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Current controversies in cholangiocarcinoma☆

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ABSTRACT

Cholangiocarcinoma represents 10% of primary liver malignancies and accounts for less than 3% of all gastrointestinal malignant tumors, with an enormous geographical variation. This neoplasia can arise from the biliary tract epithelium or hepatic progenitor cells. Depending on the anatomic localization, it is classified into three subtypes: intrahepatic, perihilar and distal. This fact is one of the main difficulties, because there are many studies that indistinctly include the results in the management of these different types of cholangiocarcinoma, without differentiating its location and even including gallbladder cancer.

There are many controversial points in epidemiology, liver transplantation as a treatment, limitations of different results by group and type of treatment, histological testing and chemotherapy. This is a narrative review about topics in cholangiocarcinoma. This article is part of a Special Issue entitled: Cholangiocytes in Health and Disease edited by Jesus Banales, Marco Marzioni, Nicholas LaRusso and Peter Jansen.

1. Introduction

Primary liver cancer is the second most important cause of global cancer mortality. Hepatocellular carcinoma is the prevalent type of primary liver cancer in most countries, accounting for around 80% of the cases. The second most common primary liver cancer is Cholangiocarcinoma (CCA), accounting for approximately 15% of the cases and < 3% of all gastrointestinal malignant tumors, with an enormous geographical variation, reflecting the exposure to different risk factors. Some reports revealed an increase in liver cancer incidence in several regions but that it declined in some countries in Asia [1].

The incidence of Intrahepatic cholangiocarcinoma (ICC) in Europe, North America, Asia, Japan and Australia has been rising over the past two decades [2–4], with the highest incidence of 96 per 100,000 men reported in Thailand [5]. This fact can be attributed to the alteration in disease classification [6] (supported by the evidence of concurrent drop in the incidence of extrahepatic cholangiocarcinoma). Some also suggested that part of the increase in ICC may be due to the advantages in diagnostic modalities that could identify early lesions and biliary malignancies that were undiagnosed previously [7]. But Shaib YH et al., demonstrated that the increase in the incidence of ICC is independent of the increased proportion of early-stage ICC or smaller size and unstaged diseases [2], the increased incidence might be associated with a rise in certain risk factors such as viral hepatitis and non-viral chronic liver diseases [8]. Like other biliary tract malignancies, the incidence of ICC increases with age, peaking between 55 and 75 years old, and is slightly higher in males than that in females [2].

CCA is a heterogeneous group of neoplasias that arises from the biliary tree. Depending on the anatomic localization, it is classified into three subtypes: intrahepatic (15–20%), perihilar (60–70%) and distal (20–30%), that have similarities but also important inter-tumor and intra-tumor differences that can affect the pathogenesis and outcome [9,10]. This fact is one of the main difficulties from our point of view. Indeed, many studies indistinctly include the results in the management of the different types of cholangiocarcinoma, without histologic confirmation, and without differentiating location and even including gallbladder cancer; despite the fact that those outcomes and interventions are not always comparable. This may change in the future due to the inclusion of intrahepatic cholangiocarcinoma with a distinct staging system in the 7th edition of AJCC/UICC (American Joint Committee on Cancer/Union for international Cancer Control) [11].

The current classification according to the World Health Organization (WHO) [12] and the Union for International Cancer Control (UICC) [13] includes only two categories, according to the anatomic origin along the biliary tract:

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- Intrahepatic cholangiocarcinoma (ICC), representing approximately 20% of the tumors; iCC develops within the liver, from the second-order bile duct and the more proximal intrahepatic bile duct.
- Extrahepatic bile duct carcinoma (eBDC), accounting for 80% of cholangiocarcinomas; eBDC includes tumors arising from large hepatic hilar bile ducts (also called Klatskin tumor) to more distal extrahepatic bile ducts excluding those arising from Vater's ampulla. As a tumor mass, at the time of diagnosis, it can extend from the hilum to intrahepatic perihilar parenchyma, making it at times difficult to determine its origin.

Cholangiocarcinoma is typically present in one of two ways: either as a mass lesion within the liver (intrahepatic cholangiocarcinoma) or as biliary tract obstruction attributable to obstruction of the large duct (ductal cholangiocarcinoma). In addition, these two distinct tumors differ in their etiology, risk factors, natural history, clinical behavior and response to therapies. Consequently, the management and outcomes of patients with these cancers are different. Intrahepatic cholangiocarcinoma presumably arises from small ducts within the liver, and can grow to a large size before the patient becomes symptomatic. In contrast, ductal cholangiocarcinoma arises from large ducts, up to the second order of branching, and the patients present biliary tract obstruction [14,15].

