

Prognostic Factors in Intrahepatic Cholangiocarcinoma - A Systematic Review

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Rezumat

Factori de prognostic în colangiocarcinomul intrahepatic - revizuirea sistematică a literaturii

Introducere: colangiocarcinoamele intrahepatice (ICCA) sunt cancere rare, agresive, care se dezvoltă în căile biliare de ordinul doi sau mai mici. Scopul acestei revizuri sistematice a literaturii este de a discuta despre cei mai importanți factori de prognostic care afectează rezultatele pe termen lung ale acestor pacienți.

Material și Metode: articolele realizate pe această temă, scrise în limba engleză, publicate în perioada ianuarie 2000 – decembrie 2023 în Cochrane Library, PubMed, Embase, MedLine, Web of Science, Elsevier, Google Scholar au fost căutate și revizuite sistematic retrospectiv.

Rezultate: ICCA sunt de obicei cancere diagnosticate târziu din cauza caracterului asimptomatic, iar procedurile curative nu sunt adesea fezabile, doar 20 până la 30% dintre pacienți fiind apti pentru operație. Prognosticul acestei malignități agresive fiind nefast, cei mai importanți factori de risc, și respectiv de

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prognostic par a fi reprezentați de factorii socioeconomici, aspectul morfologic, dimensiunile, numărul și extensia tumorii precum și marginile de rezecție.

Concluzii: odată ce acești factori sunt recunoscuți și identificați pe scară largă în fiecare caz, clinicianul va putea găsi cel mai bun tratament pentru acești pacienți pentru a îmbunătăți rezultatele pe termen lung.

Cuvinte cheie: colangiocarcinom intrahepatic, prognostic, rezecție radicală, metastaze limfatice, chimioterapie, invazie vasculară

Abstract

Introduction: intrahepatic cholangiocarcinoma (ICCA) are rare, aggressive cancers that develop in second order or smaller bile ducts. The aim of this review is to systematically review the most important prognostic factors affecting the long-term outcomes of these patients.

Material and Methods: articles conducted on this issue, written in English, published between from January 2000 to December 2023 in Cochrane Library, PubMed, Embase, MedLine, Web of Science, Elsevier, Google Scholar were systematically researched and reviewed.

Results: ICCA are usually late diagnosed cancers because of the asymptomatic character, and curative procedures are often not feasible, only 20 to 30% of patients being fit for surgery. With the prognostic of this aggressive malignancy being baleful, the most important risk factors but also prognosis factors seem to be represented by socioeconomic factors, morphological presentation, dimensions, number and extension of the tumor as well as resection margins.

Conclusions: once these factors are widely recognized and identified in each case, the clinician will be able to find the best treatment for these patients in order to improve the long-term outcomes.

Key words: intrahepatic cholangiocarcinoma, prognosis, radical resection, lymphatic node metastasis, chemotherapy, vascular invasion

Introduction

Intrahepatic cholangiocarcinomas (ICCA) are rare cancers that develop in the bile ducts, from the second order bile ducts down to the smaller branches of that biliary tree. Incidence varies, highest incidence being reported in Asia (Northeastern Thailand), but reported incidence is rising in the recent years worldwide (1). Most cases of ICCA, being a cancer with no specific symptoms, present at a late stage when the tumor advances in size and local or distal extent so the option for surgical treatment might not be feasible (2-7). There are many factors that impact prognosis of ICCA, decreasing OS (overall survival) or RFS (recurrence free survival), analyzed in

various studies. Socioeconomic factors seem to have an impact in the evolution of the disease, with decreased OS reported over the age of 65, in men and in widowed patients (8,9). It is not clear if race and ethnicity play a role in prognosis of ICCA, results on this topic being various (3,8-18). Morphological presentation influences both OS and RFS, with periductal infiltrating type having the worst prognosis (19-21). CA 19-9 and CEA are still the most widely used biomarkers for assessing mostly the response to treatment but they seem to have also some prognosis value (22-24). The list of biomarkers being researched are wide and results are promising, but currently, no prognostic biomarkers are currently used in the clinical setting, deserving more innovative

research, and international validation and consensus. Tumor size over 5 cm negatively influences prognosis, but a clear correlation between size over this threshold value and OS or RFS has not been described (25-27). Most important prognosis factors we have found after reviewing the literature are the R0 resection margins obtained by surgery, increasing OS and RFS when compared to R1 resections (28-31), and presence of lymphatic node metastasis which severely negatively impact both OS and RFS, even in R0 resected patients (32,33). Vascular invasion, both micro and macrovascular seem to impact prognosis, but surgery in the presence of macrovascular invasion of vena cava or portal vein is reported in recent studies to have good results as long as R0 margins have been achieved. (34-37).

