ijtos 2023; doi 10.22376/ijtos.2023.1.4.13-22

International Journal of Trends on OncoScience

ISSN-2583-8431

Review article

Treatment of Cholangiocarcinoma

Advances in The Treatment of Intrahepatic Cholangiocarcinoma-ICLCA

Anand Mohan Jha[1], Dr. Vinayak B Angadi[2], Hadi Kuriri[3], Dr Manam Mani Srikanth[4*] and Dr. Asmita Rohan Sakore

[1]Post Graduate Department of Chemistry, M. L. S. M. College, Darbhanga L. N. Mithila University, Darbhanga, Bihar, India

[2] Assistant Professor, Department of Panchakarma, KAHER's Shri B. M. Kankanawadi Ayurveda Mahavidyalaya Shahapur Belagavi - 590003

[3]Department of Clinical Laboratory and Blood Bank, King Faisal Medical City for Southern Regions, P.O. Box 1003, Abha 61431, Saudi Arabia

[4] Post graduate, Dept of General Medicine, Meenakshi Medical College, Tamilnadu*

[5] Assistant professor, in PDEA, Shankarrao Ursal College of pharmacy, kharadi, Pune

Abstract: Intrahepatic cholangiocarcinoma (iCLCA) is a fatal hepatobiliary tumor becoming more common. For a long time, it was largely ignored as an uncommon cancer and commonly misdiagnosed as carcinoma of unidentified origin; nonetheless, significant clinical and research attention has been dedicated to it lately. First-line (gemcitabine and cisplatin), second-line (FOLFOX), and adjuvant (capecitabine) systemic chemotherapy is the accepted standard of treatment. iCLCA is genetically unique from hepatocellular carcinoma, with multiple targetable genetic abnormalities reported to be far. Indeed, FGFR2, NTRK fusions, IDH1, and BRAF targetable mutations have been thoroughly studied, and clinical evidence on pharmacologically targeting these oncogenic drivers is emerging. In addition, the role of immunotherapy has been investigated and is a hot topic. There is a need for therapeutic interventions for these ailments. Our review focuses on Intrahepatic cholangiocarcinoma, cholangiocarcinoma, Extrahepaticcholangiocarcinoma, Vascular Epidermal Growth Factor, IDH inhibitors, and Liver Cancer.

Keywords: Intrahepatic cholangiocarcinoma, cholangiocarcinoma, Extrahepaticcholangiocarcinoma, Vascular Epidermal Growth Factor, IDH inhibitors and Liver Cancer

***Corresponding Author**

Dr Manam Mani Srikanth , Post graduate, Dept of General Medicine, Meenakshi Medical College, Tamilnadu

Received On 4 July, 2023
Revised On 28 July, 2023
Accepted On 6 September, 2023
Published On 3 October, 2023

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Dr Anand Mohan Jha, Dr. Vinayak B Angadi, Hadi Kuriri, Dr Manam Mani Srikanth and Dr. Asmita Rohan Sakore , Advances in the Treatment of Intrahepatic Cholangiocarcinoma-iCLCA.(2023).Int. J. Trends in OncoSci.1(4), 13-22 http://dx.doi.org/10.22376/ijtos.2023.1.4.13-22

1. INTRODUCTION

Cholangiocarcinoma (CLCA), which develops through the epithelial organsof the extrahepatic and intrahepatic bile ducts, is the next prevalent initial cancer of the liver, ensuing hepatocellular carcinoma. Reliant on the tumor's anatomical position in esteem to the biliary tree, CLCA is categorized. The term "intrahepatic cholangiocarcinoma (iCLCA)" refers to CLCA that develops close to the second-degree (segmental) bile passageways in the liver's periphery. Perihilar CLCA is CLCAs located more distally in the biliary tree, beyond where the right and left hepatic ducts meet to where the cystic duct enters the common hepatic duct[1]. Fibroinflammatory biliary tract disorders with the value primary-sclerosing-cholangitis, Caroli's disease, hepatolithiasis, and liver fluke violations are prerequisites for iCCA. These disorders can prime to inflammatory variations in the bile ducts that path to the tumor. The possibility for perihilarcholangiocarcinomas is complex in entities with preexisting inflammatory biliary tract diseases. Early findings and action of these diseases can reduce the possibility of developing iCLCA[2]. Cirrhosis, viral hepatitis, obesity-associated liver disease, diabetes, and other hazards are reported[3]. These possible factors contribute to tenderness in the bile ducts, which can path the cells to grow abnormally and form a tumor. Initial detection and therapy for the underlying conditions can help reduce the possibility of developing iCLCA, and reduce the possibility of recurrence.

2. EPIDEMIOLOGY/RISK FACTORS

The mainstream of ICCs develops spontaneously without a known risk factor. The impending CLCA, specifically ICC, varies greatly worldwide. From instances per a million individuals between 1975 and 1979 to 8.6 cases per a million people between 1994 and 1999, the regularity of ICC has been rising in the USA[4]. The 7th decade of life is when diagnoses are most common and related to men; women are more diagnosed than men by about 50%[5]. This pattern persists acrossethnic/racial groups and sexes, affording to a newer analysis of ICCs from 1999 to 2013; the age-adjusted incident rate for women was 9.9 cases per a million person-years from 2011 to 2013 compared to 14.5 cases per a million person-years from 1999 to 2001.The mainstream of CLCAs found in PSC patients—about 50%—are found within the very first year of the disease's diagnosis, which means they are virtually always seen in individuals with dominant strictures. These are designated in Figure 1.

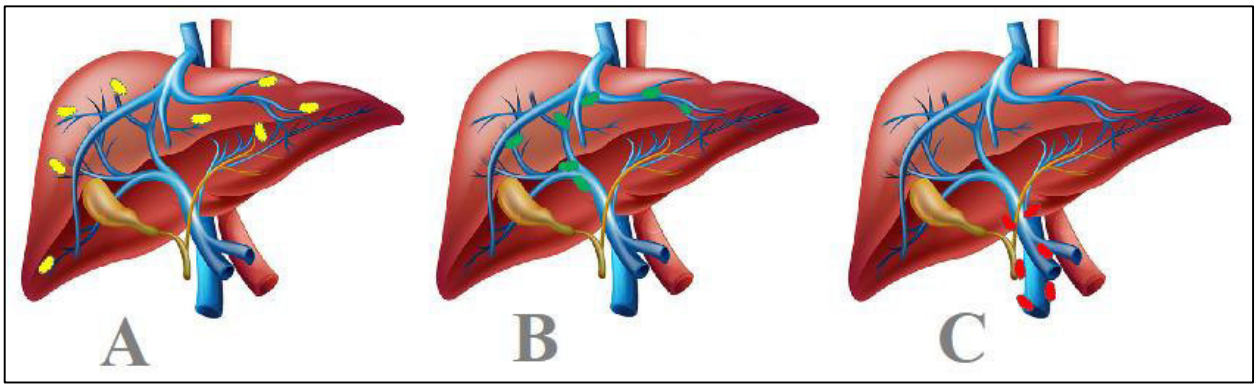

Fig. 1. Morphological discrepancies of Cholangiocarcinoma (CLCA). (A) ICLCA, Yellow Color. (B) Perihilar CLCA (PCLCA, Klatskin tumor, Green Colors). (C) Extrahepatic CLCA (ECLCA, Red Colors).

