodenum. At least 30% of liver remnant must be spared in order to make sure adequate liver function. Other simpler alternative procedure for perihilar cases includes resection of at least 3 segments of the liver, as well as the caudate lobe, extrahepatic bile ducts, and portal lymph nodes, followed by reconstruction with an hepaticojejunostomy. Vascular resection and reconstruction of portal vein might be needed to achieve R0 in some cases.[1, 2, 5]

The average post-surgery 5-year survival rate for perihilar cholangiocarcinoma is reported to reach 45%.[20, 21] However, risk of recurrence remained high in the 80% range for the first 2 years.[1] Partial hepatectomy is a viable options for some cases of perihilar cholangiocarcinoma, depending on the Bismuth-Corlette classification. Embolization of one branch of the portal vein can also be done to stimulate the growth of the liver remnant.[5]

Distal cholangiocarcinoma cases on the other hand, can only be managed surgically by using pancreatoduodenectomy method with reported lower overall survival rate than perihilar cholangiocarcinoma cases (approximately similar to the prognosis of pancreas head adenocarcinoma).[1, 5] In all cases of surgery for extrahepatic cholangiocarcinoma, biliary drainage to lower serum bilirubin level is almost always mandatory and can be achieved using ERCP, percutaneous transhepatic biliary drainage, or open surgery.[5]

Liver transplant in perihilar or distal cholangiocarcinoma can be considered for unresectable cases with no metastasis (including lymph node metastasis) and early stage disease (≤3 cm in radial diameter). Neo adjuvant chemoradiation (5-fluorouracyl, brachytherapy, and capecitabine) might also be considered prior to transplantation. It important to keep in mind the possibility of transplantation from early diagnosis, since diagnostic procedure such as percutaneous or EUS guided needle biopsy, or any other surgical incision of the tumor plane are considered to confer high risk of peritoneal seeding and therefore are contraindications for

transplantation.[22] Some data suggest that overall survival for transplant patients might reach 80% range.[1]

Adjuvant Therapy

The post-surgery recurrence rate of cholangiocarcinoma in general can reach as high as 80% in 3 years, therefore surgery cannot be considered to be the only cure for cholangiocarcinoma.[5] In all cases of intrahepatic, perihilar, or distal cholangiocarcinoma, adjuvant chemotherapy using capecitabine can be considered. This is based on the result of BILCAP study which found that patients that received 6-months course of capecitabine following resection have better overall survival than those without capecitabine. Participants of this study comprised of cholangiocarcinoma from all origin (intrahepatic, perihilar, distal), and thus capecitabine adjuvant therapy has become a standard practice for all kind of cholangiocarcinoma.[23] Addition of adjuvant course of capecitabine is also currently recommended by guidelines from AASLD and ESMO.[1, 5] Another study that supported the importance of adjuvant therapy is the Japanese ASCOT Study in which the addition of four 6-weekly cycles of tegafuregimeracile oteracil after surgery in cholangiocarcinoma cases lead to better survival rate than surgery alone.[24] Data on adjuvant radiotherapy after surgery for cholangiocarcinoma is still very limited. However, some small retrospective studies showed promising results for adjuvant radiotherapy after completion of capecitabine in selected cholangiocarcinoma cases.[4, 5]

Locoregional Therapy

Locoregional therapies are available options for unresectable intrahepatic cholangiocarcinoma cases that are locally advanced (liver limited and no metastasis). Options for this modality includes Transarterial Chemoembolization (TACE) with or without drug-eluting bead, Transarterial Embolization (TAE), Transarterial Radioembolization (TARE), and external beam radiation therapy. TACE is reported to achieve median survival of 12-15 months which can be improved with the use of drug-eluting beads. Up until now, there was no large clinical trial comparing the effectiveness of different locoregional therapies.[1] Studies on external beam radiation using Stereotactic Body Radiotherapy (SBRT) have shown low overall survival and is currently not recommended as primary treatment of cholangiocarcinoma.[5]

