Prognosis of patients with intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma undergoing liver transplantation

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ABSTRACT
Cholangiocarcinoma (CC) is the most common of tumors of the biliary tree, according to its location is classified as intrahepatic, perihilar, and distal. Intrahepatic CC (ICC) constitutes about 5-10% of all CC. Although rare, its incidence has been increasing in several parts of the world. The mixed tumorhepatocellularcarcinoma/cholangiocarcinoma (HCC-CC), which is also rare, presents histological findings of both hepatocellular carcinoma (HCC) and iCC in the same nodule. Patients with a presumptive diagnosis of HCC on imaging tests undergo liver transplantation when, in fact, they have iCC or HCC-CC. A consensus meeting of the 2014 European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) contraindicated liver transplantation (LT) in patients with iCC or HCC-CC. However, recent studies suggest that careful selection of patients with very early iCC have similar survival rates to patients transplanted by HCC, suggesting that early iCC patients should be considered for liver transplantation. Similar results were obtained in patients with HCC-CC; however, it would seem that the cutoff could be extended to 5 cm considering other post-LT variables

Keywords: Liver Transplant, cholangiocarcinoma, hepatocellular carcinoma, prognosis, recurrence, survival.

1 INTRODUÇÃO

Cholangiocarcinoma (CC), a tumor of the epithelium of the bile ducts, is the most common of the biliary tree tumors, representing 10% to 25% of malignant tumors of the liver.[1]

CC originates anywhere in the biliary tree, from the intrahepatic bile ducts – Hering canals – to the whole doc (bile duct that originates from the junction of the common hepatic duct with the cystic duct and that flows into the ampoule of Vater - second portion of the duodenum).

Anatomically they are classified as intrahepatic, peri-hilar (at the confluence of the bile duct in the hepatic hilum), and distal (lower half of the choledoc). By the growth pattern, they are classified as mass-forming – mass effect – infiltrative – growing along the periphery of the bile duct - and intra-ductal (inside the bile duct). [2,3]

Intrahepatic CC (iCC) constitutes about 5-10% of all CC. [4-6] Although rare, incidence rates have increased in the last four decades in different regions of the world. [7-11]

For example, the incidence of iCC is high in Asia. A Thai study [12] reported age-adjusted rates of 100/100,000 inhabitants among men and 50/100,000 inhabitants among women.

In the West, age-adjusted rates range from 0.5 to 2.0/per 100,000 inhabitants. [12] In the United States, between 1992 and 2000, the incidence of iCC increased by 4%. [13] Population-based studies in that country, using data from Surveillance, Epidemiology, and End-Result (SEER), described increases in the incidence of iCC three to five times more compared to other anatomical subtypes between 1973 and 1997 and then between 1975 and 1999. [7,14]

Similar form data was described in European and Japanese cohorts. [15-17] The iCC shows a predominance by the male sex with a male/female ratio of 1.2-1.5:1 and rarely occurs before the age of 40. [13]

The mixed tumor HCC-CC presents histological findings of both hepatocellular carcinoma (HCC) and iCC in the same nodule. [18]

Mixed HCC-CC tumors are rare, and it is estimated that their incidence among malignant liver tumors varies between 1% and 4.7%. [19] HCC-CC presents the same histological characteristics as iCC. [20]

Although imaging tests suggest a diagnosis of iCC [21-23], identifying these tumors is a challenge because they are not commonly seen, and because HCC and iCC can coexist in separate nodules in the same liver.

Consequently, patients with a presumptive diagnosis of HCC on imaging tests undergo liver transplantation when, in fact, they may have iCC or HCC-CC. [24,25]

2 PATHOGENESIS

Cholangiocarcinoma is a primary biliary cancer that develops from the malignant transformation of cholangiocytes rather than hepatocytes, which form the most common liver cancer, hepatocellular carcinoma. [26,27]

Precursors of CC are:

1. Intraductal papillary mucinous neoplasm of the bile duct: This is classified according to the extent of cellular atypia, reflecting the spectrum of precursor lesions of pancreatic cancer. [26,27]
2. Biliary intraepithelial neoplasia: This is the most common form of CC, which is a macroscopic lesion similar to its pancreatic counterpart. [26,27]