3. CLCA TUMOR SORTING

Three distinct kinds of ICCs are recognized: mass-forming, periductal infiltration, and intraductal growing. The mass-forming subtype makes up sixty to eighty percent of all ICCs, making it the most prevalent[6]. On imaging, this subtype of ICC often manifests as solid nodules separate from the hepatic parenchyma. Macroscopically, they are firm and resemble solid, well-demarcated, pale tumors lacking a capsule that is frequentlypoly-lobulated and lacks any visible bile duct connections. In this category, lymph node implants are frequently seen. The subtype of CLCA, which is both mass-forming and periductal-infiltrating, which makes up around twenty-five percent of all ICCs, is thought to be the greatest forceful variant shown in Figure 02.

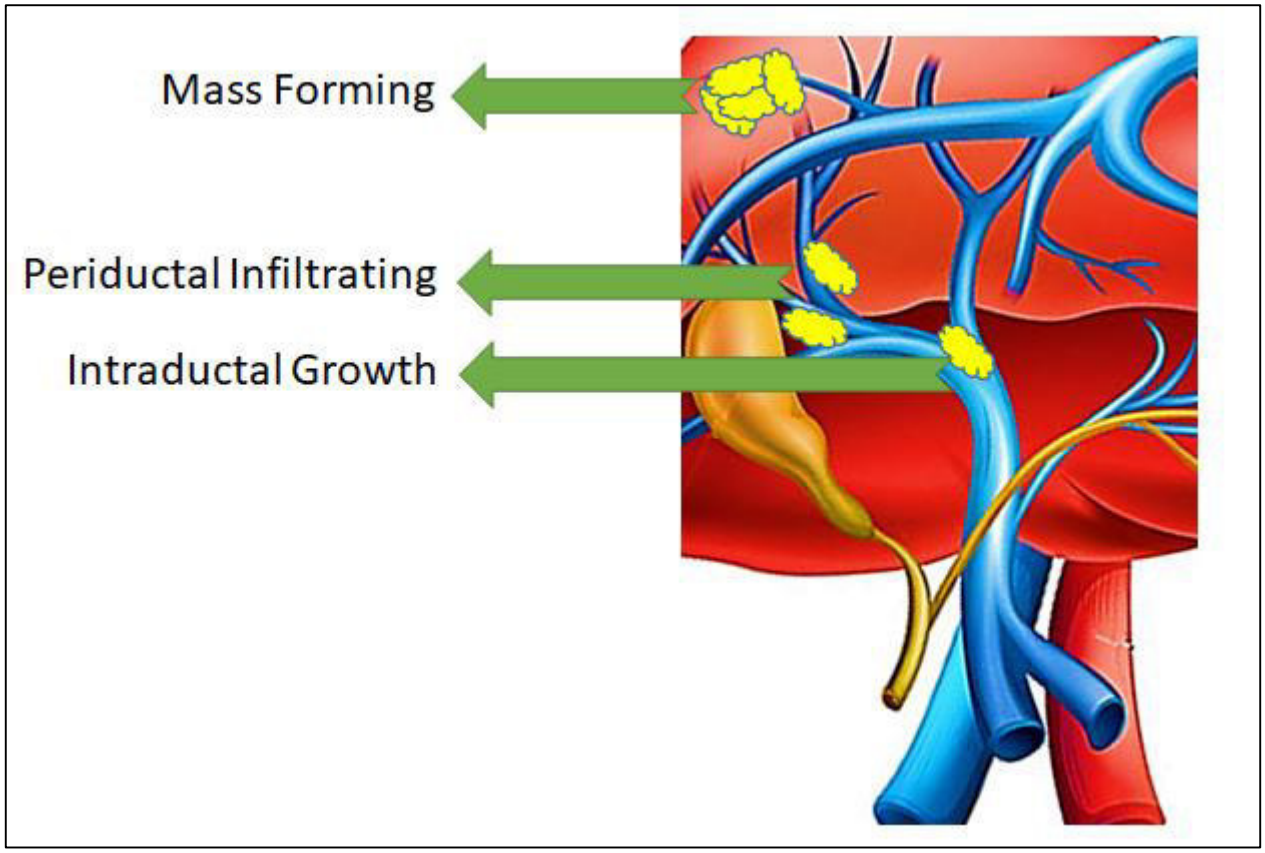

Fig 2: Variants of Substantial Cholangiocarcinoma

4. CLINICAL EVALUATION

4.1 Presentation

As a significance, individuals with ICC frequently experience ambiguous signs, including dull ache in the right upper quadrant and sometimes weight loss. This condition is not easy to diagnose as symptoms can resemble those of other diseases[7]. Imaging tests like echography or CT scans often confirm a diagnosis. Treatment routes for ICC include surgery, chemotherapy, and radiation. It is imperative to seek medical help as soon as possible, as ICC can prime to serious complications if left untreated. Initial identification and therapy can increase the chances of a positive outcome.ICC is typically discovered by accident in individuals through or without cirrhosis during cross-sectional imaging for any other purpose[8]. ICC can be grim to diagnose because it does not typically present with symptoms or cause pain until the cancer has advanced. The outcome is, Initial identification and therapy are critical as an approach to raising the chances of a positive outcome. For this reason, it is essential to monitor any deviations in the physique and seek medical help if anything arises to ensure timely identification and therapy of ICC.

4.2 Diagnosis

The process of metastatic hepatocellular-cholangiocarcinoma(HCLCA), CLCA, and innocuous liver lesions constitute the broad possible diagnoses for liver masses in individuals without a history of sclerosing cholangitis or cirrhosis[9]. It is imperative to study hepatic pathology and other cancers thoroughly. Colon cancer risk and examination for the past, alcohol history, travel history (liver flukes), iron studies (hemochromatosis), body mass index (BMI) (non-alcoholic steatohepatitis), copper studies (Wilson disease), viral and autoimmune hepatitis risk and serologies and acquaintance to hepatotoxins (Thorotrast, aflatoxin), among other factors, should all be evaluated[10]. An initial stage of the research should involve CEA, AFP, and CA 19 to 9. Echography or CT should be accustomed to sanction the diagnosis. In convincing cases, a biopsy may be essential. Finally, other tests, such as Alpha-Fetoprotein (AFP), may be required to identify the origin of the liver abnormality[11]. CEA, AFP, and CA 19 to 9 are important because they measure the quantities of certain proteins and enzymes in the lifeblood. Echography and CT scans allow doctors to understand the liver and its abnormalities better. An evaluation within the liver tissue helps to sanction the identification and determine the variety of abnormalities. Finally, Alpha-Fetoprotein (AFP) tests can be accustomed to identify tumors, infections, or other causes of liver abnormality.

