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PRIMARY LIVER CANCER: CLINICAL ASPECTS, PROGNOSTIC FACTORS AND PREDICTIVE RESPONSE TO THERAPY

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ABSTRACT – *Primary liver cancer (PLC) is the fifth and seventh most common cancer in men and women, respectively. The 85% of all PLC cases are hepatocellular carcinomas (HCCs). The 80% of all HCC results from cirrhosis, while the 20% develop in patients with no chronic hepatic disease, mostly from severe forms of non-alcoholic fatty liver disease. The Barcelona Clinic Liver Cancer is the most accepted staging system. Tumor stage and degree of hepatic dysfunction determine the treatment of HCC. Good long-term survival and 5-year survival rates (70-50%) are enabled by liver transplantation and surgical resection with radical intent. In addition, especially in early-stage nodules, loco regional treatment can also accomplish positive results.*

Intra-hepatic cholangiocarcinoma (ICC), is the second most common PLC. It arises from the bile ducts of the second-order and usually presents as a mass inside the liver. ICC can be diagnosed with CT and MRI imaging techniques showing location of the tumor, the possible multifocality of the lesion, the presence of venous or arterial invasion, and the presence of lymph node involvement or distant metastases. Three types of ICC can be described according to the type of macroscopic growth: mass forming, periductal infiltrating, and intraductal growing. The treatment of choice is radical surgical resection, the only treatment showing a long-term survival for patients. A major hepatectomy is often required to achieve radical resection. This therapeutic choice has acceptable mortality and morbidity rates.

Other PLCs (e.g., epithelioid hemangioendothelioma, fibrolamellar hepatocellular carcinoma, hepatoblastoma, sarcoma and lymphomas, combined HCC and ICC) are very uncommon, and surgery remains the treatment of choice.

KEY WORDS: *Surgery, Treatment, Liver cancer.*

INTRODUCTION

The primary liver cancer (PLC) is the fifth most common cancer in men and the seventh most common cancer in women, worldwide, with the 85% of PLC occurring in developing countries[1]. In fact, the rates in Eastern and South-Eastern Asia and Middle and Western Africa are the highes. Interestingly, in developed countries such as North America and Europe, rates are generally lower[2]. The high mortality rates associated with liver cancer are similar despite the geographic area[1]. In 2002, more than 377,000 people have died from liver cancer in Eastern Asia (about 19% of the total number of cancer-related deaths)[3]. In 2008, an estimated 694,000 deaths from liver cancer (477,000 men and 217,000 women) have been reported.

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Here, we consider the prognostic and predictive viewpoints of the clinical and pathological characteristics of hepatocellular carcinoma and cholangiocarcinoma.

CLINICAL PROGNOSTIC FACTORS OF HEPATOCELLULAR CARCINOMA (HCC)

Hepatocellular carcinoma (HCC) is the most common PLC (about 85% of all PLC cases). It is the third most frequent cause of death cancer-related and the sixth most common cancer. The median age at onset in developed countries is around 70 years, and the incidence rises with increasing of age. HCC also predominantly affects males and has a male to female ratio of approximately 2.4[4]. HCC often results from cirrhosis caused by chronic viral hepatitis C and B, alcoholic hepatitis, autoimmune hepatitis, hemochromatosis, alpha-1-antitrypsin deficiency and Wilson's disease[5]. On the other hand, roughly 20% of patients with HCC present no chronic hepatic disease. The incidence of HCC increases both in patients with cirrhosis[6] and in some subgroups of patients such as those with HIV infection[7]. Emerging clinical evidence suggests that HCC is one of the most important causes of death among patients with more severe forms of non-alcoholic fatty liver disease (NAFLD). NAFLD causes steatosis without inflammation (fatty liver), nonalcoholic steatohepatitis (NASH) and cirrhosis[8]. In Western countries about 20-30% of adults suffer from NAFLD; this prevalence increases to 70-90% among obese people or who have type 2 diabetes[8]. If confirmed in large-scale prospective studies, the potential adverse impact of NAFLD on the development of cirrhosis and HCC will deserve particular attention, especially with respect to the possible implications for screening and surveillance strategies in the growing number of patients with metabolic syndrome (MS) and NAFLD.