Materials and Methods

The PRISMA 2020 guidelines were followed in reporting this review. 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 December 2023, written in English. The review analyzes primary completed studies as well as some ongoing studies with preliminary results. The PRISMA 2020 flow diagram is presented in *Fig. 1*.

The systematic research was initially performed in August and repeated in December 2023 before ending the study, the keywords used for this research being: “intrahepatic cholangiocarcinoma”, “surgical treatment”,

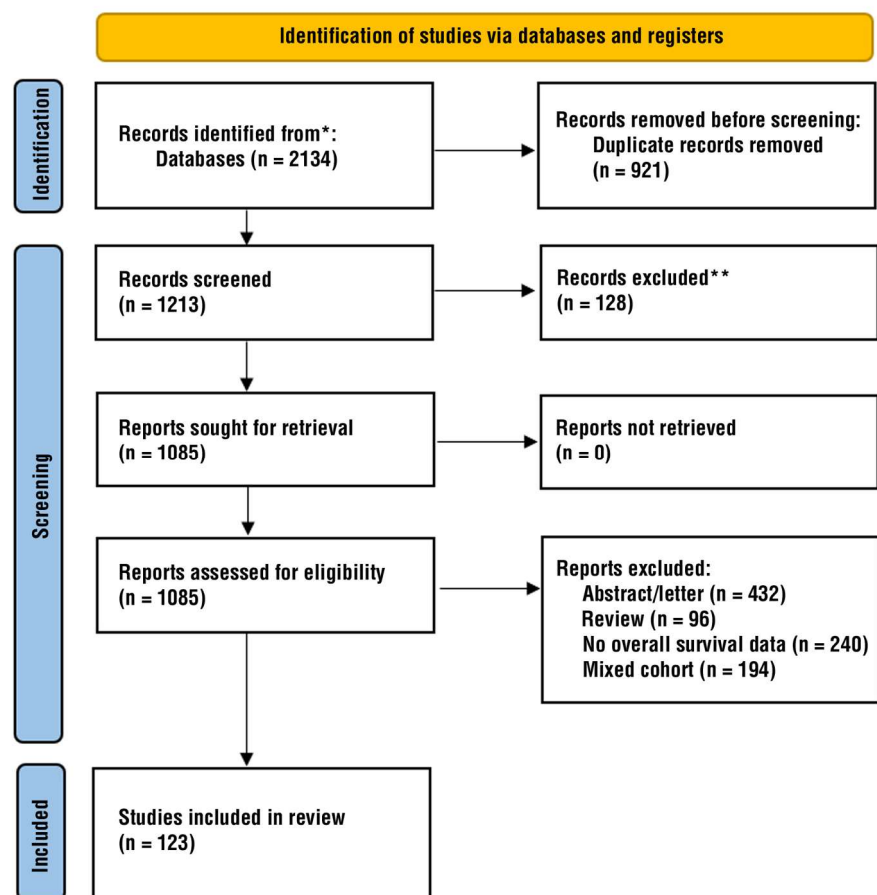


Figure 1. Prisma 2020 Flow diagram

“prognostic factors”. Two authors – CS and IB independently screened and assessed the selected papers while the third one – NB solved the discrepancies. The final selection of the studies was performed according to the PRISMA flow diagram presented in *Fig. 1*. Once these studies were identified and included in the current paper, the following characteristics were recorded: region/race, number of patients, age, sex, married status, morphological presentation, biomarkers, tumor size, number of lesions, resection margins status, extension, vascular, lymphatic or perineural invasion, administration of adjuvant or neoadjuvant therapies. Data collection was performed in a non-automated manner by the first reviewer (CS) and recorded data was assessed by the second reviewer (IB).

Results

A total number of 2134 studies were identified from the above mentioned databases. Before screening 921 duplicate studies were found and were therefore removed. Afterwards, 1085 studies were assessed for eligibility; 432 papers were excluded due to the absence of availability for full text manuscripts, 96 studies were excluded due to the absence of comparative univariable survival data, 240 studies were excluded due to the absence of overall survival data and 194 studies were excluded due to the existence of mixed cohorts. Finally a total number of 123 studies were considered as eligible and were included in the current review.