Chemotherapy

Chemotherapy is traditionally reserved for unresectable cases of cholangiocarcinoma, which comprises of majority of cases in most countries. Chemotherapy is considered to be palliative in nature. The most commonly used chemotherapy regiment for cholangiocarcinoma is the gemcitabine-cisplatin combination based on hallmark ABC-02 study from the United Kingdom and BT22 study from Japan.[25, 26] However, this regiment can only result in median progression free survival of 8 months and median overall survival of 11-13 months. Current guidelines recommended to limit treatment to 6 months since no benefit is recorded beyond this duration.[1, 2, 5] Addition of other agents to the protocol or adoption of another protocol altogether have shown promising results in early trials. Addition of the programmed death-ligand 1 (PD-L1) immune checkpoint inhibitor (ICI) durvalumab to the gemcitabine-cisplatin regiment demonstrated improved overall survival in the TOPAZ-1 study.[27] The infamous FOLFOX protocol (leucovorin, 5-FU and oxaloplatin) especially has shown promising results compared to the conventional Gem-cis and is now considered to be the best protocol for cholangiocarcinoma.[1]

Targeted Therapy

Cholangiocarcinoma, especially intrahepatic cholangiocarcinoma, are enriched with abundant molecular targets for systemic therapies. Up to 40% of cholangiocarcinoma cases harbor genetic alterations that might be used as treatment targets.[1, 5, 28] Several targeted therapies have been proposed and tested for cholangiocarcinoma and genetic testing is recommended by several guidelines, especially for intrahepatic cholangiocarcinoma. The type of recommended genetic testing was parallel sequencing of several genes using focused next-generation sequencing (NGS) instead of singe

gene examination. The currently recommended panel included evaluations for the mutations of isocitrate dehydrogenase 1 (IDH1), human epidermal growth factor receptor 2 (HER2)/ neu [v-erb-b2 avian erythroblastic leukaemia viral oncogene homologue 2 (ERBB2)], B-raf protooncogene (BRAF), fibroblast growth factor receptor 2 (FGFR2) and neurotrophic tyrosine receptor kinase (NTRK).[1, 5] Another common mutation in cholangiocarcinoma is KRAS mutations and TP53.[4] In the case of intrahepatic cholangiocarcinoma, the most common relevant genetic mutations were IDH1 and IDH2 that can be found in approximately 10-20% of patients. A specific IDH1 inhibitor, ivosidenib is currently the only targeted therapy that has been tried in a phase III clinical trial for intrahepatic cholangiocarcinoma with good results.[5] The ClarIDHy study that included 187 patients showed that the administration of oral once daily 500 mg of ivosidenib improved overall survival (median 10.3 months vs 5.1 months) and progression free survival (median 2.7 months vs 1.4 months) significantly.[28, 29] Although clinically speaking the magnitude of these improvement is modest, ivosidenib has been approved by the Food and Drug Administration (FDA) as a recommended treatment for non-naïve cholangiocarcinoma with IDH1 mutations.[5]

Another promising targeted therapy for cholangiocarcinoma is FGFR inhibitors such as pemigatinib, infigratinib and futibatinib, both of which have been approved for cholangiocarcinoma cases with positive FGFR2 mutations that had failed at least one course of systemic therapy. There were no available data from phase III clinical trials regarding these agents, but phase II trials showed overall risk reduction of up to 44% and progression free survival rate of 7 months with overall survival of up to 17 months.[30, 31]

The HER2/ neu [ERBB2] mutation has been used as target for systemic treatment of other cancer and its application in cholangiocarcinoma showed promising early results. This mutation can be identified in 5-10% of all cholangiocarcinoma and is even more common in gallbladder cancer.[5] MyPathway trial, which included 39 cholangiocarcinoma patients with amplified HER2 that were treated with intravenous pertuzumab (840 mg loading dose, then 420 mg every 3 weeks) plus trastuzumab (8 mg/ kg loading dose, then 6 mg/kg every 3 weeks) showed partial response in 23% patients, median progression free survival of 4 months, and median overall survival of 10.9 months.[32]

The BRAF mutations occurred pretty common (approximately 5%) in cholangiocarcinoma and targeted therapy with BRAF inhibitors such as dabrafenib and trametinib have been tested for cholangiocarcinoma with promising results. Available study showed median progression free survival of 9 months and overall survival of 14 months with both agents.[5] Other potential targeted therapy has also been assessed but no large trials have been conducted up until now. These agents included platinum compounds and poly (ADP-ribose) polymerase (PARP) inhibitors for patients with BRCA mutations, pembrolizumab for patients with high microsatellite instability (MSI), and larotrectinib or entrectinib for patients with NTRK fusions.[33,34,35]

Meanwhile in perihilar and distal cholangiocarcinoma, high rate of EGF receptor (EGFR) mutations makes this mutation a compelling target for treatment. Ongoing studies showed limited efficacy of various targeted agents, but no definitive conclusion can be drawn as of the publication of this article.[36]

