Chirurgia (2023) 118: 553-567
No. 6, November-December

http://dx.doi.org/10.21614/chirurgia.2023.v.118.i.6.p.553

Intrahepatic Cholangiocarcinoma – Where Do We Stand Today? Literature Review

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Received: 17.10.2023
Accepted: 14.12.2023

Rezumat

Colangiocarcinoamele intrahepatice – unde ne aflăm acum? Review de literatură

Colangiocarcinoamele intrahepatice reprezintă afecţiuni maligne rare şi agresive care se dezvoltă de la căile biliare de ordinul doi până la ramurile biliare mai mici. Scopul acestei analize narative este de a discuta despre principalele provocări diagnostice şi terapeutice cu scopul de a ajuta oncologii medicali precum şi chirurgii oncologi să se familiarizeze cu acest subiect. Au fost revizuite articole care discută despre epidemiologie, histologie, diagnostic, management perioperator şi chirurgie, care au fost publicate din Ianuarie 2000 până în Septembrie 2023, incluse în

bazele de date Cochrane Library, PubMed, Embase, MedLine, Web of Science, Elsevier, Google Scholar. Principala problemă în astfel de cazuri este legată de faptul că majoritatea cazurilor rămân asimptomatice pentru o perioadă lungă de timp şi, prin urmare, sunt diagnosticate în stadii avansate ale bolii când procedurile curative sunt fezabile prin efectuarea sacrificiului visceral extins sau chiar mai rău, nu mai sunt posibile; cu toate acestea, cea mai eficientă strategie terapeutică pentru a îmbunătăți rezultatele pe termen lung rămâne chirurgia radicală. În acest sens, atenția a fost concentrată pe îmbunătățirea acurateței instrumentelor de diagnostic şi pe identificarea opțiunilor terapeutice care ar putea creşte şansele de realizare a rezecției complete. Colangiocarcinoamele intrahepatice reprezintă tumori rare şi agresive cu prognostic nefavorabil dacă rezecția radicală nu este fezabilă.

Cuvinte cheie: colangiocarcinom intrahepatic, creşterea intraductală, infiltrarea periductală, stadializare, embolizarea venei porte, rezecție radicală, chimioterapie

Abstract

Intrahepatic cholangiocarcinomas represent rare and aggressive malignancies developing from the second order bile ducts to the smaller biliary branches. The aim of this narrative review is to discuss about the main diagnostic and therapeutic challenges in order to help medical and surgical oncologists to gain familiarity in regard to this subject. Articles discussing about epidemiology, histology, diagnostic, perioperative management and surgery which were published from January 2000 to September 2023 included in Cochrane Library, PubMed, Embase, MedLine, Web of Science, Elsevier, Google Scholar databases were reviewed. Articles reviewed in the current paper came to demonstrate that tThe main problem in such cases is related to the fact that most cases remain asymptomatic for a long period of time and therefore are diagnosed in advanced stages of the disease when curative procedures are feasible after performing extended visceral sacrifice or even worse, are no longer possible; however, the most efficient therapeutic strategy in order to improve the long term outcomes remains radical surgery. In this respect, attention was focused on improving the accuracy of the diagnostic tools and on identifying non-surgical therapeutic options which might increase the chances of achieving complete resection. Intrahepatic cholangiocarcinoma represent rare aggressive tumors with poor outcomes especially if radical surgery is not feasible.

Key words: intrahepatic cholangiocarcinoma, intraductal growth, periductal infiltration, staging, portal vein embolization, radical resection, chemotherapy

Introduction

Intrahepatic cholangiocarcinomas (ICCA) are rare cancers that develop anywhere from second order bile ducts to the smaller branches of the biliary tree. Incidence of ICCA varies worldwide, with highest incidence found in Northeastern Thailand (85/100,000) and lowest incidence reported in Canada (0.4/100,000) (1). The Liver Cancer Study Group of classification, based on growth characteristics, identifies tumors as mass-forming, periductal-infiltrating, and intraductal-growing types (2-6). The TNM staging currently used is the one presented by American Joint Committee on Cancer (AJCC) in their 8th edition (7). Patients diagnosed with ICCA usually present at a late stage and most of them do not