4.3 Imaging

Global hypodensity and peripheral rim are typical Computerized tomography scan (CTS) results[12]. Augmentation of intrahepatic CLCA 591 in the portal venous and arterial phases. Nevertheless, only around 50% to 60% of cases on CT imaging show this typical look[13]. In around 50% of ICCs, bile duct dilatation is seen as peripheral to the mass. The global hypodensity and peripheral rim on CT imaging are owing to the prevalence of a large mass pushing against the liver parenchyma. The augmentation of intrahepatic CLCA 591 in the portal venous and arterial phases results from the increased vascularity concurrent with the mass. The bile duct dilatation peripheral to the mass is considered to be the mass obstructing the Cystic ducts and causing them to become dilated[14]. There may be capsular constriction close to the

mass in up to 20% of instances. Additional tests like endoscopic ultrasound with fine needle aspiration (FNA), endoscopic retrograde cholangiopancreatography (ERCP), and magnetic resonance cholangiopancreatography (MRCP), with biopsy should be carried out if CT imaging is ambiguous for ICC in addition still a high suspicion[15]. Capsular constriction is a condition that can happen in circumstances of Intra-hepatic Cholangiocarcinoma (ICC) and can make it demanding to detect ICC through CT imaging alone. To ensure the correct diagnosis, additional tests are looked for to provide more information about the mass. As such, it is vital to consider additional tests to confirm a verdict of ICC in circumstances of capsular constriction (Figure 3).

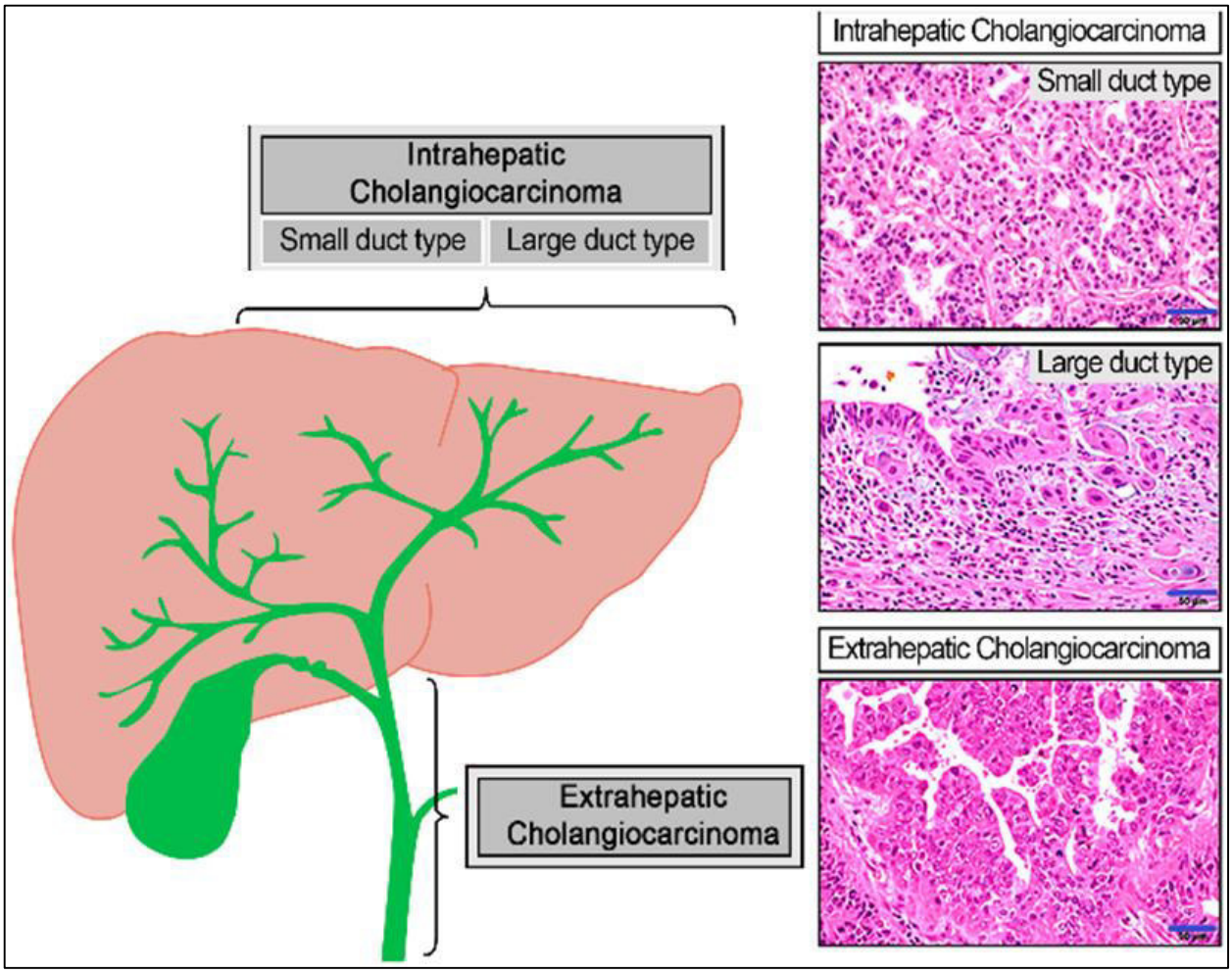

Fig: 3 - Known driver genes based on subtypes of CLCA and histologic characteristics (Scale bar = 50 μm). [16]

5. OPERATIVE MANAGEMENT

5.1 Diagnostic Laparoscopy

The inclination of the clinician still plays a large part in how diagnostic laparoscopy is used in hepatobiliary cancers. Fortunately, owing to the high popularity of subclinical metastatic disease, researchers advise a diagnostic laparoscopy before definitive surgery incision in ICC individuals[17]. The procedure is accompanied by high sensitivity and specificity for metastatic disease. Moreover, it could reduce the morbidity of surgery and improve overall survival. Up to 30% of those treated may have Subclinical metastatic disease that was not visible on beforehand cross-sectional staging imaging[18]. Therefore, laparoscopy is the best option for diagnosing ICC initially and providing effective treatment. Additionally, the laparoscopy procedure is minimally invasive and can be prepared in a shorter time frame than traditional open surgery, thus reducing the possibility of complications and providing better outcomes. Furthermore, laparoscopy has proven to be a harmless and active method for early diagnosis and therapy of ICC, allowing for quicker recovery times and improved conclusions equated to open surgery.