These tumors are characterized by slow growth, but typically with a local infiltration pattern. Carcinogenesis is characterized by the presence of desmoplastic stroma, fibrogenic process, immune response and angiogenesis [16]. Cumulative mortality rates have increased between 1979 and 2004, that are mainly attributable to rising incidence rates, especially in the group of patients ≥ 65 years, in which also 72% of cholangiocarcinoma-related deaths occurred in 2004 [17].

2. Epidemiology

The epidemiology of CCA is diverse depending on the geographic area and exposure to risk factors. Some reports show increased ICC rates in some geographic areas that are different from the areas with increasing Hepatocellular Carcinoma (HCC) rates. This characteristic suggests differences in liver cancer etiology between ICC and HCC; although these cancers share some risk factors [18].

A recent report shows a similar trend in the global rates of HCC and ICC. The analysis of high-risk populations in each continent demonstrated that the ICC rate increased in Thailand, France and Italy while the HCC rate decreased [18].

Decreased incidence in rates of liver cancers were also observed in birth cohorts in China. Control of aflatoxin and smoking, of a Hepatitis B Virus (HBV) vaccination program, of screening of blood transfusions, and healthier are the main strategies of decreased liver cancer rates [18]. The increased incidence of liver cancer is related to obesity, diabetes, metabolic syndrome and Hepatitis C Virus (HCV) infection. Indeed, in the United States of America USA the population attributable fraction (PAF) for obesity and diabetes is 36.6% and for HCV 22.4% while for HBV it is 6.3% [18].

While many studies demonstrated the increasing incidence of ICC, the incidence of hilar cholangiocarcinoma (ECC) has remained stable in the last 15 years. Considering that ICC risk factors are not well characterized, the results of recent studies suggest that the reported increase in ICC could be related to classification problems.

In order to clarify this problem, Saha et al. analyzed the data of the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute of the USA for the period between 1973 and 2012. The estimated incidence of ICC increased from 0.44 in 1973 to 1.18 cases/100,000 per year in 2012 and corresponds to a 128% increase, while, the estimated incidence of ECC barely changed, from 0.96 to 1.02 cases/100,000 per year in the same period.

Considering the tumor registry data of the last 10 years, ICC increased significantly (annual percentage of change of 4.36%, 95%CI, 3.39% to 5.33%) but this was not the case of ECC of 0.16%, 95%CI, − 0.50% to 0.83%).

On the other hand, the analysis of trends in the relative incidence demonstrated an increase of ICC and ECC incidence in Hispanic populations compared to non-Hispanic populations in the last 20 years. Likewise, populations of Asian origin were associated with the increased relative incidence of ICC and ECC compared to Caucasian populations, although, a modest decrease of ICC risk was observed in this population between the periods 1993–1997 and 2008–2012 [19].

It is difficult to establish the incidence and prevalence of this neoplasia due to the poor cancer registry that exists in many regions, and even with the data from Globocan, it is not possible to discriminate between cholangiocarcinoma and hepatocellular carcinoma (the two most frequent primary tumors of liver); additionally in 62 out of 184 countries (33.7%) no data regarding cancer incidence is available, and only 66 countries (35.9%) reported the availability of high quality data to estimate the incidence of this tumor [1].

The problem of poor quality data is attributable to the limited resources available to treat costly diseases such as cancer, its diagnosis, classification and prevention. If the detection of cancer is problematic in developed countries [20], the possibility of even higher levels of underestimation in developing countries is greater, due to a combination of poor databases and the lack of screening facilities [21]. The problem of the estimation of tumors in the world is well established for example in hepatocellular carcinoma (HCC), where a study suggests that at least 120,722 cases of HCC might have been missed in 2012, which translates into a revised global incidence of 12.0 versus an observed 10.1 per 100,000 in the Globocan data of 2012 [22].

3. Risk factors

The risk factor in many CCA cases is not identified. However, the infection with liver flukes and primary sclerosing cholangitis are well-recognized risk factors in East Asia and in the populations in developed countries, respectively.

Eating freshwater fish transmits the infection by flukes *Clonorchis sinensis* and *Opistorchis viverrini*. The fluke infects the liver, inducing chronic inflammation mainly in the small intrahepatic ducts and gall bladder. *C. sinensis* is identified as carcinogenic to humans while *O. viverrini* is probably carcinogenic to humans according to the International Agency for Research on Cancer (IARC) [23].