Socioeconomic Factors

(Age, Gender, Race, Ethnicity and Married status)

Age is established as an independent prognostic factor for intrahepatic cholangiocarcinoma. This is partially due to the fact that younger patients are more often fit for surgery and their adherence to treatment and oncological surveillance is usually better. Multiple studies have analyzed the relation between age and prognosis of ICCA. Although ICCA more is more often diagnosed after the age of 65,

its prevalence in younger population has increased (8,9).

A recent study by Rithva Rahman et al (17) analyzed the incidence of ICCA patients on a population of 14,083 patients diagnosed with biliary cancer (gallbladder cancer, ICCA, perihilar cholangiocarcinoma and distal cholangiocarcinoma) between 1993-2019. The study divided the patients in “younger” (aged 20-54) and “older” (55-84). They divided the time-range into three intervals - (1993 - 2001, 2002 - 2010, and 2011 - 2019), identifying an increase in incidence of ICCA and perihilar CCA, especially in young adults (APC 3.01, 95% CI: 1.84 - 4.20 and 3.93, 95% CI: 2.08 - 5.81) (17). This might mean that the age threshold of 65 years might not be applicable anymore for splitting populations with ICC.

A study by Jung Hun Kim et al (38) analyzed 133 patients diagnosed and treated between 2005 and 2016 at Konkuk University Medical Center, splitting the patients into two groups (under and over 65 years old). The median survival time was 338 days in the younger group (95% CI, 191.4 to 484.6) compared to 194 days in the older group (95% CI, 111.7 to 276.3) ($p=0.017$), with a better adherence to treatment on the < 65 y group and a lower recurrence rate (62.5% vs 72.1%) (38).

Race, ethnicity and gender seems to play a role in the prognosis of ICCA. Studies have been conducted mostly in the American continent. The results were variable, but most studies have concluded that Hispanics have a higher mortality than non-Hispanics, also with high mortality rates among American-Indian, American-Alaskan and Asian-Pacific islander population, but with Asian-Pacific islander women population mortality rate decreasing (8,13,39). In contrast, a study by Fenggang Ren et al (12) analyzing a SEER database of 30,954 patients, concluded that although race and ethnicity has a role in the prognosis of Hepatocarcinoma, it seems not to influence the prognosis in ICCA (12). In all of this studies, gender played a significant role in survival rate, with women having a better prognosis (3,8-18).

Defining the influence of age race and

ethnicity as a prognosis factor for ICCA is needed because it can guide risk factor assessment and screening for populations at higher risk of disease.

Married status was recently evaluated in a couple studies as a prognosis factor in ICCA. It was unanimous in these studies that married status plays a role in prognosis, with married patients having a better OS (overall survival) and CSS (cancer specific survival) than un-married / widowed ICCA patients (40-42). In one of these studies, there was no significant difference between never-married and married status, but with significant higher mortality in the widowed population (40).

Another socioeconomic factor which was considered in a handful of studies is the insurance status, and it seems to play a role in prognosis in multivariate analysis (43), but, with insurance notion being different for different states, its impact has not been analyzed properly yet.

Morphological Presentation

Based on growth characteristics, The Liver Cancer Study Group of Japan distinguishes tumors as mass-forming, periductal-infiltrating, and intraductal-growing types (44-46). The mass-forming cholangiocarcinomas are most usual, being the presentation form of 60-65% of ICCA (47,48), developing as a single mass lesion with central necrosis in the liver parenchyma. Periductal-infiltrating type (~6% of ICCA) (44) presents as a longitudinal tumor developed along the wall of large bile ducts. The intraductal-growing type (~25% of ICCA) (47,48) is a tumor usually growing towards the inside of the duct, and can associate characteristics either from mass forming or periductal infiltrating type (44,47).

Out of the three morphological types, intraductal cholangiocarcinoma seems to have the best prognosis (49-51), followed by the mass-forming type (19,27,52) and worst prognosis being attributed to the periductal infiltrating type with highest recurrence rate and high mortality (19-21). Some

authors found similar OS between intraductal and mass forming types (53).