5.2 Liver Resection

The surgical techniques used on ICC patients are a hepatic ectomy with margins of error and a portal lymphadenectomy[19]. The surgery usually involves the exclusion of the tumor, along with surrounding lymph nodes and a serving of the liver. The intention is to ensure that any enduring cancer cells are destroyed. Following the operation, chemotherapy and/or radiation may extinguish any lasting cancer cells. Morbidity and transience following liver resection have significantly decreased over the past several decades and are thanks to perfections in preoperative assessment, intraoperative surgical procedures, and postoperative treatment. This is because preoperative assessment has improved, allowing doctors to identify better individuals at risk for complications. Additionally, surgical techniques have improved, allowing doctors to execute the surgery with less risk to the patient. Finally, postoperative treatments, such as chemotherapy and radioactivity, have remained refined to make them more effective in destroying

lasting cancer cells. As an outcome, the realization rate of cancer surgeries has improved significantly, giving patients a better chance for survival.

5.3 Vascular Resection

Significant vascular activation is frequently observed in ICC. The cardiovascular intrusion was established to be an autonomously unfavorable predicting variable in a multinational, multicenter evaluation of many patients with histologically confirmed ICCs who received curative-intent ablation[20]. The incidence of significant vascular activation was attendant with an amplifiedhazard of local tumor progression and death. The findings suggest that significant vascular activation might be avital factor in expecting the hazard of tumor development. Therefore, its presence should be reflected when making treatment decisions. By understanding the incidence of vascular activation, doctors can better understand the progression of the tumor and make more informed decisions for its treatment. Vascular activation can be assessed through imaging tests such as MRI or CT scans, enabling doctors to make more effective treatment decisions. Individuals lacking any vascular damage had the greatest median survival time, at 45 months, according to a study's examination of the effects of both macroscopic and microscopic vascular invasions on overall survival[21]. The study establishes that individuals with microscopic vascular offensive had a median persistence time of 38 months, while those with macroscopic vascular annexation had a median persistence time of only 15 months. The study concludes that vascular invasion significantly impacts overall survival. Therefore, it is perfect that the extent of vascular invasion is an important predictor of survival outcomes in individuals with this type of cancer.[22]

5.4 Minimally Invasive Resection

In the earlier few years, the adoption of a minimally invasive method for liver lesions has enlarged. This procedure, known as laparoscopic liver resection, offers several advantages over traditional open liver surgery. It can reduce recovery time, reduce postoperative pain, and reduce the risk of infection. Laparoscopic liver resection is much less invasive than open surgery, meaning the risk of complications is much lower[23]. It also allows for smaller incisions, reducing recovery time and postoperative pain. Additionally, it reduces the risk of infection since fewer incisions are made. According to earlier retrospective research, individuals who underwent minimally invasive liver resections experienced squatter hospital halts and fewer problems than those who endured open liver resections[24]. Minimally invasive liver resection also results in a lower risk of worries, such as bleeding and bile outflow. Furthermore, it can remaincast-off to treat tumors that are too complex to be preserved with open surgery. Minimally invasive liver resection involves making a few small incisions instead of a larger cut for open surgery. This allows the surgeon to access the liver without causing as much trauma to the surrounding tissues, resulting in a shorter hospital stay and a lower risk of complications. Additionally, the smaller incisions allow the surgeon to access tumors that would be too complex to treat with open surgery. This minimally intrusive surgery also provides individuals with a much shorter recovery time, allowing them to return to normal activities more quickly.

5.5 Adjuvant Chemotherapy and Radiation

Few observational or systematic investigations have used standardized adjuvant chemotherapy for individuals with RO (Reactive Oxygen) Extirpation. Combined treatment using gemcitabine and cisplatin may offer some survival advantage based on randomized managed studies of unelected biliary tract malignancies[25] Gemcitabine and cisplatin may be beneficial for individuals with R^0 Extirpation. However, further research is desired to confirm its efficacy. Additionally, studies should be directed to determine the optimal duration and dosage of the combination therapy. Randomized managed studies have recommended that Gemcitabine and cisplatin can offer a survival advantage to individuals with unelected biliary tract malignancies. However, it is still being determined if the combination is beneficial for individuals with RO resection, and further studies should be accompanied to limit the optimal dosage and duration for the combination therapy. The recent BILCAP study assessed the technique of prophylactic capecitabine between individuals with invasive gallbladder cancer and CLCA among those with resected tumors[26]. The BILCAP study originated that prophylactic capecitabine was concomitant with enhanced overall survival related to those who received standard care, suggesting a potential benefit for individuals who resected tumors. However, the study was limited to those with resected tumors only and did not consider those with R^0 Extirpation. Therefore, additional research is necessary to determine if combination therapy benefits individuals withR^0 Extirpation. Despite the probable benefit found in the BILCAP study, the ability of the combination therapy for individuals with RO Extirpation is still unknown, warranting further investigation.

5.6 Systemic, non-targeted, cytotoxic chemotherapy for iCLCA

Only certain randomized trials have been conducted on iCLCA. A great deal is grouped together in series and include gallbladder cancer (GBC), intrahepatic, perihilar, and distal CLCA. In several of these investigations, studies of biliary tract cancer (BTC) simply included CLCA and GBC. In one randomized research, chemotherapy was the best therapy for CLCA individuals[27]. In research that comprised individuals with pancreatic cancer, Glimelius and colleagues examined the 5-fluorouracil, etoposide, and leucovorin combination in 37 patients with CLCA[28]. Because of their distinct biological properties, iCLCA is likely to devour a better prognosis in self-determining the kind of chemotherapy administered.

6. SPECIALIZED REMEDIES IN ICLCA

6.1 EpGFR and VEpGF Inhibitors

Prior attempts were concentrated on blocking recognized targets associated with the carcinogenesis of CLCA, such as the Vascular-Epidermal-Growth-Factor (VEpGF) and its receptor (VEpGFR), as well as the Epidermal-Growth-Factor-Receptor (EpGFR). Randomized phase II studies were carried out, permittingthe compelling case for targeting EGFR in BTCs and encouraging preliminary findings from single-arm phase II trials that suggested the benefits of EpGFR inhibitors, either as single agents or in amalgamation with chemotherapy, but failed to prove the advantages of targeting EpGFR in advanced BTCs[29]. Modern molecular genetic analysis and significant research have provided new insights that have aided in the realization of tailored therapeutics for

BTCs, notably iCLCA. The molecular heterogeneity of BTCs has been shown by selective and entire exome analysis, which has also improved the genetic landscape of iCLCA(Figure-4).