benefit from surgical resection, which is the only potentially curative treatment at present (8-11). Diagnosis is set using imaging evaluations (ultrasound, contrast enhanced CT, MRI, and PET CT) (12) as well as biomarkers (usually CA 19-9 and CEA but novel biomarkers are emerging that could provide a more precise diagnosis and possibly a more accurate prognosis) (13). Endoscopic ultrasound (EUS) with fine needle aspiration (FNA) can be used to assess the presence of malignant regional lymph nodes (14). Biopsy is not required when curative surgery is indicated (15). Surgery is suitable in less than 30% of patients and should ensure R0 resection with negative margin (8-11). There is a strong case for lymphatic note dissection, most authors recommending it to be performed routinely (7,16-19). Laparoscopic or robotic surgery is safe to use as an alternative to open surgery, potentially bringing a benefit to perioperative morbidity with no impact on survival (20-24). Liver transplant has been used as treatment for both early lesions (25,26) of cholangiocarcinoma and for unresectable ICCA (27), both with good results in respective studies, but new prospective randomized study results are needed before establishing an indication for this treatment. Adjuvant chemotherapy is usually indicated and current standard of care is represented by 6 months administration of capecitabine (28). Neoadjuvant chemotherapy was analyzed in multiple retrospective studies proving efficient, but prospective studies are needed to determine a clear benefit (29). Several such studies are currently ongoing. For unresectable ICCA, systemic chemotherapy (30,31) can be associated with locoregional therapies such as: transarterial chemoembolization, transarterial radioembolization, thermal therapy, radiation, hepatic artery infusion of chemotherapy (32-34).

Materials and Methods

Literature on intrahepatic cholangiocarcinoma was searched in multiple databases: Cochrane Library, PubMed, Embase, MedLine, Web of Science, Elsevier, Google Scholar. The literature that we reviewed consists mostly of studies from January 2000 to September 2023, published in English. The review analyzes primary completed studies as well as some ongoing studies with preliminary results.

Incidence and Risk Factors

Patients diagnosed with intrahepatic cholangiocarcinoma (ICCA) are a small part of all patients with cholangiocarcinoma admitted for surgery (35,36). The incidence of cholangiocarcinoma (CCA) United States has been increasing for the past 5 decades, and global trends since 1990 are showing an increase in ICC and extrahepatic cholangiocarcinoma (ECCA) incidence worldwide (37).

Intrahepatic cholangiocarcinoma is slightly more common in males and more often presents after the age of 65 (38). The highest incidence is found in Asia, specifically in northeastern Thailand with an incidence of 85/100,000 which is the highest reported value in the world, to 0.4/100,000 in Canada1. Most authors attribute these variations in incidence to differences in local risk factors and maybe genetic predispositions (1).

Most cases in cholangiocarcinoma arise de novo (39), but several risk factors have been identified such as primary sclerosing cholangitis (PSC) (40 41), alcohol consumption (42,43), liver cirrhosis, viral hepatitis B and C (42). The presence of chronic inflammation of the biliary epithelium associated with bile stasis is a characteristic of most of the risk factors (1).

Another significant risk factor for the population of Asia, especially Thailand is the infection with Opisthorchis viverrini and Clonorchis sinensis both causing cholangiocarcinoma in endemic regions (44).

Histology

ICC is a cancer located in the periphery of the second-order bile ducts and can develop anywhere from the segmental ducts to the smaller branches of the biliary tree.

Microscopically, approximately 90% of cholangiocarcinomas are adenocarcinomas (3).

The Liver Cancer Study Group of classification, based on growth characteristics, identifies tumors as mass-forming, periductal-infiltrating, and intraductal-growing types (2-6). The common histological appearance is that of a well-differentiated or moderately differentiated tubular adenocarcinoma within a prominent, dense, desmoplastic stroma (6). Histological types of CCA include papillary adenocarcinoma, signet-ring carcinoma, squamous cell, mucoepidermoid carcinoma, lymphoepithelioma-like form carcinoma (3,6,45).

Mass-forming cholangiocarcinomas are most common, accounting for approximately 60-65% of all Icca (4,5,45,46) and it usually appears as a single mass lesion in the liver parenchyma. It is considered to arise in the small intrahepatic bile ducts (3,47) and it usually develops central necrosis or scarring (2). The periductal-infiltrating type is found in approximately 6% of ICCA and it presents as a growing longitudinal mass along the wall of the large bile ducts spreading along portal tracts (3,4). It is associated with aggressive behavior and a poor outcome (48). The intraductal-growing type usually presents as a tumor growing towards duct lamina (6,48,49). It can associate both infiltration of the parenchyma and longitudinal growth (50,51) combining characteristics from both mass-forming and periductal-infiltrating cholangiocarcinomas. These are responsible for approximately 25% of all cases (5,45).

Staging

The TNM staging system of American Joint Committee on Cancer (AJCC) for interhepatic cholangiocarcinoma is widely used to characterize advancement and resectability of ICCA, currently in its eight edition, consisting of four stages which are presented din *Table 1.*

Tumor Markers

Factors that impact the prognosis and can improve staging, in addition to those presented in the AJCC TNM classification, include elevation in serum of carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), lympho-neuro-vascular invasion and serum alkaline phosphatase, this being but a few of the biomarkers currently under analysis.