Diagnosis

Histological-proven biopsy used to be the gold standard for the diagnosis of HCC, but recently, in patients with cirrhosis, the guidelines recommend a diagnosis based on radiological criteria[9-11]. The commonly accepted criteria for the diagnosis of HCC are contrast enhancement (wash-in) in the arterial phase and wash-out in the venous/late phase, which is referred to as the "wash-in wash-out pattern" (Figure 1). The American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) are the guidelines most frequently applied in clinical practice, for the diagnosis of HCC in Western countries[11]. In both sets of guidelines, the diagnosis of HCC is indicated by hepatic nodules larger than 2 cm in size with a "wash-in wash-out pattern" in one of the imaging techniques (CT or MRI). However, for nodules between 1 and 2 cm, EASL guidelines advise that the typical pattern that is observed in two imaging techniques should agree. Biopsy of the nodules is recommended by both the AASLD and the EASL in the absence of a wash-in wash-out pattern, but no contrast-enhanced ultrasound nor levels of serum alpha-fetoprotein are considered in the diagnostic criteria by either set of guidelines. In Japan, the most widely accepted guidelines are those of the Japanese Society of Hepatology (JSH), which have been updated in 2012[10]. The diagnostic criteria of these guidelines are the wash-in wash-out pattern observed in one type of imaging modality (CT, MR, and even contrast-enhanced ultrasound), an AFP serum value more than 200 ng/dL, a PIVKA-II serum value more than 40 ng/dL, or AFP L3 > 15%.

Staging Systems

Several consensus conferences and clinical guidelines have emphasized the importance of staging systems in HCC. In the literature, the best staging system for

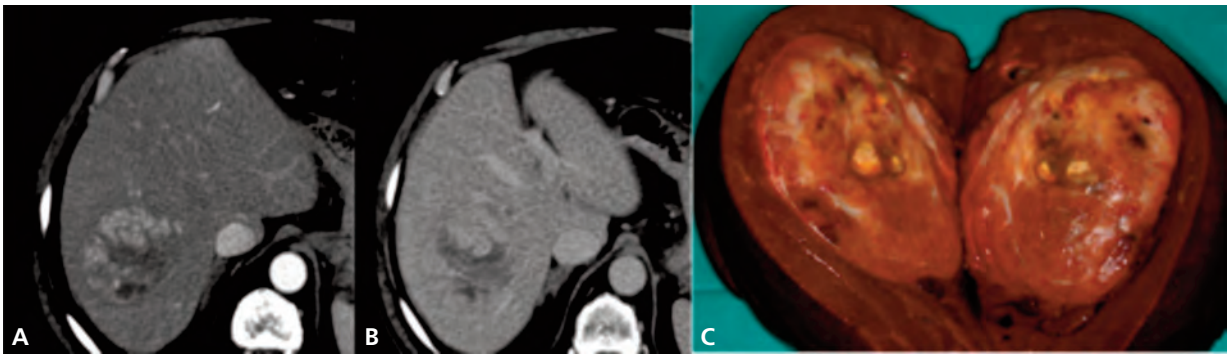

Figure 1. CT scan showing a hepatic nodule with a "wash-in wash-out pattern", diagnosed as HCC. *A,* Arterial phase. *B,* Venous phase. *C,* Surgical specimen confirmed the diagnosis.