7. FORTIFIED THERAPIES IN ICLCA

7.1 IDH Inhibitors

IDH mutations in iCLCA have remained recruited and characterized by a figure of organizations. iCLCA exhibits these alterations more frequently than extrahepatic CLCA[30]. iCLCA is also acknowledged to be more resistant to conventional therapies than other CLCA. Early studies have exposed that IDH mutations are concomitant with improved prognosis in iCLCA patients[31]. Further research is looked-for to understand the implications of these mutations fully. In particular, some studies have recommended that IDH mutations might be connected with a decreased risk of metastatic spread and a decline in tumor recurrence after conventional therapies. However, more research is needed to confirm these findings and better understand the mechanisms behind them. Mutant IDH develops a new capacity to create the oncometabolite 2-hydroxyglutarate (2-HG), which may be recruited in the blood and tumor while losing its usual enzymatic function. IDH inhibitors have been revealed to limit proliferation in tumor cell lines that carry certain IDH mutations[32]. These findings suggest that targeting mutant IDH with IDH inhibitors may be a promising therapeutic approach. Medical prosecutions have been accompanied to estimate the facility of IDH inhibitors in treating certain categories of cancer. The consequences of these tribunals are currently being analyzed. The analysis of these trials is expected to provide new insight into the capacity of IDH inhibitors for cancer treatment. It may open the door for more targeted approaches to cancer therapy.

8. TARGETED THERAPIES IN ICLCA

8.1 FGFR Inhibitors

The subsequent identification of FGFR2 fusions in ^{11}–45% of patients with iCLCA has quickly developed into an inhibitor of treatment with high potential. This Antagonizer, such as erdafitinib, has been established to be operational in treating iCLCA, with complete responses reported in up to twenty percent of individuals. Moreover, these Antagonizers have been recruited to have fewer side effects than additional forms of treatment. This is prospective because FGFR2 inhibitors specifically target the FGFR2 gene, meaning they have a more targeted effect and are less likely to affect other body portions. In addition, research has found that FGFR2 Antagonizers have effectively treated iCLCA in a wide range of individuals, with complete responses reported in up to 2^0%, indicating that they are an effective form of treatment[33]. These second-generation antagonists are an enhancement over the first-generation FGFR-activating multikinaseAntagonizer (such as dovitinib and ponatinib), which previously lacked the selectivity and efficacy to treat FGFR-driven tumors successfully. FGFR2 inhibitors are now becoming the standard of care for iCLCA, and are increasingly actuality castoff in synergistic with other remedies to improve outcomes and diminish the hazard of relapse. This is a breakthrough in administering iCLCA, and will improve patient outcomes significantly. Consequently, the enlargement of FGFR2 inhibitors is a cause for celebration among the medical community(Figure-4).

8.2 Tumor Genetics

Tumor genetics can distress the possibility that a tumor will be immunogenic; specific mutations cause aberrant tumor proteins to be expressed and presented by tumor cells via major histocompatibility structures or by antigen-presenting cells like macrophages in the microenvironment around the tumor[34]. This can trigger an immune response, prominent to activating T-cells that can attack the tumor cells. Mutations in the tumor cells can cause them to produce proteins the body recognizes as foreign. This triggers an immune response, activating T-cells that can attack the tumor cells and potentially eliminate the tumor. This immunogenic response can be exploited to develop treatments targeting tumors with these mutations. Tum MMR protein deficiency predicts ICI susceptibility across tumor types, which leads to the genetic hallmark of microsatellite instability (MSI), with high somatic mutation rates and elevated secretion of cancer-associated antigens. Spanning all tumor types, tumor mutational load (TML), also known as tumor mutational burden (TMB), is another genetic characteristic connected to the chance of responding to ICI. MMR proteins are accountable for the repair of DNA destruction. When they are deficient, errors accumulate in the DNA, leading to a growth in somatic mutations and manifesting many neoantigens in the tumor cells[35]. These increased mutational load escalations the chance of response to ICI therapy(Figure-4).