As presented by our colleagues from University of Medicine and Pharmacy, Cluj-Napoca, Lavinia-Patricia Mocan et al 13 in a recently published article, there is a wide list of biomarkers that could be used in assessing the diagnosis and prognosis of cholangiocarcinomas.

Non-invasive biomarkers that have been shown promising in the studies so far are represented by circulating nucleic acids, proteins, and cytokines. Circulating nucleic acids can be found in most fluids in the body and includes fragments of genomic DNA (cfDNA), RNA (cfRNA), and long non□coding RNAs (lncRNAs) (13, 52, 53). Proteins and cytokines – CA 19-9 and CEA are the most studied biomarkers in the serum (53, 54). The downside of using these markers is that both CA 19-9 and CEA provide a wide range of sensitivity (47.2–98.2%) and specificity (89.7–100%) (54). Recently one of the more studied cytokines is the CYFRA 21-1 (cytokeratin 19) as it was studied in a comprehensive meta-analysis and it showed a high sensitivity of 81% with a specificity of 86% for ICCA diagnosis53. As data suggest, CYFRA 21-1 showed a higher

Table 1. TNM staging according to AJCC, the eight edition

TNM staging according to AJCC 8th edition
T1a: solitary tumor ≤ 5 cm without vascular invasion
T1b: solitary tumor ≥ 5 cm without vascular invasion
T2: solitary tumor with intrahepatic vascular invasion or multiple tumors with or without vascular invasion
T3: Tumor perforating visceral peritoneum
T4: tumor involving local extrahepatic structures by direct invasion
N0: no regional lymph node metastases
N1: regional lymph node metastasss present
M0: no metastases
M1: metastases in other organs present
IA: T1a N0 M0
IB: T1b N0 M0
II: T2 N0 M0
IIIa: T3 N0 M0
IIIb: T4 and/or N1, M0
IV: any T, any N, M1

diagnostic ability when compared with CA19-9 or CEA and positively correlated with tumor stage (55,56) representing a separate predictor of lower recurrence-free survival and overall survival (55–57). Also, the urokinase-type plasminogen activator receptor (uPAR) (13,52,53) could be used for suggesting CCA diagnosis from HC with a high sensitivity of 95% and a specificity of 90% (13). Transforming growth factor-β1 (TGF-β1) differentiates CCA from benign inflammatory conditions as well as HC (13,52).

The list of analyzed biomarkers is broad, studied in comprehensive reviews, including: Mutations in TP53 and KRAS proto-oncogene, epidermal growth factor receptor (EGFR), mucin 1 (MUC1), MUC4, fascin (FSCN) expression (fibroblast growth factor receptor 2 gene (FGFR2) part of MAP kinase signaling, isocitrate dehydrogenase 1 and 2) (53,54,58). A number of clinical trials are currently ongoing and recruiting patients.

The KRAS mutation is relatively frequent in cholangiocarcinomas (23%) and it was strongly associated with a shortened survival and higher tumoral aggressiveness (58). Testing for KRAS mutations could be valuable for new treatments and improving prognosis of patients with multifocal cholangiocarcinoma (52-54, 58).

As concluded in the study by our colleagues - Lavinia-Patricia Mocan et al (13), the focus in the near future should be of validating or infirming the benefits of current biomarkers, not on finding new molecules (13).

Diagnosis

Patients with intrahepatic cholangiocarcinoma usually present with nonspecific symptoms (59) - pain or tenderness in the right upper abdomen (dull, continuous) night sweats, weight loss, cachexia, malaise(15,59). Jaundice can be present when the tumor grows towards the biliary confluence (8). Some cases are discovered incidentally in screening programs or during workup for abnormal liver blood tests in asymptomatic patients (60,61). Because of the lack of specific symptoms, the diagnosis of ICCA is often established when the patient is not suitable for surgical resection (8-11).

Transabdominal ultrasonography is the first imaging examination recommended in the presence of right upper quadrant pain and abnormal liver blood tests. Intrahepatic cholangiocarcinoma may be identified as mass lesions in the liver.

The diagnosis of pre-malignant lesions and also resectable stages of CCA by ultrasound screening highly improves clinical outcome (8,62,63). Until new biomarkers become available ultrasonography should be used in regions where ICC are endemic or incidence is rising (60,62,64).