Conversion of normal to malignant biliary epithelium through one of these precursor lesions likely requires a gradual accumulation of successive genetic abnormalities, similar to the sequence of events underlying colorectal carcinogenesis. However, the level of understanding of the molecular pathogenesis of CC is significantly lower than that of other gastrointestinal cancers. [26,27]

The molecular pathogenesis of cholangiocarcinoma involves different signal transduction pathways. At the molecular level, carcinoma precursors remain poorly characterized, although they appear to harbor mutations in p53 and loss of SMAD4. [26,27]

A variety of molecular defects have been described in samples of invasive tumors of the biliary tract, involving:

1. Oncogenes: RAS, ERBB2, BRAF, EGFR, PIK3CA, CTNNB1
2. Tumor suppressor genes: p53, SMAD4, CDKN2A.

The abnormal expression of KRAS is found in 45% to 54% of intrahepatic CCs; and in 10% to 15 % of extrahepatic CCs. The presence of these genetic alterations seems to be associated with a more aggressive tumor phenotype. [26,27]

2.1 EXTRAHEPATIC CHOLANGIOCARCINOMA

Perihilar CC is the most common subtype of cholangiocarcinoma and represents approximately 60% of malignant neoplasms of the biliary tract.

Most cases occur spontaneously, and although chronic inflammation and biliary stasis have been identified as risk factors, the precise etiology remains unclear. [2]

Specific genetic mutations that have been identified include K-ras, C-myc, p53, and Bcl-2. K-ras mutations in particular have been reported in up to 60% of patients and are seen more frequently in perihilar tumors larger than 3 cm and patients with lymph node metastases; they are often associated with poor survival. [2]

2.2 INTRAHEPATIC CHOLANGIOCARCINOMA

In intrahepatic CC, the KRAS mutation is frequently seen. About 20% of intrahepatic CCs have a loss-of-function mutation of the P53 oncogene.

In addition, mutations in isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) have recently been seen in 10% and 23% of cases [2] Mutations in the gene encoding isocitrate dehydrogenase 1 (IDH1) have been identified in 25% of intrahepatic CCs but not in extrahepatic CCs or gallbladder carcinomas.

The frequency of mutations in the IDH1 and IDH2 genes was higher than the combined frequency of activating mutations in other genes (e.g., AKT1, KRAS, NRAS, and BRAF) in intrahepatic CCs; suggesting the potential to target this pathway in intrahepatic CC. [2]

3 DIAGNOSES

When diagnosing CC, which is a form of CCA, (write out CCA) it is necessary to consider three possible scenarios, (a) asymptomatic cholestatic pattern, with symptoms or imaging findings related to a hepatobiliary malignancy, or a patient with known ulcerative colitis. (27)

Risk factors include age (between 50-70 years), increased incidence, (increased incidence of what?), male sex, and Asian ethnicity (possibly about liver staves' infection) (12). At the time of taking the medical history, it is important to investigate a history of gallstones, inflammatory bowel disease, and hepatitis. (28)

Biochemical analysis showed elevated alkaline phosphatase at twice the normal levels. Elevated GGT and bilirubins, as well as chronic biliary obstruction by an intrahepatic CC, can also alter the values of transaminases and INR (spell out this and other abbreviations the first time they are used and then use the abbreviations as much as necessary). It should be noted that these changes are not specific to CCA in that they are also altered in other pathologies, so it is necessary to make an adequate differential diagnosis. (12)

Symptoms such as weight loss, malaise, choluria, pruritus, among others, may be present in these patients, all being nonspecific, but suggesting an obstructive process of the bile duct secondary to a neoplastic process. However, clinical symptoms of CCA do not usually appear until the disease is at an advanced stage. (28)

In the analysis of the tumor antigen CA 19-9, values higher than 100 U /ml, provides a sensitivity for CCA between 50% and 70%. However, its usefulness may be limited by the false positives that can occur in benign diseases of the gallbladder and bile duct (29).