Primary sclerosing cholangitis (PSC) is a disease characterized by chronic inflammation of bile ducts resulting in obliterative cholangitis that could progress to end-stage liver disease. Patients, that mainly are males, present the risk of developing CCA estimated at 0.5–1.5% per year, with a lifetime prevalence of 5–10% [16,24].

Other risk factors of CCA have been identified such as exposure to the radiopaque medium Thorotrast, hepatolithiasis, Caroli disease, bile duct cysts and metabolic syndrome [16,24,25].

In addition, HBV and/or HCV infection have been suggested as CCA risk factors. The relationship of viral hepatitis and CCA has been evaluated in several studies, but the results are controversial [8,26–33].

A recently meta-analysis of 13 case-control studies and 3 cohort studies found that HBV (OR = 3.17, 95% CI, 1.88–5.34) and HCV (OR = 3.42, 95% CI, 1.96–5.99) infection are associated with increased risk of ICC. The case control-studies included one from Thailand, Taiwan, Italy and Japan and three from Korea, China and the USA; among them, the controls were obtained from hospital-based cases in 11 studies and from population-based cases in 2 studies. The three cohort studies were from Japan (blood donors), USA (veteran populations) and Taiwan (pregnant women). The association of ICC and viral infection was established using the serological markers HBsAg and Anti-VHC; unfortunately viral genome detection was not available in these studies. Another limitation of this meta-analysis is the heterogeneity of the studies by differences in study design, population demographics and epidemiology of each country [34].

Regarding the association of HCV infection and CCA, the meta-analysis of 16 case-control studies performed by Li et al. demonstrated that patients with HCV infection have a 5.44-fold increased risk of CCA compared with patients without HCV infection. The Odds Ratio (OR) of ICC was 3.38 (95% CI, 2.72 to 4.21) while the OR of ECC was lower (OR = 1.75 95% CI, 1.00 to 3.05). Interestingly, the analysis of ICC risk by geographic region showed a difference between North America (OR = 6.48) compared to Asia (OR = 2.01) [35].

The analysis of liver explants from the tissue registry at Mayo Clinic demonstrated that cases of alcohol cirrhosis and/or HCV infection were related to biliary intraepithelial neoplasia of the large intrahepatic bile ducts. This bile duct dysplasia is considered a precursor lesion for CCA. Indeed, a dysplasia-carcinoma sequence has been described in cases of primary sclerosing cholangitis. The results of this study showed a morphological evidence of alcohol and/or HCV infection as risk factors of biliary intraepithelial neoplasia and a plausible explanation for the increasing incidence of CCA in the USA [36].

Although the oncogenic properties of HCV have been well described in HCC, the mechanisms of CCA development have so far not been elucidated. One of the mechanisms could be the expression of viral oncoproteins and the induction of chronic inflammation as a consequence of the bile duct epithelium infection [37]. Another possible mechanism is the induction of carcinogenesis by HCV in cholangiocytes using the same strategies as described in hepatocytes; this hypothesis is proposed taking into account that hepatocytes and cholangiocytes have the same progenitor cells, the reactive ductular cells [38,39].

The HCV replication in cholangiocytes was recently evaluated using primary cultures and ICC (CC-LP-1 and CC-SW-1) and ECC (Sk-ChA-1 and Mz-ChA-1) cell lines. The *in vitro* assays using pseudo-particles of HCV (HCVpp) demonstrated that primary cholangiocytes were refractory to viral infection. On the other hand, entry of pseudo-particles expressing HCV glycoproteins was demonstrated in CC-LP-1 and Sk-ChA-1 cell lines. In addition, replication of the viral genome was barely demonstrated using cell-culture-derived infectious HCV (HCVcc) in the Sk-ChA-1 ECC cell line compared to the level of HCV RNA observed in the hepatoma cell line Huh-7. One of the restriction factors for HCV replication in cholangiocytes could be the lack of expression of microRNA 122 (miR-122) in the CC-LP-1 and Sk-ChA-1 cell lines [40].

Although the normal function of miR-122 is the regulation of cholesterol biosynthesis in the liver, exceptionally it has been demonstrated that miR-122 promotes HCV replication through interaction with the 5′ untranslated region of the viral genome [41]. Further studies are necessary to demonstrate the direct and/or indirect mechanisms of HBV and/or HCV infection involved in CCA development.