A prospective study by Prakongboon Sungkasubun et al (62) analyzed 4,225 individuals for screening. ICCA was detected in 32 patients, and 21 of them were operated. Prognosis was very good in resectable cases with 100% survival after 1 year and 77.8% at 2 years, compared to the average survival of ICCA patients (90.9% and 61.5%) suggesting that ultrasound screening allowed for detection of early stage ICCA and premalignant lesions (11 detected with 100% 3 year survival) (62). Another prospective study by Narong Khuntikeo et al (63) comparing the results of a walk in group and a screening group, resulted in 762 CCA cases confirmed by histology reports, 161 patients in screening group and 601 in the walk-in group. Of all patients presenting cholangiocarcinoma, early-stage CAA was diagnosed in 84.5% in the screening group, compared to 21.6% in the walk-in group, thus proving ultrasound to be a safe and easy screening tool for cholangiocarcinoma detection (63).

Contrast enhanced computed tomography (CE-CT) is utilized at large to diagnose and stage cholangiocarcinoma (15,65). It characterizes liver masses and distant metastases and also brings information about vascular invasion and nodal involvement (66), although the specificity and for nodal involvement are not high. The arterial phase of the CE-CT helps to differentiate HCC from CAA (HCC more often demonstrates arterial enhancement) (12, 65), and guides anatomical resection (67). As a characteristic of CAA, the

fibrous stroma is accentuated in the delayed phase (65).

MRI has higher sensitivity and specificity than CE-CT for assessing spread of tumor along bile ducts because of the superior soft tissue contrast. It is accepted as the reference imaging examination for diagnosis and staging ICCA (65,68). Magnetic resonance cholangiopancreatography (MRCP) is the most precise method for characterization of the biliary system (65,69).

MRI, much like CE-CT, demonstrates low sensitivity and specificity for positive lymph nodes (70).

PET CT is an imaging technique that assesses the metabolic processes of a malignant disease. The sensitivity of PET CT for diagnosing intrahepatic carcinoma is high (>90%) (15,59,65). Two major meta-analyses aimed to assess the importance of PET CT in improving the diagnosis and correct staging by providing information on lymph node metastasis and distant metastasis, one published by Lamarca et al (71) in 2019 and the second one published by Huang et al (72) in 2020. Both meta-analyses present results that support the use of PET scanning for better identifying lymph node and distant metastasis (71,72).

Endoscopic ultrasound (EUS) with fine needle aspiration (FNA) can be used to assess the presence of malignant regional lymph nodes, as this would exclude curative oncological resection and liver transplant. We have found only one study that presents data on the use of EUS FNA in ICCA. The study performed by Malikowski T. et al (14) reports : For ICCA, endoscopic ultrasound detected a higher percentage of regional lymph nodes compared to CT/RMN (83% vs. 50%), with malignant regional lymph nodes identified in 4 of the 158 patients in the study cohort. The presence of at least one malignant lymph node was associated with a lower survival (353 vs 1050 days) (14), thus indicating the importance of EUS FNA in identifying malignant regional lymph nodes.

Preoperative biopsy is not necessary in cases where curative resection is planned and there is sufficient imagistic and biomarker evidence for the diagnosis (15). Biopsy should be obtained in unresectable cases, completed by immunostains, in order to start systemic or locoregional therapy (73).

Preoperative Management

Portal vein embolization (PVE) is frequently applied in patients with resectable tumors that would have a future liver remnant volume of less than 30% after resection, thus decreasing mortality due to post-operative liver failure (74,75).

The effects of PVE have been evaluated in multiple studies. Glantzounis G. et al (76) reports important decrease in postoperative liver failure and 90 days mortality after major liver resections. The study by Ebata T. et al (77) from 2012 had similar reports after evaluating 494 cases of patients that underwent PVE. Patients with chronic liver disease might not achieve sufficient liver growth. Even if it is a procedure that has low morbidity and mortality, the technique is limited by the slow growth of FRL and high rate of inadequate liver regeneration and also tumor progression (75,76,78,79).

Surgery

Surgical treatment of ICC is indicated when R0 resection with microscopic negative margins can be safely achieved (7). Resectability should consider a patient's comorbidities and assess their tolerance for major operations, and can be achieved with a correct preoperative evaluation (80). Surgery should achieve resection of the diseased liver segments and maintain sufficient liver remnant. If that is not possible, patients might require PVE, ALPPS or the emerging LVDA for hypertrophy of the healthy liver (81,82).

Regarding the margins of resection, Yu Shi Dai et al published a meta-analysis evaluating the influence of resection margin width in patients with ICCA. The analysis included 11 articles comprising 3007 patients and concluded that resection margin of more than 1 cm is desirable, especially for patients with no

lymph node metastasis and early-stage cancer. When this margin cannot be achieved, it is recommended to ensure at least a margin of 0.5 cm (83).