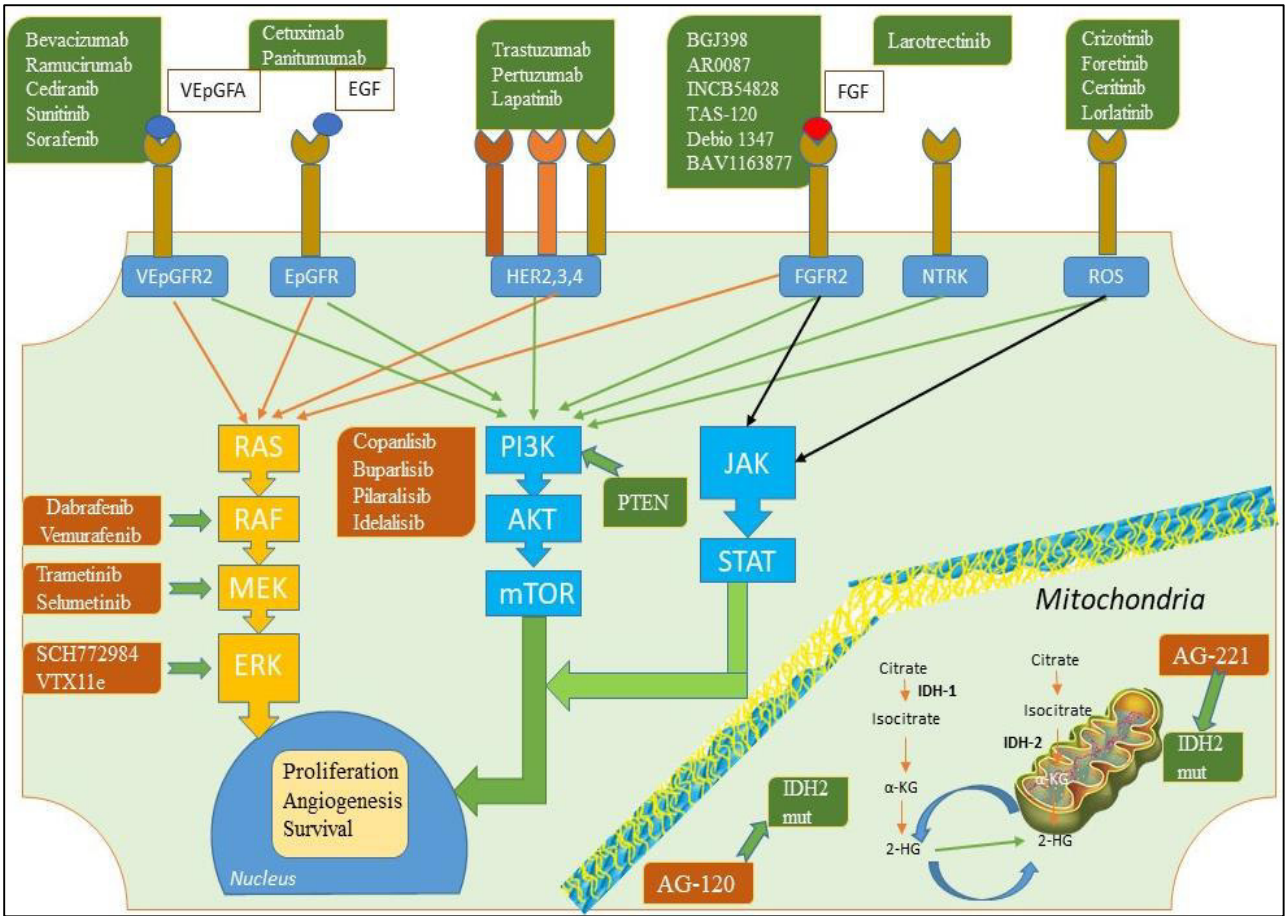

Fig 4 - Mechanisms of obtainable oncogenic signaling in iCLCA - ROS (Reactive Oxygen Species)

8.3 Recent Data About Cells of Origin of ICCS

The latest study has revealed various fresh perspectives into the biological genesis of iCC (a normal cell that gets the initial cancer-initiating mutation), indicating the possibility of various cell lineages. The clinical problem is the intricacy of histogenesis and the many molecular pathways behind the distinct development patterns of this disease. It is now thought that iCC can emerge from any liver cell owing to cellular plasticity mediated by remodeling processes. iCC develops from topographically diverse cholangiocytes at various levels of the biliary tree. Cylindrical mucin-producing cholangiocytes surround big BDs, while cuboidal non-mucin-producing cholangiocytes form ductules, which house bipotential hepatic progenitor cells (HPCs) (stem cell niche).

8.4 Biliary Drainage and Portal Vein Embolization

When an ICC tumor progresses regarding the liver hilum, it may result in biliary blockage. In the initial surgical situation with repairable illness and the palliative setting, biliary drainage may be necessary. Biliary drainage may be achieved via percutaneous or endoscopic approaches or surgical resection. Biliary stenting may also be used to relieve the obstruction. This can improve the symptoms and prolong the survival of patients with unresectable ICC. Biliary evacuation seeks to enhance liver function and stimulate appetite. Biliary evacuation is necessary because it helps to reduce the biliary pressure, which is caused by the accumulation of bile in the ducts[36]. This helps to develop the overall functioning of the liver and stimulate appetite, which can improve the worth of life for individuals with unresectable ICC. Preoperative biliary drainage may also enrich liver regeneration and lessen the fortuitous of subsequent liver failure. This can also reduce the hazard of postoperative complications, such as biliary strictures and bile leakage. Biliary evacuation can also reduce the necessity for postoperative biliary stenting and associated complications[37]. The biggest disadvantage of biliary drainage is bile duct colonization, which frequently leads to cholangitis. To ensure the realization of this procedure, it is essential to pay close attention to infection control and post-operative care to ease the hazard of bile-duct colonization.

9. RISK FACTORS

9.1 Chemical Exposure

Although several environmental exposure hazards, like radon, asbestos, and thorium dioxide contrast, were thoroughly characterized earlier, they are mostly historically important and will not be further treated here. Newer environmental exposure hazards, such as air pollution, mercury, and lead, are of more immediate concern and require further study and research. The effects of these hazards on human health must be better understood to ensure that people are not unduly exposed to potentially harmful levels of pollutants. Air pollution, mercury, and lead are particularly concerning because they can be found in everyday environments, such as our homes, workplaces, and schools. These pollutants can be demanding to distinguish and can have long-term impacts on human health, including increases in respiratory illnesses, neurological disorders, and cancer. Consequently, it is vital to research and understand the potential impacts of these environmental hazards. CLCA has been linked in two investigations to workplace exposure to 1, 2-dichloropropane (1, 2-DCP) and dichloromethane

(DCM) in a Japanese printing facility[38]. The research shows these two chemicals are carcinogenic and have increased CLCA rates in exposed workers. As such, it is essential to research and understand the potential impacts of such pollutants to prevent further harm to human health. To further shield human health, it is imperative to identify and limit exposures to similar chemicals that may also be linked to CLCA.

9.2 Biliary Tract Disease

A recognized ICC vulnerability is parasitic infection with the liver flukes Clonorchissinensis and Opisthorchis viverrini[39]. These flukes are communicated to individuals through ingesting raw or undercooked fish and can cause serious health problems such as liver cirrhosis and cancer. Treatment is available, but prevention is an excellent strategy. A key part of prevention is educating people about the risks associated with eating raw or undercooked fish and ensuring that those handling and preparing fish know proper food safety protocols. Additionally, improved sanitation and water treatment systems can help reduce the prevalence of flukes in the environment. These microbes were recently classified as category carcinogens by the World Health Organization because they produce bile duct inflammation that increases the risk of ICC[40]. Therefore, it is critical to maintain proper sanitary conditions and avoid contact with contaminated water sources to diminish the risk of contamination. Vaccination and proper medical treatment are also important to prevent the spread of this infectious disease. Additionally, it is critical to practice proper hygiene, such as frequent handwashing, to diminish the hazard of acquaintance with these carcinogenic microbes.

9.3 Liver Flukes

This was just lately demonstrated that ICC and viral hepatitis are related. Hepatitis C virus (HCV) and hepatitis B virus (HBV) infection and ICC have been linked in several research from Europe and Asia[41]. ICC is more common in individuals with chronic viral hepatitis than in the general population. Immunosuppressive therapy for chronic hepatitis can also increase the risk of ICC. Thus, it is vital to consider hepatitis screening in individuals with ICC. Patients with chronic viral hepatitis can have a higher risk of developing ICC due to the immunosuppression caused by the virus. Furthermore, immunosuppressive treatments for viral hepatitis can further increase the risk. Therefore, it is vital to consider screening for viral hepatitis in individuals with ICC in demand to identify those at higher risk. Screening for viral hepatitis in ICC patients can be especially beneficial, as it can reveal those at an increased risk of developing the condition and help inform immunosuppressive treatments that may further increase the risk.