There are other tumor antigens such as carcinoembryonic antigen (CEA), matrix metalloproteinase-7, and a cytokeratin-19 fragment, which can be elevated in CC, but have a low sensitivity, and specificity and are only present on a subset of tumors.

Thus, they are not useful in clinical practice. (30) These data suggest that a combination of these tumor antigens can increase the sensitivity and specificity of CC detection up to 90% so an adequate clinical decision should be made. (31)

If a patient presents an elevation of liver enzymes that cannot be explained, complementary imaging studies should be performed.

These include magnetic resonance or magnetic resonance cholangiopancreatography, which are the ones of choice since they offer a sensitivity of 88% and a specificity of 75% to 85%. even if contrast is available to perform the imaging study, the sensitivity will increase by 10% as long as there are no contraindications, such as kidney failure or allergies.

The underscored sentence is not clear. When pathological findings in these studies such as a mass, ductal dilation, stenosis, among others are found, an invasive evaluation with sampling for histopathological studies is recommended. (32) In patients who have liver masses, iCC should be differentiated from other possible causes, the use of contrast and the characteristics of the images may help differentiate the type of pathology. (33)

The differentiation between an HCC and an iCC is that the latter presents a progressive uptake in both arterial and venous phases. (33) Magnetic resonance imaging can help differentiate between these two tumors, although it is not always definitive. (34)

If a lesion such as iCC is suspected, the metastatic disease should be evaluated, so the request for a chest tomography is important. (35)

Perihilar tumors are less frequent than iCC, which in imaging studies are presented as well-defined or nodular masses.

The involvement of the portal vein and the hepatic artery can be evaluated by a CT scan, with a sensitivity of 89% to 92% and 83% to 93% respectively. (35)

However, magnetic resonance cholangiopancreatography is the preferred imaging study for its ability to better characterize the biliary tree as well as the extent of the lesion. (32)

In patients suspected of perihilar cholangiocarcinoma, endoscopic retrograde cholangiopancreatography (ERCP) has become the test of choice for tissue diagnosis. (37) It can be used as a complement to intraductal ultrasound for the visual confirmation of lesions that are difficult to characterize.

Among physicians with experience to perform this study, the sensitivity reaches 93%, although practical use is limited by the difficulty in collecting tissue samples for cytology or detecting regional adenopathy. (38)

A Chronic inflammatory cholangiapathy such as primary sclerosing cholangitis (PSC), is characterized by progressive cholestasis, fibrosis, and stenosis, (39). Patients who suffer from it are twice as likely to develop cancers such as CCA, CRC, and HCC compared to the general population. (40)

The main cause of mortality in patients who have been diagnosed with PSC is CC (40) and the lifetime risk is approximately 10% to 15%, with an annual incidence of approximately 1%(41). Initial

reports indicate that, within one year of diagnosing PSC, 50% present with CCA (42). This finding suggests that the diagnosis of primary sclerosing cholangitis is made only after the development of malignant stenosis.

When a primary PSC has recently been diagnosed or there is a high suspicion of it being present, studies such as magnetic cholangiopancreatography and laboratory studies (liver tests and a CA 19-9) are the initial steps indicated. Such tests have two purposes, to identify any possible malignant stenosis and two to be a baseline in the case of laboratory changes, symptoms, or imaging in the future. (43)

4 TREATMENT AND PROGNOSIS

4.1 LIVER RESECTION

The treatment of choice for iCC is surgical resection. North American researchers [44] evaluated 270 patients with iCC, of whom 82 underwent surgical resection. At a mean follow-up of 26 months, disease-free survival was 36 months, with a recurrence rate of 62%. Liver tumors, regional lymph nodes, and large tumors were independent predictors of poor recurrence-free survival.

Similarly, a study conducted in South Korea [45], with 64 patients undergoing surgical resection, showed median recurrence-free survival of 12.3 months, recurrence in 41 patients, and a 5-year survival rate of only 39.5%. In the multivariate analysis, the presence of metastatic lymph nodes (HR 3.31) and the degree of tumor differentiation (HR 3.15) were significantly associated with poor survival.