An interesting study conducted on the issue of resection margin length has been recently published by Zhu et al in The American Journal of Surgery; the authors demonstrated that resection margins smaller than 1 cm were significantly associated with poorer long-term survival in both anatomical and non-anatomical resection. When it comes to the influence of the resection margin length on the recurrence risks, the authors underlined the fact that only a resection margin higher than 1 cm seems to have a prognostic significance in order to distinguish cases which are at risk to experience recurrent disease. Therefore, in this study group, the incidence of recurrent disease was of 17.5 among cases with resection margins smaller than 1 cm and 8.3% among those with larger than 1 cm resection margins; moreover, when recurrence occurred, intrahepatic and extrahepatic metastases were more commonly encountered among cases with smaller negative resection margins (84).

Interestingly, in the study conducted by Spolverato et al the authors came to demonstrate that a linear relationship is observed between the dimensions of the resection margins and the disease free and respectively the overall survival; therefore, the authors underlined the fact that resection margins larger than 1 cm, respectively between 5 and 9 mm, 1-4 mm and positive resection margins are associated with incremental shorter progression free and overall survival ($p<0.01$) (85). Interestingly, in the study conducted by Lafaro et al the authors came to demonstrate that resection margin of 1 cm should be established as cut-off, a larger resection margin (for example of 1.5 cm having no impact on the long-term outcomes) (86).

Regarding the outcomes of patients with lower than 1 cm resection margins, although it should be expected to have a significantly higher number of cases with local recurrences, this fact is not always associated with a statistical significance (85). Another interesting aspect is not related only to the length of resection margins per se but also to the type of resection; therefore, in certain cases, patients submitted to anatomical resections had a significantly better overall survival when compared to those in which non-anatomical resections were performed irrespective of the length of resection margins (87). However, this finding was inconstant, other authors demonstrating that anatomical resections are associated with poorer outcomes due to the fact that cases necessitating anatomical resections usually present larger or multicentric tumors (84).

Another interesting correlation which has been established is the one between resection margins, lymph node status and overall survival; therefore, in the study conducted by Watanabe et al and published in 2019 the authors underlined the fact that if lymph node metastases are present, resection margin status has not such a strong influence on the long-term outcomes (88).

However, the issue of resection margins is strongly debatable in almost all solid tumors and has different significance; therefore, while for cases diagnosed with oral cavity cancer, breast, prostate, colon, bladder, thyroid, lung, uterine, and bronchus a positive resection margin is associated with significantly poorer outcomes, in kidney, renal pelvis or ovarian cancer positive resection margins are not considered as prognostic factors and therefore are not included in the cancer guidelines for the association of adjuvant therapeutic strategies (89). Therefore, these data come to underline the fact that resection margin itself represents a prognostic factor only in association with the histology of the tumor.

NCCN and AJCC/ UICC guidelines suggest that surgical resection is usually not suitable in the presence of multiple lesions or positive regional lymph nodes because these are often indications of metastasis (7,90,91).

Multicentric tumors have been considered contraindication for surgery, but more recent studies have demonstrated that resection of multiple lesions is feasible, and brings a small benefit in survival compared to systemic

therapy along with considerable post-operative mortality, especially in friable patients (90,92).

Laparoscopic staging is not routinely recommended (16), but can be used for patients with high risk of metastasis, otherwise not detected by the preoperative imaging evaluations (93). These are patients with high CA 19-9 levels, possible micro-vascular invasion, suspicion of carcinomatosis. For such cases, reports from multiple studies indicate that 34-37% of unnecessary laparotomy can be avoided with laparoscopic staging (93-95). In the 8th edition of the AJCC staging of intrahepatic cholangiocarcinoma and in the EASL-ILCA clinical practice guidelines, recovery of at least 6 lymph nodes is recommended for complete nodal staging (7,16-19).

The median OS after curative-intent resection is on average 30 months with a 5-year OS of approximately 30% (85,96-98).

In cases in which per primam radical resection is not feasible in order to achieve faster hypertrophy of the remnant liver, ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) gained popularity over the past years (75). A comprehensive review by Li J, Moustafa M et al (99) analyzed 102 patients who underwent ALPPS and showed a better survival in the patients of the ALPPS group when compared to palliative chemotherapy (26.4 months vs 14 months; 1, 2, and 3 year survival rates: 82.4%, 70.5% and 39.6% vs 51.2%, 21.4% and 11.3%, respectively). Several other studies show similar results (100). Even with good results, morbidity and mortality at 90 days is still high (21.2%), indicating that better selection of candidates and utilization of minimally-invasive surgery might lead to better results in the future (101).

Liver venous deprivation (LVD) refers to simultaneous embolization of the ipsilateral portal vein and hepatic artery. LVD before major hepatic surgery is safe and, according to the available literature, it generates a greater and faster liver hypertrophy than just portal vein embolization (102), but the literature on the topic is not sufficient to make a case for it at this point.