HCC in patients with cirrhosis has yet to be identified and it is still debated because the association between neoplasms and chronic liver disease. Many staging systems have been proposed in the last two decades, but no convincing evidence has suggested the golden standard. Moreover, the characteristics of the cohort of patients enrolled and the type of treatment utilized influence the predictive value of each system. Currently, the most accepted system is the Barcelona Clinic Liver Cancer (BCLC) staging system, which has been updated in 2011[9]. The BCLC system has been validated by several groups in Europe and the United States and has showed good performance in both surgical and nonsurgical patients[12-16]. This staging system includes factors of both tumor morphology and degree of impairment of liver function, and it can be used to assign the correct treatment to patients with HCC, according to their liver function, the PS, and the tumor stage. Recently, several authors have criticized this treatment allocation due to the exclusion from surgical resection of patients who might potentially benefit from this type of therapy, such as patients with macroscopic vascular involvement[17-19]. The TNM system of the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC)[20] is used in surgical patients despite some controversies about its value in HCC due to the absence of variables related to liver function. Furthermore, clinical studies have shown non-homogeneous stratification of risks among individuals of different stages due to the defined criteria of the T-stage. The Cancer of the Liver Italian Program (CLIP) proposed in 1998 a system[21] based on a retrospective study of HCC 435 patients identifyng five independent variables: Child-Pugh class, tumor size, number of tumors, presence of portal thrombosis, and serum AFP. The validity of this system has been confirmed by large validation studies in Italy, Canada, and Japan[22,23]. The greatest criticism of the CLIP classification is that it includes a large set of advanced stage morphologic criteria, which reduces its value in patients with early-stage HCC. The Japan Integrated Staging score (JIS)[24], a combination of the Child-Pugh score for liver function and the modified TNM classification according to the Liver Cancer Study Group of Japan (LCSGJ), has been proposed in 2003. The JIS score has been validated by a statistical analysis of patients after surgical resection of HCC, but this system has not been validated in other cohorts of patients who have been treated with nonsurgical therapies.

Management of HCC

The treatment of HCC varies in relation to the tumor stage and the degree of hepatic dysfunction. Classically, the best survival results have been reported when the following indications were satisfied: single tumors and good liver function (no portal hypertension, normal bilirubin) for resection, single tumors ≤5 cm or three nodules ≤3 cm for liver transplantation, and single tumors ≤3 cm in Child-Pugh A patients for percutaneous treatments. A survival of 50-70% at 5 years can be achieved following these indications[25].

Early HCC

Liver transplantation enables an excellent 5-year survival (70-75%) during early stages of the disease and is associated with low rates of recurrence (10-15%)[26]. Unfortunately, only a few patients can benefit from this resource because of the shortage of organs and the strict selection criteria. In contrast, surgical resection is applicable to approximately 20-30% of patients. Surgical resection is safe and is associated with low rates of mortality (0-3%) and morbidity (25-30%). In patients with moderate liver impairment, resection requires a careful preoperative assessment of liver function with biochemical and dynamic parameters, such as the indocyanine green retention test[27]. Surgical resection with radical intent allows good long-term survival: 40-50% at 5 years[17]. In HCCs smaller than 3 cm, the 5-year survival is greater than 60%, with a 10-year survival of 20%[28]. Until a few years ago, portal hypertension has been considered an absolute contraindication to surgical resection. However, recent data show that in patients with moderate portal hypertension who were classified as Child-Pugh class A limited (up to two segments), liver resection can be performed with results comparable to patients without portal hypertension[17]. Patients with small HCCs (less than 2 cm in size), can benefit from percutaneous local treatments (e.g., radiofrequency ablation) with good long-term results comparable to those achieved after surgery[29]. A recent review of the literature in which the authors concluded that it is reasonable to offer radiofrequency ablation to patients with HCCs less than 2 cm in size confirmed these data. On the contrary, for larger nodules or in tumor locations in which ablation is not expected to be effective or safe, and surgical removal is chosen (Figure 2)[30].

Intermediate-advanced HCCA

Approximately 20% of HCC patients are classified as intermediate-stage with an expected 2-