3.1. Surgery

The objective in surgery for hilar and intrahepatic cholangiocarcinoma is to remove the entire tumor with disease-free margins. The margin status include R0 margin (no residual tumor), R1 margin (microscopic residual tumor), and R2 margin (macroscopic residual tumor). Patients with R1 margin or R2 margin have a dismal survival. Of all clinicopathological factors affecting long-term survivals, R0 resection is the only factor which can be modified by the surgeon. This resection will have different technical challenges according to the location of the tumor and the relationship with vital structures that are close to it, and according to the general evolution of hepatobiliary surgery, it is ideal to be done by expert hands and in centers of reference to impact on postoperative morbidity and mortality. Unfortunately, only 20–30% of cases have the option of being subjected to a radical tumor resection with curative purpose. The minimal hepatic remnant should be kept in mind to avoid organ failure, which is generally achieved by leaving 25 and 30% of the total liver volume, considering that most of these patients do not have established liver cirrhosis.

In terms of margins of resection, the scenario in hilar tumors is more complex since it should always be done with resection of the bifurcation of the main ducts and in this place there are vital structures and is difficult to determine the exact length and width of microscopic tumor extension preoperatively and intraoperatively. Hilar Cholangiocarcinoma has a biological nature that involves microscopic spread of the disease beyond the palpable macroscopic boundaries of the primary hilar mass and intraoperative frozen-section examination of ductal margins has a sensitivity, and specificity of only 75.0, and 46.7%, respectively [42–44]. When a positive resection margin is diagnosed intraoperatively with frozen section, if technically possible, further resection is recommended to remove the entire tumor, but even in high-volume centers, the reported incidences of positive resection margins ranged from 64.6 to 88.2% [45,46].

In hilar cholangiocarcinoma, bile duct resection combined with major hepatic resection is the standard surgical procedure due to the increased R0 resection rate and improved survival, but for type I or II tumor (according to the Bismuth Classification), is still controversial due to the limited data available [47,48]. Some groups consider that tumor resection with an adjacent small wedge of liver parenchyma is sufficient in these cases [49,50], others recommend central hepatectomy resecting segment 5 and segment 4b only [51]. However, it should be noted that although existing evidence comes primarily from observational studies, major liver resection should accompany resection of hilar cholangiocarcinoma to achieve a tumor-negative resection margin and improve long-term survival, as shown by most series of centers of excellence, with high rates of recurrence if only bile duct resection is done [45].

Another important aspect to take in mind for surgical resection is the anatomic relationship between hilar cholangiocarcinoma and the caudate lobe, that had not been fully recognized until two decades ago, because of this, routine caudate lobe resection should be carried out for curative treatment of hilar cholangiocarcinoma to deal with the high chance of biliary or parenchymal invasion in this segment of the liver [52,53], only a small group of authors does not recommend this surgical strategy, which seeks to achieve a margin of resection as wide as possible to avoid recurrence of tumor in the follow-up [54,55].

It is clear that vascular resections can be part of the surgical procedure frequently in hilar cholangiocarcinoma, because of its anatomical location, so, when portal vein is compromised, portal vein resections are clearly indicated as this do not affect negatively the prognosis, but, when the hepatic artery is involved in the tumor, their resection and reconstruction is more disputed due to the increase in morbidity without improving survival [56–58].

In both types of tumor, resection must be done avoiding the risk of hepatic insufficiency, with a liver remnant of > 25% of the hepatic volume, since usually the liver is not cirrhotic and this is the minimum amount of liver necessary to maintain their function.

Lymphadenectomy is another important issue, there is still much controversy in the literature around it, what's the exact role, if it is only useful for improving tumor staging, or if really plays a role in improving tumor control by increasing the radically of the procedure, at this moment there is no agreement between the authors [59,60]. Since lymph node dissection is not a procedure that increases mortality, most centers of experience recommend it as an integral part of surgical management, and the 2015 expert consensus on ICC treatment recommends that regional lymphadenectomy should be performed as a standard part of surgical therapy due to high incidence of node metastasis, its prognostic importance and the potential therapeutic benefit in decreasing locoregional recurrence [61].

3.2. Liver transplantation

Liver transplantation for cholangiocarcinoma was first reported in Nebraska, USA [62], but the most important experience nowadays is from the Mayo Clinic. The liver transplantation proposal arose from the need to extirpate tumors in which there was a contra-indication for

liver resection due to extensive hilar invasion, bilateral hepatic involvement or vascular encasement. Initial trials led to poor results with 5-year survivals below 50%; the Cincinnati Transplant Tumor Registry reported 28% of 5-year survival with a 51% tumor recurrence rate [63], reported in the first two years, for these bad results. Along with other reports in the world, liver transplant was contra-indicated in these cases [64–66].