9.4 Viral Hepatitis

This was just lately demonstrated that ICC and viral hepatitis are related. Hepatitis C virus (HCV) and hepatitis B virus (HBV) infection and ICC have been linked in several research from Asia and Europe. ICC is more common in individuals with chronic viral hepatitis than in the general population. Immunosuppressive therapy for chronic hepatitis can also increase the risk of ICC. Thus, it is imperative to consider hepatitis screening in individuals with ICC. Patients with chronic viral hepatitis can have a sophisticated risk of developing ICC owed to the immunosuppression caused by the virus. Furthermore, immunosuppressive treatments for viral hepatitis can additionally intensify the risk. Therefore, it is imperative to consider screening for viral hepatitis in individuals with ICC in directive to identify those at higher risk. Screening for viral hepatitis in ICC patients can be especially beneficial, as it can reveal those at amplified risk of developing the condition and help inform immunosuppressive treatments that may raise the risk.

10. CONCLUSION

Considering an involved tumor and immunological microenvironment with signs suggesting anticancer immune responses, ICI monotherapy has demonstrated minimal effectiveness in BTCs. However, the safety profile has been encouraging and comparable to other cancer types. Because of the strong and long-lasting outcomes of ICI treatments in MSI-high and MMR-deficient solid tumors, including CCA, testing for tumor MSI/MMR status is recommended for all patients with advanced biliary malignancies. We demand this examination at the time of advanced disease evaluation or after resection in cases with a severe recurrence risk; Patients are currently treated with advanced MSI-high or MMR-deficient CCA with pembrolizumab early in the course of advanced disease soon after first-line chemotherapy fails.

11. FUTURE DIRECTIONS

Severe iCLCA is still a tough condition to cure, and treatment is only palliative. Future research needs to continue to focus on genetic mutations (FGFR2, IDH, BRAF, and so on). We must learn which agents are well tolerated and which pharmacological combinations are most successful. Further research is needed to determine the use of ctDNA and tumor cells in detecting these genetic abnormalities, particularly those that contribute to medication resistance. The stroma of cancer-associated fibroblasts is also abundant in iCLCA. Targeting these cells therapeutically may also be advantageous in this malignancy. Indeed, these cells have been therapeutically addressed with CLCA suppressive effects in preclinical mouse models of iCLCA.

12. AUTHORS CONTRIBUTION STATEMENT

Dr. Anand Mohan Jha and Dr. Vinayak B Angadi, Hadi Kuriri conceptualized and gathered the data about this work. Dr Manam Mani Srikanth and Dr. Asmita Rohan Sakore contributed to this manuscript's writing and design.

13. CONFLICT OF INTEREST

Conflict of interest declared none.

14. REFERENCES

1. Compton CC, Byrd DR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A, Washington MK. Perihilar bile ducts. AJCC cancer staging atlas: A companion to the seventh editions of the AJCC cancer staging manual and handbook; 2012. p. 269-76.
2. Varma K, Singh A, Misra V. Cutaneous metastasis from cholangiocarcinoma presenting as thigh mass. J Clin Diagn Res. 2016 Sep;10(9):ED23-5. doi: 10.7860/JCDR/2016/21524.8584, PMID 27790452.
3. Talamantes S, Lisjak M, Gilglioni EH, Llamoza-Torres CJ, Ramos-Molina B, Gurzov EN. Non-alcoholic fatty liver disease and diabetes mellitus as growing aetiologies of hepatocellular carcinoma. JHEP Rep. 2023 Jun 9:100811. doi: 10.1016/j.jhepr.2023.100811.
4. Van Dyke AL, Shiels MS, Jones GS, Pfeiffer RM, Petrick JL, Beebe-Dimmer JL, et al. Biliary tract cancer incidence and trends in the United States by demographic group, 1999-2013. Cancer. 2019;125(9):1489-98. doi: 10.1002/cncr.31942, PMID 30645774.
5. Chapman MH, Webster GJM, Bannoo S, Johnson GJ, Wittmann J, Pereira SP. Cholangiocarcinoma and dominant strictures in patients with primary sclerosing cholangitis: a 25-year singlecentre experience. Eur J Gastroenterol Hepatol. 2012;24(9):1051-8. doi: 10.1097/MEG.0b013e3283554bbf, PMID 22653260.
6. Lendvai G, Szekerczés T, Illyés I, et al. Cholangiocarcinoma: classification, histopathology.
7. Aiyadurai S, Garg T, Sayeed T, Shahbaz Z, Adewole IO, Nguty Nkeng EN et al. A case of prostatic metastasis from intrahepatic cholangiocarcinoma: an extremely rare event. Cureus. 2023 Feb 17;15(2):e35100. doi: 10.7759/cureus.35100, PMID 36938164.
8. Ilkovska B, Trifunova BK. Human epididymis PROTEIN 4 values in different age groups of females in Bitola, North Macedonia measured by abbot alinity CI analyzer in 2022 year.
9. Fernandes ED, Almeida TR, Correa RR, Braga EP, Girão CL, Pimentel LS et al. Urgent liver retransplantation due to transmission of intrahepatic cholangiocarcinoma by donor: the first report in the literature. ABCD Arq Bras Cir Dig (S Paulo). 2023 Jul 7;36:e1740.
10. Shao M, Xu R, Qi W, Luo Z, Liao F, Fan S. Application of 18F-FDG PET/CT imaging in gallbladder inflammatory pseudotumor with elevated CA199: a case report and review of literature. Front Oncol. 2023 Jun 5;13:1136876. doi: 10.3389/fonc.2023.1136876, PMID 37342187.
11. Saeed U, Uppal MR, Uppal MS, Uppal R, Khan AA, Hassan A et al. Hepatitis C virus associated ALT, AST, GGT, Bili T, HB, HBA1C, CREAT, PT, aPPT, AFP, CEA, CA 125, CA 19-9, iPTH biomarkers, computed tomography and HCV burden of disease during pre COVID-19 era (2018-2019) and post COVID-19 era (2020-2022) in Pakistan. Braz J Biol. 2023 Jun 19;84:e271451.
12. Abou-Ghaida J, Ali AA, Anasseri S, Walker L, Barber T. Adenocarcinoma of an unknown primary site [presentation]. Diagnosis, and management. Cureus. Vol. 15(6); 2023 Jun 28.
13. Rimini M, Burgio V, Antonuzzo L, Rimassa L, Oneda E, Soldà C et al. Updated survival outcomes with ivosidenib in patients with previously treated IDH1-mutated intrahepatic-cholangiocarcinoma: an Italian real-world experience. Ther Adv Med Oncol. 2023 Jul;15:17588359231171574. doi: 10.1177/17588359231171574, PMID 37457302.
14. Do RK, Boll DT, Do RK, Boll DT. Diseases of the gallbladder and the biliary tree. InDiseases Abdomen Pelvis. 2023-2026: Diagnostic Imaging;2023(Mar 17):(121-30).
15. Patil S. The Accuracy of transabdominal ultrasound in obstructive jaundice as compared to magnetic resonance cholangiopancreatography.
16. Kim KH, Yi HS, Lee H, Bae GE, Yeo MK. Targeting the sequences of circulating tumor DNA of cholangiocarcinomas and its applications and limitations in clinical practice. Int J Mol Sci. 2023 Apr 19;24(8):7512. doi: 10.3390/ijms24087512, PMID 37108676.
17. Ruff SM, Pawlik TM. Surgical management of intrahepatic cholangiocarcinoma.
18. Olthof PB, Franssen S, van Keulen AM, van der Geest LG, Hoogwater FJH, Coenraad M et al. Nationwide treatment and outcomes of intrahepatic cholangiocarcinoma. HPB. 2023. doi: 10.1016/j.hpb.2023.06.019.
19. Raoof M, Dumitra S, Ituarte PH, Melstrom L, Warner S, Fong Y et al. Intrahepatic cholangiocarcinoma: ambitious operations and outcomes. JCO. 2016;34(4_suppl):345-. doi: 10.1200/jco.2016.34.4_suppl.345.
20. Fighera A, Cardano G, Mazzaro A, Zamboni GA, Ruzzenente A. Mansueto G. CT enhancement pattern of intrahepatic cholangiocarcinoma predicts the presence of metastatic lymphnodes at resection. European Congress of Radiology-ECR 2019.
21. Spiers HV, Jegatheeswaran S, Stathakis P, Sheen A, Jamdar S, Siriwardena A. Staging laparoscopy is unnecessary in the presurgical work-up of patients with peri-hilar cholangiocarcinoma (PH-CCA). HPB. 2021 Jan 1;23:S334-5.
22. Reames BN. EjazA. J Surg Oncol. 2017;116:133-9.
23. Tripepi M, Conci S, Campagnaro T, De Bellis M, Poletto E, Marchitelli I et al. Laparoscopic hepatic resection for intrahepatic cholangiocarcinoma: a narrative review of the current literature. Laparosc Surg;6:36-. doi: 10.21037/ls-22-17.
24. Piccolo G, Barabino M, Lecchi F, Santambrogio R, Nava C, Opocher E et al. Laparoscopic indocyanine green fluorescence imaging for intrahepatic cholangiocarcinoma. Am Surg. 2022 May 23:00031348221103659:31348221103659. doi: 10.1177/00031348221103659, PMID 35605160.
25. Borad MJ. Updates in the management of hepatobiliary cancers. J Natl Compr Canc Netw. 2023 May;21:(5.5):1-3.
26. Chrystle M, Sanyo D. Prolonged survival with first-line chemotherapy in advanced extrahepatic cholangiocarcinoma. BMJ Case Rep. 2023 Mar 1;16(3):e249681. doi: 10.1136/bcr-2022-249681, PMID 36863754.
27. Moffat GT, Hu ZI, Danner De Armas A, Ross JS, Javle MM, Knox JJ. Characterizing KRAS allele variants within biliary tract cancers. JCO.