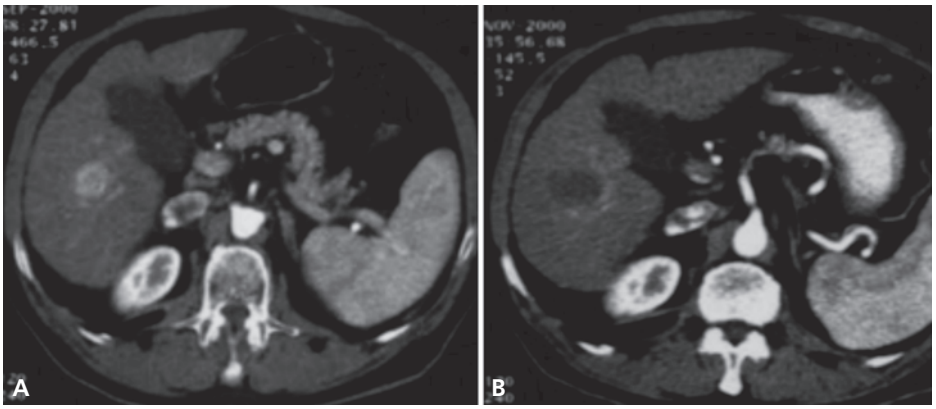

Figure 2. *A*, CT scan in the arterial phase showing HCC nodules 23 mm in size. *B,* A hypodense nodule in the control CT scan demonstrated a complete response after radiofrequency ablation.

year survival rate of 50%[31]. Intermediate-stage HCC is a heterogeneous population of patients with different tumor burden, liver function and disease etiology[32,33]. Patients in intermediate stage (i.e., large and/or multinodular HCC in asymptomatic patients without a neoplastic vascular invasion) showed a 3-year survival rate of 50% compared to more advanced stage patients, who showed a 3-year survival rate of 8%[34]. Resection may still be a valid option in selected patients[35]. Radical resection can be considered in patients with large single HCC nodules with well-compensated liver function and adequate remnant liver volume as wel as in selected patients with multinodular HCC or in patients with limited macroscopic vascular invasion. The 5-year survival rates are 46% in patients with multifocal HCC and 20% in patients with macroscopic vascular invasion[19,35]. However, transarterial chemoembolization (TACE), particularly selective or superselective TACE, is considered the standard treatment in patients with compensated liver function (Child-Pugh A and Child B up to 7 points), with large single nodules (<5 cm) or multifocal HCC not occluding the portal venous vessels and in patients with no extrahepatic spread[35]. Survival benefits of TACE in comparison to symptomatic treatment, have been reported in the literature, with a 2-year survival rate of 30%[36]. Many patients (35–90%) experience TACE-associated adverse events, usually transient and manageable. The more frequent are post-embolization syndrome (fever, abdominal pain), relevant liver function deterioration, ascites and gastrointestinal bleeding[36]. Selective/superselective TACE may determine a higher rate of tumor necrosis than the standard TACE, with fewer reported adverse events[37].

Radioembolization is a form of brachytherapy in which intra-arterially injected radioactive microspheres loaded with yttrium 90 (^{90}Y) are used for internal radiation purposes in order to deliver tumoricidal doses of radiation to liver tumors while sparing the normal liver. All the evidences supporting radioembolization in cases of HCC have been based on retrospective series or non-controlled prospective studies. In patients who are not amenable to TACE, some evidence has been provided that radioembolization can prolong survival over non-specific therapy. This evidence is further supported by the comparison of numerous studies that have reported survival rates in the range of 9-16 months[38].

Medical Treatment

The only chemotherapeutic agent demonstrating a significant improvement in time to progression and in overall survival of advanced HCC patients is sorafenib. It is an oral molecular-targeted multi-kinase inhibitor of the vascular endothelial growth factor receptor and the platelet-derived growth factor receptor. The adverse effects are easily managed and treatment-related mortality results absent[39,40]. Its use is recommended for patients with Child-Pugh class A advanced HCC demonstrating good performance status (PS) and for patients without other treatments' options[41]. The median overall survival reported in these patients is 10.7 months[40].

End-stage HCC

Patients with end-stage disease present as Okuda stage III or with a PS of 3-4 reflect a severe tumor-related disability, also patients with C Child-Pugh score tumors also account for a very poor prognosis. The 6-month survival rate in these patients is 5%[5].