Intrahepatic cholangiocarcinomas can cause jaundice if the tumor extends towards the hilum. In resectable cases, preoperative biliary drainage is not recommended (75), colonization of the biliary tract and cholangitis being the major drawback of this technique. Biliary drainage is recommended in palliative treatment (103).

Recurrence is common in resected patients, especially in patients with tumor size greater than 5 cm, cirrhosis, lymph note metastasis, vascular invasion or multiple lesions. A study published by Gaya Spolverato et al (96) analyzed 563 patients undergoing curative-intent surgery. Results are as follows - average follow-up was 19 months. For the study cohort, treatment was resection for 98.8% of the patients and resection + ablation for the rest. Five-year survival was 23.6. Recurrence was present in 71.0 % of the patients with a disease-free survival of 11 months. Recurrence was intrahepatic only (59.8 %), extrahepatic only (14.5 %), or intra- and extrahepatic (25.7 %). Two hundred and ten (52.5 %) of these patients received palliative treatment, and 190 (47.5 %) patients were treated with systemic chemotherapy-only (24.2 %) or repeat liver-directed therapy (resection+ ablation in 28.5%, ablation alone in 18.7% and intra-arterial therapy (IAT) in 52.8%) ± systemic chemotherapy (75.8 %). Median survival from recurrence was 11.1 months (palliative treatment 8 months, systemic chemotherapy 16.8 months, resection/ablation /IAT 18 months). In the subgroup of repeat liver directed therapy, median survival of patients who were treated with resection of recurrent ICCA was 26.7 months and only 9.6 months for patients who had IAT (96).

Outcome of survival after surgery is related to several factors. Most studies have identified that R0 resection, the number of tumors (single versus multiple), presence of vascular invasion and lymph node metastases as the main factors of prognosis (80,96,104-111).

According to multiple authors, the presence of lymph node metastasis is the most important factor in predicting survival,

even more important than R0 resection (80,104-111).

In this regard, Scott Kizy et al (106) published a study in 2018 assessing the long-term survival of resected node-positive patients. In their study, they analyzed a SEER database of 169 node positive ICC patients. They report a median OS of 19 months after resection, comparable to the survival of patients with systemic chemotherapy alone (median OS 20 months), questioning the benefit of surgery in these patients and underlining the importance of preoperative assessment of lymph node metastasis in selecting proper treatment (106).

Minimal-invasive surgery (laparoscopic or robotic) is increasingly being used for resection of ICC. The last consensus conference on this topic was held in 2008 and concluded that laparoscopy is feasible when tumor size is < 5 cm and tumor is located in segments 2-6 (112).

Since then, numerous studies have evaluated the benefits of laparoscopic surgery in ICCA and showed improvement in estimated blood loss, operating room time, perioperative morbidity, most importantly with no difference regarding oncological outcome (R0 resections, lymphadenectomy performed, disease free and survival) (21-24,112,113).

Also, in trained centers, major laparoscopic hepatectomies have been performed with similar results indicating that minimal-invasive surgery is safe and significantly lowers perioperative morbidity and hospital stay, with comparable oncological result with open surgery (20-24).

In most of the world, ICC represents a contraindication for liver transplant, considering the high recurrence rate, microvascular invasion and poor tumor differentiation (25). Liver transplant for ICCA was evaluated by Sapisochin G et al (114) in 2016, and found the following results: median follow-up was 35 months; the 1, 3, and 5-years recurrence risk was 7%, 18% and 18% in ICCA patients with tumor smaller than 2 cm as opposed to 30%, 47% and 61% for patients with a tumor greater than 2 cm. The 1, 3, and 5-year survival was 93%, 84% and 65% for ICCA < 2 cm vs. 79%, 50% and 45% for ICCA > 2 cm (114) The results of the study are favorable for arguing that liver transplant could be the right tool for selected patients.

De Martin et al (115) published a study in 2020 comparing liver resection versus liver transplant in a multicenter analysis with a group of 75 patients diagnosed with ICCA or combined HCC-CCA. Liver transplant patients were found to have lower tumor recurrence (18% vs 46%) and a significantly higher 5-year recurrence free survival (75% vs 36%). In the liver transplant group, 5-year survival reached 69% and 65% in patients with tumors ≤2 cm and >2-5 cm. Survival was similar between ICCA and HCC-CCA patients (115).