A French multicenter study [46], using retrospective analysis, compared the outcomes of cirrhotic patients diagnosed with iCC or HCC-CC ≤ 2 cm undergoing LT or liver resection between 2002 and 2015.

The diagnosis of iCC or HCC-CC was incidental in 100% of patients undergoing LT and in 81% of patients undergoing hepatectomy, of this group only 5 (19%) patients had a previous histological diagnosis of iCC or HCC-CC. [46]

Regarding prognosis, after a follow-up of 25 months, no significant difference was found between liver resection and LT regarding overall survival in 1, 3, and 5 years (P=0.17) However, recurrence-free survival (RFS) rates were statistically higher (P=0.004) in the group that underwent LT in 1, 3, and 5 years (87%, 79% and 75% versus 69%, 45% and 36%, respectively). The rate of tumor recurrence was statistically lower in the LT group compared to liver resection (18% versus 46% P = 0.01). Therefore, for patients with tumors ≤ 2 cm, LT presents better results in liver resection. [46]

According to the International Liver Transplantation Society (ILTS) consensus guidance, liver resection continues to be the first-line treatment for patients with iCC. However, if the tumor lesions are ≤ 2 cm the LT can be considered. [47]

However, if the tumors exceed this cut-off, LT with curative intent can only be offered if the disease remains stable after neoadjuvant treatment. [47]

4.2 LIVER TRANSPLANTATION

A consensus meeting of the EASL in 2014 and the AASDLD guideline contraindicated liver transplantation in patients with iCC or HCC-CC due to the high recurrence rates and low recurrence-free survival rates recorded so far. [48,49]

However, recent research has shown encouraging results in patients submitted to LT, in addition, groups of researchers have identified a subgroup of patients with histopathological diagnosis of very early iCC who may benefit from LT with results like other causes.

De Martin et al. [46], using retrospective data from 3 French centers compared the outcomes of cirrhotic patients diagnosed with iCC or HCC-CC undergoing LT or liver resection. The authors concluded that for tumors ≤ 2 cm overall survival showed no difference between LT and liver resection, but the LT group showed RFS rates in 1, 3, and 5 years older and a lower recurrence rate.

In the same study, a subgroup analysis was performed with 45 patients with tumors □ 2 cm but ≤ 5 cm, 21 of them underwent LT and 24 liver resections.

After a follow-up of 24 months, there was no statistically significant difference in overall survival between LT and liver resection at 1, 3, and 5 years (88%, 65%, 65% versus 95%, 58%, and 35%, respectively, P = 0.41) In the multivariate analysis, the largest tumor diameter was the only associated prognostic factor are survival (HR 1.11; 95% CI, 1.03-1.19; P = 0.005) [46].

Regarding RFS rates despite being higher in the LT group, there was no statistical difference when compared with the liver resection group (P=0.06), recurrence rates in this subgroup of patients were lower in the LT group but without statistical difference. (P=0.06).

In the multivariate analysis, 3 factors were associated with lower tumor recurrence: tumor differentiation (HR, 4.16; 95% CI, 1.37-12.66; P = 0.01), median size of the largest nodule (HR, 1.10; 95% CI, 1.02-1.73; P = 0.007), and LT (HR, 0.23; 95% CI, 0.07-0.82; P = 0.02) [46].

Despite the LT, showing some advantage in the prognosis of these patients, the authors suggest prospectively confirming these results, as well as coining efforts to assess pre-LT tumor differentiation. [46]

In a recent study [50], the authors compared the results after LT of patients transplanted for suspected HCC in imaging tests and that the histopathological analysis of the explant showed to be, in fact, iCC.

After a 35-month follow-up, the cumulative risk of recurrence at 1, 3, and 5 years was 7%, 18%, and 18% respectively for the very early iCC group and 30%, 47%, and 61% respectively in the advanced iCC group (p 0.01).

Survival rates at 1, 3, and 5 years for patients with very early iCC (single tumors ≤ 2 cm) were 93%, 84%, and 65% respectively, and in the group with advanced iCC (□ 2 cm tumors) were 79%, 50%, and 45%, respectively (p 0.02).