Recurrence

The major downside of potentially curative treatments is the recurrence of HCC. Even after curative resection, recurrences are very common, occurring, within 5 years of treatment, in about 70-100% of cases[42]. Recurrence could be related to the presence of intrahepatic metastases or to neocarcinogenesis in the liver residue. Many prognostic factors related to recurrence have been identified, and among these, the most important are size, absence of a pseudocapsule, presence of satellite nodules, vascular invasion, tumor grading and serum levels of alpha-fetoprotein[43]. The activity of the underlying liver disease, the type of viral infection and the degree of fibrosis are related to the development of neocarcinogenesis' secondary recurrence[44]. Recently, new molecular markers related to early recurrence have been proposed, helping the understanding of the biological subclasses and optimizing the benefits from molecular therapies. Actually, no molecular classification has demonstrated its ability to precisely predict survival and recurrence of HCC in a clinical setting. A study published in 2013 have appeared to prove that *C-MYC* status is an important prognostic factor. The amplified *C-MYC* status has been associated with a risk of recurrence that is significantly higher compared to disomic and polysomic status. Furthermore, amplified *C-MYC* status has been the strongest prognostic factor for OS in both univariate and multivariate analyses[45].

INTRAHEPATIC CHOLANGIOCARCINOMA (ICC)

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer. It accounts for 3% of all gastrointestinal cancers, and the most common histologic type is adenocarcinoma because it arises from the epithelial cells of the bile duct[46]. Intrahepatic cholangiocarcinoma occurs from the bile ducts of the second order and typically it presents as a mass inside the liver[47]. Patients usually present in the sixth and seventh decades of life. the prevalence of the ICC is estimated to be between 0.01% and 0.5%, according to data from autoptic studies. The incidence and mortality of ICC are increasing, both in industrialized and developing countries. The incidence registered in the U.S. is 1-2 cases per 100,000, with 3,500 new cases yearly[48,49]. The highest rates of incidence are in Southeast Asia (Thailand, Cambodia, Laos), because the greater prevalence of risk factors[50] such as congenital anomalies of the biliary tract, congenital cysts of the biliary tree, primary sclerosing cholangitis, hepatolithiasis, liver fluke infections, bile duct adenoma, and environmental toxins (e.g., tobacco,

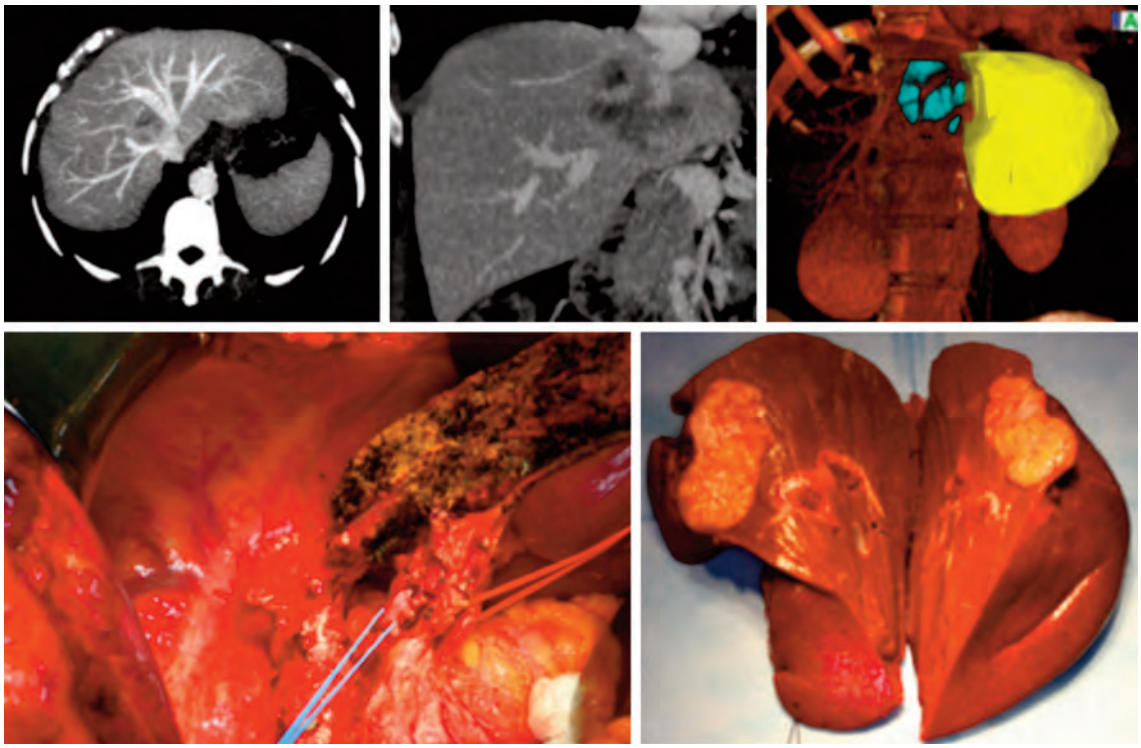

Figure 3. ICC nodules in the right lobe of the liver that surround but do not infiltrate the middle hepatic vein, as demonstrated in preoperative planning with 3-D reconstruction. Right hepatectomy was performed with negative margins.