Biomarkers

The high mortality rate of cholangiocarcinoma (CCA) is due, in part, to the lack of non-invasive approaches able to accurately detect this silent tumour at early stages, when therapeutic options can be potentially curative or may at least increase the overall survival of patients. No prognostic biomarkers are currently used in the clinical setting, deserving more innovative research, and international validation and consensus. Important efforts have been made in the last few years to identify accurate non-invasive biomarkers, by using innovative techniques and high-throughput omics technologies.

ICCA has a very high mortality rate, in part due to the absence of non-invasive tests that can accurately detect this cancer in early stage, when treatment options can be curative or, if not, significantly increase OS. Currently no prognostic biomarkers are clinically used, in await of international consensus.

Circulating nucleic acids represent parts of genetic material (DNA or RNA) circulating in various fluids (serum, bile, urine). Cell-free DNA was the first nucleic acid to be studied and correlated with tumor size and aggressiveness (54). Cell-free non coding RNA have been studied as biomarkers, showing relative specificity, long term stability and presence in multiple fluids. miR-21, present in serum, urine or plasma, have been shown to correlate well with tumor stage and OS (55). miR-26a, present in serum, correlated with tumor stage, metastatic disease, differentiation and survival, also decreasing significantly after surgery (56).

Of the protein based biomarkers, CA 19-9, CEA and CA 125 have been the most analyzed and most used. CA19-9 is the most used biomarker in CCA. The diagnostic sensitivity and specificity of CA 19-9 is not great, with 72% and 84% respectively (57). The use of this protein comes from its role in prognostic and evaluation of treatment response (58,59).

When it comes to surgery, preoperative elevated CA 19-9 is an independent marker of poor prognosis in ICCA (22-24). Also, preoperative elevated levels of CA 19-9 that do not decrease to normal postoperatively, is also an important indicator of poor prognosis (24,60,61).

Several studies demonstrated that patients with surgical resection of iCCA but with preoperative levels of CA 19-9 higher than 200 UI/ml have lower OS than those with normal levels (62). During chemotherapy, if levels of CA 19-9 decrease more than 50%, OS significantly improves (63)

CEA has been historically used as a biomarker for colorectal cancer, but in the last decades its use in ICCA increased. Diagnosis value is not high with low specificity and sensitivity (48%-90%, 42%-79%) (64) but CEA real value is in its prognostic value. CEA levels has been correlated with survival at 1, 3 and 5 years after resection (65,66), being confirmed in multiple factors, with highest predictive value when used in combination with CA 19-9 (67).

Since the objective of this article is not reviewing biomarkers alone, and since the available literature is rich in reviews of biomarkers that might predict outcome for ICCA, we will list the biomarker that seem to have predictive value.

Biomarkers associated with poor outcome: CYFRA 21-1, Urokinase-type plasminogen activator (uPA) and its receptor (uPAR), Platelet-to-lymphocyte ratio (PLR), C-reactive protein-to-albumin ratio (CAR), Tumor-infiltrating immune cells, Circulating tumor cells (CTCs), Fibroblast growth factor receptor 2 (FGFR2), Isocitrate dehydrogenase-1 and -2 (IDH-1/-2) mutations, BRAFV600E mutations, Human epidermal growth factor receptor 2/3 (HER2/3), Programmed death-ligand 1 (PD-L1) (59).

Tumor Size and Extension

Tumor size as prognostic factor in intrahepatic cholangiocarcinoma is a long disputed topic in literature. The AJCC 8th edition classification presents a cut-off value at 5 cm diameter as a

predictor of prognosis and is currently the widely used classification (50). While there are multiple studies that conclude that tumor size correlates with OS (25,68-70), other studies argue that tumor size is not an independent prognosis factor and that the OS is influenced more by the microvascular invasion and the tumor grade that larger tumors usually associate (71).

A meta-analysis published in 2015 by Michael N. Mavros et al. (33) concluded that, based on the studies included in the analysis, tumor size although does not influence recurrence-free survival, tumor size associates with the OS, lowering OS for every 1-cm increment (32,33,72,73).

Major registry studies as well as institutional studies support the notion that a tumor size of >5cm is an important predictor of OS (25-27). It is not clearly stated in the reviewed literature if any increase in tumor size beyond the 5 cm cut-off further correlates with the OS and further studies are needed for this assessment.