A more recent study by McMillan R. (27) et al published in 2022 analyzed neoadjuvant chemotherapy followed by liver transplant in otherwise advanced, unresectable intrahepatic cholangiocarcinomas as follows - Patients undergoing liver transplant had to have stable disease for 6 months on neoadjuvant therapy with no extrahepatic disease. According to the study protocol, 32 patients were proposed for liver transplant and 18 of them received the transplant. For these patients, an average of 2 ICCA tumors were present, with a median cumulative tumor diameter of 10.4 cm. Survival at 1-, 3-, and 5-years was 100%, 71%, and 57%. There were seven cases on recurrence, all treated with systemic chemotherapy (27). Although recurrence rate was high, overall survival was highly improved when compared to systemic therapy alone, making a case for the use of liver transplant in unresectable cholangiocarcinomas.

Current extensive data on liver transplant for cholangiocarcinoma are missing (116). From the studies so far, it seems that liver transplant could be of use for "verry early" intrahepatic cholangiocarcinoma on cirrhotic liver as Sapisochin G et al (26) defines it, as well as in selected cases of unresectable ICCs which undergo neoadjuvant therapy with stable disease for 6 months prior to transplant (117-121). Further data are needed to assess these indications.

Chemotherapy after Resection

Adjuvant chemotherapy commonly is used after resected ICCA and aims to decrease chances of tumor recurrence. Studies that analyze adjuvant chemotherapy in resected ICCA alone are rare, most analyses including patients with other biliary tract cancer.

Current standard of care adjuvant therapy for patients with resected ICCA has become capecitabine for 6 months, since the publishing of results from the BILCAP trial (28). This was a phase 3, multicenter, randomized trial that included 447 patients, dividing them into two groups – receiving capecitabine or no adjuvant chemotherapy. It presented a better median OS (53 months in the capecitabine group vs 36 months in the no therapy group) and also a median recurrence-free survival of 25.9 months in the capecitabine group vs 17.4 months in the group that received no therapy (28).

The use of gemcitabine associated with oxaliplatin was evaluated in the PRODIGE 12 - ACCORD 18 study, but it failed to present any statistically significant benefit in recurrence free survival (122).

Gemcitabine associated with cisplatin (123) was also considered one of the better options for adjuvant treatment. Currently the ACTICCA-1 (124) study is ongoing and aims to compare the benefits of this treatment when compared to observation alone (124). JCOG1202 study is currently comparing the benefits of administrating S1 chemotherapy in patients with ICCA (125). The results for these studies are eagerly expected as they could shift the course of adjuvant therapy.

Neoadjuvant Chemotherapy

Currently, the indication for neoadjuvant chemotherapy in ICCA is unclear. Despite the theoretical benefits of neoadjuvant chemotherapy (126) (downstaging tumor size to ensure R0 resection, improving patient selection by identifying patients with aggressive disease and rapid progression, lowering micrometastatic disease, initiation of treatment during patient optimization for surgery) (127), there is no consensus on the matter of improving outcome when compared to upfront surgery.

A series of retrospective studies have demonstrated better results when neoadjuvant treatment is associated, most notably a study published by Mason MC et al (128), with a more than 4000 cohort study, that indicated a 23% reduced risk of death in patients who were administered neoadjuvant therapy (128). Also, the results published by Yadav S et al (29) indicate a benefit of neoadjuvant therapy when compared to just R0 resection+chemotherapy, showing significant improvement in OS (40.3 months vs 32.8 months respectively) (29).

Additional ongoing prospective trials are aiming at making a case for the routine use of neoadjuvant treatment in ICCA and other biliary tract cancers.

Regional Therapy for Unresectable ICCA

When resection for ICCA is not possible, a series of treatments have been studied for palliative treatment; moreover, this aspect is particularly important due to the fact that death usually occurs due to local disease progression and not due to distant spread. Development of regional therapies in order to provide local control and palliation has a significant importance due to the fact that it avoids side effects usually encountered when administrating systemic therapies (129).

These therapies can be used for selected patients and include percutaneous, vascular or radiation oncology procedures such as transarterial chemoembolization (130), transarterial radioembolization (34), thermal ablation (131), radiotherapy (32), and hepatic artery infusion pump chemotherapy (33).

Radiofrequency ablation consists of passing an electrical probe at the site of the tumor and creating a heating zone and coagulative necrosis. The rate of success depends on the location and dimensions of the tumor while the most commonly encountered side effects are represented by pain, cholangitis, infection

of the necrotized tumor or bleeding (129).

Vascular therapies consist of tumoral approach via hepatic artery in order to provide a better local control and consist of hepatic artery embolization, hepatic artery infusion, transarterial chemoembolization or transarterial radioembolization. All these methods are based on similar principles: inducing tissue hypoxia by blocking the hepatic arterial supply with an embolic agent, targeted distribution of chemotherapeutic agents at the level of the tumor and respectively yttrium infusion into the blood vessels of the tumor in order to induce mechanical embolization and local radiation delivery. In a multi-institutional study conducted by Hyder et al the authors came to demonstrate that these methods are associated with similar benefits in terms of survival; therefore, the median overall survival rate was of 13.4 months for patients submitted to transarterial chemoembolization, 14.3 months for cases submitted to hepatic artery embolization and 11.3 months for cases submitted to selective internal radiotherapy (132).