The Institutions that perform liver transplantation in cholangiocarcinoma use very strict criteria, that include radiotherapy, chemosensitization, and appropriate patient selection for unresectable hilar tumors (intrahepatic and distal cholangiocarcinoma are not included in these protocols); staging laparotomy (before or during transplantation) is always done, and histological diagnosis is not always acquired by biopsy. The diagnosis can be made by the presence of suspicious biliary stenosis accompanied by positive brush cytology or positive intraluminal biopsy. The level of Ca 19-9 above 100 ng/ml in a malignant-looking stenosis is also considered diagnostic of cholangiocarcinoma. Aneuploidy demonstrated with digital image analysis (DIA) and fluorescent in situ hybridization (FISH) have been considered equivalent to cytology [67,68], but the sensitivities and specificities for CC in PSC patients never reaches 100% [69,70].

Something striking is that the results in the different centers are not the same, as well as the protocols of neoadjuvant, mainly with respect to the use of brachytherapy, and the type, dose and maintenance time of this chemotherapy [71].

3.3. Limitations of different results by group

A review of the experience of several high-volume transplant centers in the USA shows the differences between the groups in terms of protocol and outcomes; additionally, five-year survival by intention-to-treat is lower in this review, compared with the individual data of the center of greater experience: 53% vs. 58% by intention-to-treat analysis and 65% vs. 82% in transplant patients [71,72]. It should be noted that in the paper by Darwish Murad et al., 11% of the cases included in the analysis were not hilar cholangiocarcinoma exclusively (there were some with intrahepatic cholangiocarcinoma or distal cholangiocarcinoma associated with hilar cholangiocarcinoma), which could have affected the results.

3.4. Histological testing is a challenge

Even though getting a tissue for histological testing in intrahepatic cholangiocarcinoma is not a challenge, the final diagnosis must be very carefully established, due to the presence of many liver metastasis from different gastrointestinal tumors that can reassemble ICC [18]. Indeed, diagnosis of ICC is frequent in metastatic disease from a cancer of unknown primary (CUP) as demonstrated in two molecular studies that predicted the origin of the tissue in carcinoma in around 20% of CUP cases in liver [73,74].

The immunohistochemistry is the best way to ascertain the origin of the tumor, but to date, no specific markers exist. ICC tumor cells are positive for the biliary subtype of cytokeratins 7 and 19 and negative for HepPar1. However, some metastatic adenocarcinomas could present an IHC profile similar to ICC characterized by positive staining of CK7 and CK19 [75].

Tumor heterogeneity may be underlined by immunohistochemical expression and gene expression profiling. For example, expression of N-cadherin is significantly increased in ICC compared with extrahepatic cholangiocarcinoma (ECC), with a specificity for the diagnosis of ICC of 88% that may reach 98% if combined with CK7. Hepatocytic markers are observed occasionally in ICCs that are otherwise devoid of hepatocyte morphology, such as HepPar1 and arginase 1 [76]. Albumin mRNA in situ hybridization (ISH) is a sensitive and highly specific diagnostic tool to distinguish ICC, from perihilar adenocarcinoma but also from metastatic adenocarcinoma, particularly pancreatic ductal adenocarcinoma [74,76,77]. The ICC classification criteria could include mutations in some genes such as point mutations in Isocitrate dehydrogenase (IDH)1 and IDH2, described in 10–36% of tumors, and translocation of the Fibroblast Growth Factor Receptor 2 (FGFR2) tyrosine kinase fusions, described in 11–45% of ICC [78,79].

Biopsy in a hilar cholangiocarcinoma does represent a challenge, due to the difficulty in obtaining a sample of tissue suitable for diagnosis, in view of the poor performance that exists with current methods, either brushing or biopsy [80]. When there are predisposing entities such as primary sclerosing cholangitis, because of their known risk in the development of these tumors, the correlation between the images of a predominant stenosis and an elevation of the tumor marker Ca 19-9 has been considered sufficient for diagnosis. However, the diagnosis of cholangiocarcinoma by imaging criteria only, has so far not been accepted, as it has been established according to the guidelines for the diagnosis of hepatocellular carcinoma in patients with cirrhosis [81,82].