Resection Margins and Multifocal Tumors

Surgical resection remains the main therapy for the treatment of ICCA, but only 20-30% of patients are eligible for curative-intent surgery (74). The prognosis of this patients is highly increased for this patients (median OS 19-34 months) compared to patients that only receive systemic treatment (12 months). Surgical resection aims at achieving disease-free margin (R0) which is considered to be gold standard, and is an independent prognostic factor of increased survival (28-31). In patients with nodal disease (N1), microscopically positive resection (R1) seems to not influence the survival, but indicates a poor prognosis if the patients has no nodal disease (N0) (75). The presence of R1 margins associates with a shorter recurrence free survival (RFS). The width of the margin on R0 resection also was found to have a linear correlation with worsening of median survival (≤ 1 mm 15 mo, 2-4 mm 36 mo, 5-9 mm 57 mo, ≥ 1 cm 64 mo) (28,43,75). The incidence of R1 resections is

relatively high (16-23%) even in major tertiary hepatobiliary centers (28,30,31,75). This might be to the fact that ICCA patients usually present at advance stage, have large tumors and the ones that are fit for resection usually require major hepatectomy (28,75). The R1 resections are more common in patients that require extensive hepatectomy, potentially due to the fact that this patients associate large tumors, perineural invasion. 5 year survival for this patients was found to be less than half than the survival of patients with R0 resection and a margin of more than 1 cm (19,31,49,75).

In a large meta-analysis published earlier this year by Yu Shi Dai et al (76), included 11 papers and over 3000 patients. In nine of their papers, 1, 3 and 5 year RFS and OS were compared between ≤ 10 mm group and ≥ 10 mm group, with the ≥ 10 mm margin group having a significant improvement of OS and RFS. Also in a subgroup analysis, ≥ 5 mm margin resection had a better prognosis than ≤ 5 mm margin group.

Current literature estimates that approximately 50% of patients with ICCA develop multiple hepatic lesions before developing distal metastasis (33). Currently multifocal disease is classified as T2 in the AJCC classification and if lymph node metastasis is not present it is assigned as Stage II (50). Some authors suggest that, because multifocal disease is usually caused by hematogenous intrahepatic spread (metastasis), the clinical prognosis of this patients is closer to those with M1 disease rather than those with early disease (77,78). Furthermore, patients with multifocal ICCA are usually treated with chemotherapy rather than surgery, and its not particularly clear if these patients benefit from resection (77,78). A recent study by Linlin Yin et al (79) analyzed the relation between primary tumor resection and prognosis in patients with multifocal ICCA. This study enrolled, SEER database, 580 patients that were referred to surgery and 429 patients who were treated with chemotherapy. They found that primary tumor resection improved significantly the OS in multifocal ICCA. The median

survival was 25 months for the resected patients vs 8 months for those treated with systemic therapy. The 1,3 and 5 year survival was also disproportionate(1 year 79.34% vs 32.17%, 3 year survival 34.01% vs 4.72%, 5 year survival 12.91% vs 0%). As a conclusion of this study, patients with multifocal disease have a worse OS than patients with a single lesion and resection of primary lesion for patients with multiple tumors greatly improves survival (79). In other studies, such as the one of Dario Ribero et al (31) from 2012, or more recently the study of Stefan Buettner et al (80) (2019), the results suggest that resection of multifocal ICCA does not improve prognosis. In Stefan Buettner's study (80) study, results indicated that patients with multifocal ICCA associate lymph node metastasis (25.4% vs 15.5%), present more often distal metastasis (15.8% vs 5.9%), require usually major resections (72.4% vs 55.9%), have more complications after surgery (49.7% vs 41.8%) and usually have higher chance of recurrence (74.1% vs 52.4%). The median OS was 43.2 months for single lesions, 21.2 months for two lesions and 15.3 months for three or more tumors. This suggests that multifocal disease is an independent factor of poor prognosis, but, although chemotherapy is usually the suggested treatment for this patients (81,82), when comparing the OS of resected multifocal ICCA patients with the median OS for systemic chemotherapy or loco-regional ablative therapy, rarely exceeding 12 months (83-88), surgical resection seems to improve OS.