2023;41(16_suppl):4088-. doi: 10.1200/JCO.2023.41.16_suppl.4088.
28. Glimelius B, Hoffman K, Sjoden PO, Jacobsson G, Sellstrom H, Enander LK, et al. Chemotherapy improves survival and quality of life in.
29. Boucher E, et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, openlabel.
30. Gopal P, Robert ME, Zhang X. Cholangiocarcinoma: pathologic and molecular classification in the era of precision medicine. Arch Pathol Lab Med. 2023 Jun 19. doi: 10.5858/arpa.2022-0537-RA, PMID 37327187.
31. Borger DR, Tanabe KK, Fan KC, Lopez HU, Fantin VR, Straley KS, et al. Frequent mutation of isocitrate dehydrogenase (IDH)1 and IDH2 in.
32. Cigliano A, Strain AJ, Cadamuro M. Signaling and molecular networks related to development and inflammation involved in CCA initiation and progression. Hepatoma Res;9(14). doi: 10.20517/2394-5079.2023.09.
33. Brown ZJ, Ruff SM, Pawlik TM. Developments in FGFR and IDH inhibitors for cholangiocarcinoma therapy. Expert Rev Anticancer Ther. 2023 Mar 4;23(3):257-64. doi: 10.1080/14737140.2023.2176846, PMID 36744395.
34. Feriz AM, Khosrojerdi A, Lotfollahi M, Shamsaki N, GhasemiGol M, HosseiniGol E et al. Single-cell RNA sequencing uncovers heterogeneous transcriptional signatures in tumor-infiltrated dendritic cells in prostate cancer. Heliyon. 2023 May 1;9(5):e15694. doi: 10.1016/j.heliyon.2023.e15694, PMID 37144199.
35. Chen K. Biomarkers and immunotherapy for colorectal cancer. Highlights Sci Eng Technol. 2023 Mar 21;36:1356-66. doi: 10.54097/hset.v36i.6252.
36. Comoglio P. Comprehensive evaluation of docking algorithms for therapeutic peptides ([doctoral dissertation]. Politecnico di Torino).
37. Nimura Y. Preoperative biliary drainage before resection for cholangiocarcinoma (Pro). HPB (Oxford). 2008;10(2):130-3. doi: 10.1080/13651820801992666, PMID 18773090.
38. Tavolari S, Brandi G. Mutational landscape of cholangiocarcinoma according to different etiologies: a review. Cells. 2023 Apr 22;12(9):1216. doi: 10.3390/cells12091216, PMID 37174616.
39. Pakharukova MY, Lishai EA, Zaparina O, Baginskaya NV, Hong SJ, Sripa B et al. Opisthorchis viverrini, Clonorchis sinensis and Opisthorchis felineus liver flukes affect mammalian host microbiome in a species-specific manner. PLOS Negl Trop Dis. 2023 Feb 13;17(2):e0011111. doi: 10.1371/journal.pntd.0011111, PMID 36780567.
40. Hembasat T, Chaiyadet S, Ittiprasert W, Smout MJ, Young ND, Loukas A et al. Peptide derived from progranulin of the carcinogenic liver fluke, Opisthorchis viverrini stimulates cell hyperproliferation and proinflammatory cytokine production. Res Sq. 2023. doi: 10.21203/rs.3.rs-2586058/v1, PMID 36993607.
41. Teixeira SV, Prates GS, Fonseca LAM, Casseb J. Can persistent infections with hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and human T- lymphotropic virus (HTLV) be eradicated? AIDS Res Hum Retroviruses. 2023 Jul 6. doi: 10.1089/AID.2022.0116, PMID 37409405.