This fact does not represent a limitation in cases of hepatic resection [83,84], but in cases of liver transplantation it does, since in the published series, the percentage of patients with explants but without tumor is almost 50%. This is assumed to be due to a complete tumor response to neoadjuvant therapy, but in order to draw this conclusion, a pre-transplant positive histological diagnosis in all these cases is required; otherwise, it could be assumed that some patients without tumor were transplanted. This fact is accepted by one of the groups with more experience in transplantation in patients with hilar cholangiocarcinoma, who implicitly indicate in one of their publications that it is probable that patients will be transplanted within the current protocols without cholangiocarcinoma, although they suggest that this does not alter their final results [85]. However, this fact not only decreases the pool of donors for patients with liver disease, but also leads to a transplant in a patient without malignancy. The difficulty lies in the type of dissemination of hilar cholangiocarcinoma that is intramural (periductal-infiltrating or sclerosing), explaining the high rate of almost one third of negative or inconclusive biopsies in these cases [71].

The diagnosis of malignant bile stenosis, in the absence of histological evidence, requires a clinical course that corroborates this by either local or distant progression of the disease in images, or death due to deterioration secondary to the disease. If during a period of follow-up of 18 months or more, there is no evidence of progression of biliary stenosis (without histological corroboration), this can be assumed to be a benign lesion [86].

3.5. Chemotherapy

This is one of the topics where it is frequently found that results in the literature include different types of cholangiocarcinoma regardless of their location, and sometimes also including gallbladder cancer, which as mentioned at the beginning of this article, affects the interpretation of the results [87,88].

The information that exists about the use of adjuvant chemotherapy in these tumors is not abundant given its low prevalence and the fact that the resectability rate is only 20–35%, although the high rate of recurrence after resection would suggest that it is necessary to consolidate radical management with some type of additional adjuvant treatment [87]. Despite the lack of definitive proven survival benefit from randomized controlled trials, the available data suggest that chemotherapy can decrease the risk of distant relapse while radiotherapy (RT)/chemo-RT can reduce the potential local failure mainly in patients with node-positive or microscopically positive (R1) margins [87,89]. The National Comprehensive Cancer Network (NCCN) recommendations for intrahepatic cholangiocarcinoma, suggest observation for R0 resections, or some type of adjuvant therapy for R1; nowadays referral centers also advocate an adjuvant therapy in R0 patients [89,90].

The use of chemotherapy is currently clearly indicated in the

management of patients not operated due to unresectable, metastatic disease, or recurrent cholangiocarcinoma [87,91]. Almost all protocols include gemcitabine and cisplatin (or oxaliplatin if a contraindication for cisplatin exists), as the first line treatment on the basis of the significant survival benefit from the gemcitabine-cisplatin association over gemcitabine monotherapy in a large phase III trial [88]. Recent studies assessed the potential role of human equilibrative nucleoside transporter 1 (hENT1) expression as a predictive marker of gemcitabine efficacy in this setting [92]. Limited studies on second line chemotherapy have been conducted [93].

Targeted therapies (angiogenesis inhibitors, anti-EGFR antibodies, EGFR tyrosine kinase inhibitors, the MEK1 and MEK2 inhibitors, proteasome inhibitors) have also been tested for this tumor in different clinical trials, without results that changed the clinical practice. Hence, their use is still limited and these drugs cannot appear in a standard therapeutic algorithm for cholangiocarcinoma, due to the fact that genetic characterization and the overall molecular pathogenesis of this malignancy still remain poorly defined. Although the ideal therapeutic regimen will include drugs specifically tailored for the unique genetic make-up of the individual subjects, the genetic characterization of cholangiocarcinoma is a great challenge for the scientific community and for sure will be in the future for the treatment, not only for this tumor [40,41,94].

In the future, the identification of the fusion genes that are often drivers, can be targets for therapeutic interventions. A Japanese group performed comprehensive whole-exome and transcriptome sequencing of 260 cholangiocarcinomas, approximately 40% of this tumors had potential driver genetic alterations, and some of them were found exclusively in intrahepatic cholangiocarcinoma (FGFR gene) and others in extrahepatic cholangiocarcinoma (the PRKACA and PRKACB fusion genes) [95,96].

4. Conclusions

Despite the progress made in the treatment of cholangiocarcinoma, there are still many controversial points that will lead to an even greater development in the management of this disease. Undoubtedly, it is necessary to unify inclusion criteria in research protocols and publications, not only from the point of view of anatomical location, but also to advance more in basic research that allows a better classification and stratification of these tumors. Although attempts have been made to define genetic changes in cholangiocarcinoma, their use for classifying these cancers remains premature.

Disclosures

None.

Transparency document

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