Microwave ablation represents another thermal ablative method which actions by generating heat by the use of an electromagnetic field. In the study conducted by Yu et al the authors reported a median overall survival rate of 10 months after microwave ablation; however, we should not omit the fact that a significant number of cases was submitted to other local or systemic therapies in association with microwave ablation; therefore, the improvement in terms of survival cannot be associated with microwave ablation (133).

Stereotactic body radiotherapy represents another therapeutic option for unresectable intrahepatic cholangiocarcinoma which is based on the principle of administrating a highly localized external beam radiotherapy with a high dose per administration; therefore, a higher dose of radiation is administrated on a specific volume of tissue, thus minimizing the effect of radiations on normal, healthy tissues. A recent study by Jung et al conducted on 58 patients with unresectable cholangiocarcinomas submitted to stereotaxic body radiotherapy reported a median overall survival of 10 months; in terms of postoperative complications, the authors reported that mild complications developed in 29% of cases while severe complications were encountered in 10% of cases, a single case of postprocedural death due to gastric perforation being seen (134).

Chemotherapy for Advanced Unresectable ICCA

With less than 30% of patients with ICCA being fit for surgery, systemic chemotherapy plays a key role in the management of unresectable patients. From the data we have so far, Gemcitabine + Cisplatin is the preferred first line of treatment for these patients. Multiple alternatives have been studied. Phelip JM et al analyzed the efficacy of mFOLFIRINOX (oxaliplatin associated with irinotecan and infusional fluorouracil) in a cohort of 191 patients, demonstrating inferiority of this treatment when compared to gemcitabine+cisplatin (median survival 11.7 months in the mFOLFIRINOX lot vs 13.8 months in the gemcitabine+cisplatin lot) (135). A Phase 2 Clinical Trial evaluated the addition of nab-paclitaxel to the standard gemcitabine+cisplatin, with improved preliminary results (19.2 months survival vs 13.8 for standard chemotherapy) (30,31).

Immunotherapy in Intrahepatic Cholangiocarcinoma

Due to the fact that standard chemotherapy is not associated with significant improvement in terms of survival, attention was focused on identifying other therapeutic lines which might be able to improve the outcomes of these patients. Therefore, the fifth pillar of cancer, immunotherapy (along with surgery, chemotherapy, radiotherapy, and targeted therapies) began to gain more popularity in the last decade (136). Nowadays, the most frequently cited immunotherapeutic options include adoptive cell therapies, peptide, and dendritic-

based vaccines alone or, most often, in association with chemotherapy. The largest studies published to date refer to programmed death-ligand 1 (PD-L1) targeted therapies such as Pembrolizumab or Nivolumab which are usually administrated as second or later line therapies; in terms of efficacy, administration of such products is associated with five to eight months survival (137). In order to improve these outcomes, ongoing studies came to propose association of immunotherapy with FOLFOX or gemcitabine-based chemotherapy. Therefore, in a recently published paper, the authors underlined the fact that association between gemcitabine, cisplatin, and programmed death-ligand 1 immunotherapy (durvalumab) led to a significant improvement in terms of survival without notable increase of additional toxicity. According to this study, patients receiving durvalumab in association of gemcitabine and cisplatin as first line therapy for unresectable cholangiocarcinoma reported a 24 -month overall survival of 24.9% while cases submitted to chemotherapy alone reported a 24-month overall survival of only 10% (138).

Conclusions

ICCA represent aggressive malignancies associated with poor outcomes especially if radical resection is not feasible. Therefore, a diagnosis in an earlier stage is important in order to improve the long-term outcomes. Moreover, association of perioperative chemotherapy seems to improve the long-term outcomes especially if radical resection is consolidated with adjuvant chemotherapy; meanwhile, when it comes to neoadjuvant therapies, there is no clear consensus, larger studies still being needed in order to establish a standard therapeutic approach.

Author's Contributions

Conceptualization: S.P.; C.B.; methodology: L.T.; validation: M.E.; C.D.; formal analysis: A.H.; investigation: C.M.; resources: Ce.S.; data curation: G.P.G.; L.P; writing — original draft preparation: Ca.S.; V.V.; writing — review and editing: I.B.; visualization: B.G; supervision: N.B.; project administration: M.S. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest and Funding

The authors have no conflicts of interest to declare and received no grants or funding for this study.

Competing Interests

The authors declare that they have no competing interests

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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