Vascular Invasion

Vascular invasion is considered to be one of the strongest predictors of worse prognosis in patients with ICCA after surgery. Vascular invasion incorporates macrovascular invasion (MaVI), which represents tumor invasion into major vessels. MaVI can be identified before surgery through radiological imaging exams. On the other hand, microvascular invasion (MiVi) is defined as the presence of tumor emboli in portal radical vein, vascular space between endothelial cells or capsule vessels

(89). Detection of MiVi is usually achievable only through microscopical examination. According to the AJCC 7th and 8th edition classification, the detection of vascular invasion splits tumors into T1 and T2 categories (50). A recent large study by Yifan Chen et al (89) analyzed MiVi in a lot of 700 patients, presenting large differences in both survival and RFS OS: 1,3 and 5 years was 55.6, 27 and 18% in the MiVi positive and 76.3, 44.0 and 33.0% for MiVi negative group.; RFS rates: 1,3 and 5 years after curative resection was 35.9, 23.2 and 19.3% for MiVi positive group and 57.8, 40 and 35.7% for MiVi negative group). These results are consistent for most of the literature we have found on this topic (89–96).

At initial diagnosis, approximately 50% of patients with ICCA have invasion in one of the surrounding organs or major vascular structures such as vena cava or portal vein, decreasing median survival of this patients severely (20 months vs 41 months for patients with no vascular invasion) (36). Traditionally, invasion in vena cava or portal vein has been considered a contraindication for surgery. Recently, studies have been published that indicate that association of major R0 hepatectomy with vascular resection did not significantly reduce OS when compared with patients that did not need vascular resection (34–37). Firstly, a multi-institutional analysis was published in 2017 by Reames et al (36) comparing the outcomes of patients that associated vascular resection (portal vein or vena cava) with those that did not, resulting in similar OS and RFS. Similar results have been found in the studies of Conci et al (35), Shahzad et al (34) and Palen et al (37). The literature review of Alikhanov et al (96) presented that best results in case of vascular invasion are obtained with multimodal approach, including neoadjuvant chemotherapy, radiotherapy, and adjuvant treatment for ICCA (96).

Perineural Invasion

Perineural invasion (PNI) has been studied and recognized as a predictor of worse progno-

sis in various cancers. Studies of its impact in ICCA are not as rich as in other cancers and the results are not as conclusive. The study of its impact in ICCA was studied for over 20 years but still current results in various studies are conflicting. As it stands right now, perineural invasion is not considered a prognosis factor in AJCC 8th edition (50) classification or in other guidelines. While there are many studies that analyze and report its significant impact in OS and RFS (97), others concluded that its impact is not significant. Ahm et al (98) in a study that comprised 292 cases of resected R0 ICCA, found in univariant and multivariant analysis that LNI is an individual prognosis factor for both OS and RFS. Also, on a smaller batch of patients, Fisher et al (73) reported same results. A recent published study by Zhang et al (99) on a lot of 150 patients also reported same findings. On the other side, we found two studies (100,101) that report through univariant and multivariant analysis that PNI did not significantly influence either OS or RFS. Larger studies and meta-analysis are required to determine if PNI actually can be considered and independent prognostic factor.

Lymph Node Metastasis

Lymph node metastasis has been proven to have significant impact on outcomes and is currently considered the most important prognosis factor in ICCA (32,33). The impact on OS is important, with studies reporting that N1 patients sometimes live half as much as N0 patients (25,28,69,72,92). Therefore, presurgical assessment of LNM is of high importance, especially in high risk patients who might not benefit from extensive surgery, but its not always possible (43). Presurgical imaging routinely performed, as performant as they are, often can not provide an accurate prediction of staging. Lymph node dissection is important in determining the presence of lymph node metastasis, provide an correct staging and asses the prognosis accurately. Neoadjuvant chemotherapy might be useful for improving outcome in patients with

lymph node metastasis (102-106). Minimally invasive surgery harvesting at least 6 nodes is of use, since liver transplant can only be performed on LNM negative patients (104-109). The AJCC 8th edition staging system recommends routine harvesting of six lymph nodes to have adequate N staging (50,82). Multiple studies on the benefits of routinely performing lymphadenectomy have been published with conflicting results.

A study published by Hu et al (110) analyzed a lot of 422 patients. 73 patients had undergone surgery that associated routine lymph node dissection (LND) out of which 15 had confirmed lymph node metastasis. Recurrence rate 65.8% (LND) and 63.9% (no LND). The analysis of survival showed that, neither the OS (LND 32.2 months vs. no-LND 46.2 months; $p = 0.16$) or RFS (LND 23.1 months vs. no-LND 17.0 months; $p = 0.09$) (110). Another review and meta-analysis published by Zhou et al (111) included 13 studies and over 1300 patients, revealing only small differences between the LND and no-LND groups regarding both OS and RFS, concluding that LND does not seem to increase OS or RFS, but on the contrary, morbidity was higher in the LND group (111). In contrast, there are multiple studies that indicate a better OS and RFS in patients that routinely underwent LND (112-116).