Another promising treatment options in the field of oncology is the retrovector agent such as DeltaRex-G (former names: Mx-dnG1, dnG1 or Rexin-G). This agent is tumor targeted, murine leukemia virus (MLV)- based retrovector displaying a Signature-pan-collagen binding decapeptide on its gp70 envelope protein. It can also encode a truncated N-terminal deletion mutant construct of the human CCNG1 oncogene under the control of a hybrid LTR/CMV promoter. It has excellent result in in-vivo studies especially in pancreatic cancer, sarcoma, breast cancer, osteosarcoma, and lymphoma. It has been proposed as an alternative for chemotherapy resistant metastatic solid malignancies.[37,38] Currently no significant data are available on the efficacy of DeltaRex-G for cholangiocarcinoma. The only study that involved cholangiocarcinoma patients was the BLESSED Study that included

17 patients with various solid malignancies, including one patient with cholangiocarcinoma. Unfortunately the cholangiocarcinoma patient was not among the surviving patients at the end of the study course.[39]

Palliative and Best Supportive Care

Although significant advances have been made in the treatment of cholangiocarcinoma, for some patients with advanced diseases best supportive care is still the best option. Best supportive care can also be implemented for patients undergoing systemic therapy with palliative settings. Apart from the general cancer supportive care such as pain management and nutritional therapy, supportive care in biliary tract malignancy must include the identification and management of biliary and gastric obstruction.[40] Palliative obstruction release can be achieved through several approaches including surgical procedures, percutaneous drainage, or endoscopic drainage by either nasobiliary drainage or internal biliary stenting.[41,42] With recent advances in endoscopy technology, endoscopic drainage is generally more preferred nowadays compared to surgical drainages. Endoscopic stent placement is effective and relatively safe, with risk of post-ERCP pancreatitis averaging at 3.5%. Issues regarding endoscopic biliary drainage technique usually revolves around unilateral vs bilateral stent or plastic vs metal stent. The first issue typically requires further consideration of tumour location, complexity, and feasibility of bilateral stenting. In most cases, bilateral stenting should be pursued whenever possible.[43]

Plastic biliary stents are easier to insert, but they are usually smaller in diameter and may form biofilms that will cause stent obstruction. This type of stent can last for 3 months and can be easily placed and removed at will. Plastic stents are beneficial as temporary drainage option for patients with a more definitive curative treatment options.[44,45] However, plastic stents tend to be easily clogged due to their small caliber (10-20 fr), with clogging rate as high as 20-40%. Plastic stents can also easily migrate.[46,47] On the other hand, Self-Expandable Metal Stent (SEMS) are harder to insert but yield better patency, up to 6-12 months or even longer. Diameter of this kind of stents can also be increased to up to 30 fr.[48,49,50] Percutaneous transhepatic drainage is usually reserved for when endoscopic drainage is not feasible and can be used to place metal stents as well. Patients should be informed and educated about the patency and duration of stents and the possibility of obstruction or infection. In the case of existing obstruction, biliary infections with accompanying sepsis can be devastating and should be evaluated and treated comprehensively using combination of drainage and antibiotics.[5,50-52]

Follow Up

There is currently no established recommendation on the post treatment follow up program for cholangiocarcinoma. The ESMO guideline stated that surveillance may be conducted once in 3-6 months during the first 2 years after treatment and should include clinical examination, laboratory investigation, tumour markers and CT scan of the thorax, abdomen, and pelvis.[50,51] The interval of the visits is then increased regularly to achieve yearly visits after 5 years since treatment. During these visits, long term complications of surgery should be evaluated, including malabsorption and chronic diarrhea due to pancreas insufficiency, as well as biliary stenosis and jaundice. In these cases, rehabilitation might help to maximize quality of life. Treatment and disease impact on psychological well being of the patients should also be evaluated and managed accordingly.[52]

CONCLUSION

Cholangiocarcinoma is one of the most common biliary malignancies with significant mortality and morbidity. Cholangiocarcinoma can be further divided into intrahepatic, perihilar, and distal depending on their origin. Surgery is still the best treatment option for early stage diseases, but most patients will require further treatment modalities with chemotherapy or locoregional therapy. Targeted systemic therapies are promising options in cholangiocarcinoma due to the abundance of molecular target.

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