Thus, the results suggest that liver transplantation could be an effective form of treatment in patients with early iCC. [50]

A retrospective multicenter study [51] studied the risk factors for tumor recurrence after liver transplantation of cirrhotic patients diagnosed with CCI in the histopathological analysis of the explant.

The authors concluded that patients with very early CCI – single tumors ≤ 2 cm have very satisfactory survival rates in one, three, and five years, being 100%, 73%, and 73% respectively. The factors associated with tumor recurrence were higher number and tumor size, microvascular invasion, and poor degree of tumor differentiation. [51]

North American researchers, [52] using propensity-matched analysis, compared the post-LT hepatic results of patients diagnosed with HCC-CC versus HCC in the histopathological study of the explant.

Patients with HCC-CCA were matched 1:3 with patients with HCC for the pretransplant (pre-LT AFP levels and cumulative radiologic tumor diameter) and posttransplant variables (diameter of the tumor in the explant, grade of tumor differentiation, and vascular invasion). Considering the pre-LT variables, there was no statistically significant difference in recurrence rates in 1, 3, and 5 years between recipients with HCC-CC and HCC (16%, 50%, and 50% versus 14%, 19% and 22%, P=0.07), as well as a clear trend for lower rates of override and RFS, but, without statistical significance. [52]

Considering the post-LT variables, the results were similar, patients with HCC-CC had slightly higher recurrence rates but without statistical significance (P=0.13) and equivalent rates of general survival and RFS, in the same way, without statistical significance. [52]

According to the results, the authors suggest that tumor differentiation would play an important role in the post-LT prognosis since patients with low-grade and moderately differentiated HCC-CC would have excellent survival with a low risk for post-LT recurrence when compared with patients with HCC of the same characteristics. In this way, identifying the histopathological characteristics of the mixed tumor would allow these patients to be listed for LT under well-defined criteria. [52]

Recent research, [53,54] points to similar results and suggests that patients with HCC-CC could be considered potential candidates for LT provided they have a judicious evaluation. Variables such as vascular invasion, tumors □ 2cm "early stage" and multifocal disease, were associated with worse post-LT outcomes.

Despite these results, the ILTS expert panel continues to consider that there is insufficient evidence or experience and that before including patients with HCC-CC formally as potential

candidates it is necessary to identify prognostic factors that allow improving the selection and thus the post-LT results. [55]

5 CONCLUSIONS

Currently, iCC and HCC-CC are considered absolute contraindications to LT, by their worse prognosis, recent research suggests that better selection and evaluation of candidates would improve post-LT outcomes.

Although these studies have followed retrospective outlines, the use of propensity-matched analysis applied in most analyses has provided greater methodological rigor and confidence in the results obtained.

In all studies, the diagnosis of iCC and HCC-CC in patients undergoing LT was made by histopathological study of the explant.

Regarding the iCC, the results are satisfactory – the overall survival and RFS in 5 years for very early tumors – ≤ 2 cm, has been acceptable. However, the 2 cm cut-off is extremely limited, due to the challenge of its preoperative radiological diagnosis, for this reason, researchers suggest that these results be validated in multicenter and prospective studies.

Regarding HCC-CC the conclusions are more encouraging, the results after transplantation are like those obtained in patients transplanted by HCC. In this subgroup of patients, the degree of tumor differentiation plays an important role since the best results have been observed in patients with well-differentiated tumors.

Other variables related to prognosis have been tumor invasion, multifocal disease, and tumor size - ≤ 2 cm.

Although the 2 cm cut-off seems safe, researchers showed adequate results in a subgroup of patients with tumors □ 2 cm and ≤ 5 cm, in this way, patients with mixed tumors could be considered potential candidates, however, it is mandatory

Prospectively identify prognostic factors that allow improving the selection and thus the post-LT results.

On the other hand, transplant oncology is an emerging discipline that aims at multidisciplinary work between transplant oncologists, hepatologists, gastroenterologists, transplant hepatobiliary surgeons, interventional radiologists, and immunologists to expand and improve post-transplant outcomes in different types of cancer.

Conflict of Interest

The authors declare no conflict of interest.

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