Adjuvant and Neoadjuvant Chemotherapy

Adjuvant chemotherapy is used after resection of ICCA and the aim of this is to prolong RFS. The positive response to chemotherapy is an important prognosis factor. Most studies analyze adjuvant therapy for ICCA together with other biliary cancers.

Since the publishing of the results from BILCAP trial (117) standard adjuvant therapy for ICCA after resection has become capecitabine for 6 months. BILCAP trial (117) is a phase 3, multicenter, randomized prospective clinical trial including 447 patients, dividing them in two groups – patients that have been administered oral capecitabine or no treatment after resection. The results of

this study show that patients that receive capecitabine have better OS (53 months vs 36 months) and also a better RFS (25.9 months vs 17.4 months) (117).

Other treatments such as Gemcitabine + oxaliplatin use has been evaluated in the PRODIGE 12 - ACCORD 18 trial but it showed no significant improvement in OS and RFS associated with the use of this treatment (118).

The association of Gemcitabine with cisplatin (119) is also considered one potential treatment following resection of ICCA. This treatment is evaluated in an ongoing study ACTICCA-1 (120) comparing the benefits of this treatment when compared with no chemotherapy (120). Another ongoing study is the JCOG1202 study and it aims to evaluate ICCA response to the administration of S1 chemotherapy (121). Results for this studies are highly expected as they could have significant impact in common practice.

As for neoadjuvant therapy, currently, there is no standard indication of it. Although it has theoretical benefits. Despite the theoretical benefits of neoadjuvant chemotherapy (104) (downstaging tumor size, facilitating R0 resection, better patient selection by identifying patients with rapid progression, lesser chance of micrometastatic disease, ensuring time for optimizing patient for surgery) (102), studies so far have not clearly shown superior outcome when compared with surgery + adjuvant therapy.

Retrospective studies have shown promising results regarding the administration of neoadjuvant therapy. A study published by Mason MC et al (122), analyzing a cohort of more than 4000 patients, indicates a 23% reduced post-operative mortality in patients that benefited from neoadjuvant therapy (122). Supporting these results, a study by Yadav S et al (123) shows improvement in OS (40.3 months vs 32.8 months) in patients that received neoadjuvant therapy followed by surgery and adjuvant therapy vs surgery + adjuvant chemotherapy (123).

While these studies are promising, there is a need for multicenter, randomized prospective clinical trials to confirm these

results. If these results were confirmed the administration and positive response to neoadjuvant chemotherapy could be an important prognostic factor in ICCA.

Conclusions

Intrahepatic cholangiocarcinomas are aggressive cancers that usually present at late stage, making curable resection suitable for less than 30% of the patients. With a rise in incidence of ICCA worldwide, prognosis factors are important to understand the likely evolution of the disease and ensure suitable treatment. While reviewing the literature, we have found that the most important factor of prognosis is the lymphatic metastasis, severely shortening the overall survival of patients, including those with R0 resections. In this case, routine lymph node dissection seems like an important step in assuring proper treatment. Achieving R0 resection margins is also of high importance, as it has been proven that every increment under the R0 margin correlates with a decrease in survival. Vascular invasion of vena cava or portal vein, traditionally considered contraindications for surgery, does not seem in recent studies to impact the survival of patients, as long as R0 margins are achieved. For diagnosis and prognosis of ICCA non-invasively, research on biomarkers has been increasing in recent years, with good results and most likely will become clinically available biomarkers in the near future. It is not clear yet how chemotherapy impacts the survival of patients. Since the publishing of the BICAAP trial, standard of care following resection has become capecitabine, which seems to considerably improve survival. There is no clear benefit of neoadjuvant chemotherapy, but it is currently tested pre-transplant, for its usually benefits of downstaging and identifying patients with rapid progression. It is also analyzed in ongoing studies in association with surgery and adjuvant chemotherapy.

Authors' Contributions

Conceptualization: S.P.; A.Z.; methodology: L.T.; validation: M.E.; A.H.; formal analysis: A.H.; investigation: C.M.; resources: I.B.; data curation: G.P.G.; writing — original draft preparation: C.S.; 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.

Conflict of Interest Disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with Ethical Standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

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