dioxin, vinyl chloride)[48]. There are three types of ICC according to the type of macroscopic growth: mass forming (MF), periductal infiltrating (PI), and intraductal growing (IG). The MF type presents as a nodular growth with a well-defined margin, while the PI type presents as a diffuse infiltrative growth along the axis of the portal tracts without a clearly defined mass. The IG type manifests as a papillary growth inside of a bile duct. Mixed forms are classified by the specification of the most represented macroscopic features (i.e., type MF + PI)[51].

Diagnosis

ICC occurs frequently without specific symptoms, such as tenderness in the abdomen, weight loss, malaise and anorexia. In some cases, the only finding is an abdominal mass that can be detected during radiological examinations. The laboratory tests show moderately elevated levels of alkaline phosphatase, gamma-glutamyl transferase and bilirubin in the serum, while the 85% of patients present with high levels of CA 19.9. The serum levels of CEA (in 30% of cases) and CA 125 (in 40-50% of patients) can also be elevated. Bile duct obstruction, if present, can cause an increase in prothrombin time and a reduction in fat-soluble vitamins. Impaired hepatic function due to the replacement of the liver parenchyma by the tumor could occur in advanced stages[52]. Abdominal ultrasound is the first-line imaging technique indicating the presence of a hypoechoic mass in the liver suspected to be ICC. CT imaging is the most useful imaging modality for the diagnosis of ICC; it demonstrates the location of the tumor, the possible multifocality of the lesion, the presence of venous or arterial invasion, and the presence of lymphadenopathy or distant metastases[53]. ICC is characterized by a typical contrast enhancement pattern with hyper-density in the late venous phase, segmental dilation of peripheral bile ducts and retraction of Glisson's capsule in the segments near the tumor. Magnetic resonance imaging (MRI) is also important for the evaluation of the involvement along the bile duct and the detection of satellite nodules. MRI also allows, when contrast-enhanced methods are used, the detection and better definition of the vascular involvement[53]. PET still has a limited role in diagnostics because of low sensitivity and specificity. However, it can be helpful for the detection of distant metastases[53].

Staging Systems

The most common staging systems are the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM classification (7th edition)[20] and the Liver Cancer Study Group of Japan (LCSGJ) TNM classification[54].

UICC/AJCC TNM Classification (7th Edition)

The UICC/AJCC TNM classification (7th edition) has been published in 2010[20] after several criticisms have been raised about the 6th edition. The 6th edition of UICC/AJCC TNM classification for ICC was the same for HCC due to the lack of prognostic data with respect to ICC. Nevertheless, its prognostic value has never been validated in case series of literature. In addition, ICC and HCC exhibit different neoplastic behaviors and have different prognoses. Therefore, the UICC/AJCC TNM classification 7th edition have proposed a different classification for ICC. It focused on vascular invasion, the multinodularity of the tumor and the invasion into adjacent structures regardless of the size, and incorporated the pattern of growth first described in 1997 by the LCSGJ. Remarkably, the periductal infiltrating pattern has been classified as T4, and regional lymph-nodal involvement has been classified as N1. As in the Japanese classification, the presence of tumor in the celiac, periaortic and caval lymph-nodes is considered to be distant metastasis (M1). The prognostic value of the UICC/AJCC TNM classification 7th edition has been validated by a recent multicenter analysis of 434 patients who underwent curative resection for ICC[55].

The LCSGJ TNM Classifications

This classification is used for the MF type of ICC. It evaluates three criteria: single nodule, tumor 2 cm or less and no invasion into the portal vein, hepatic vein or serous membrane. This staging system defines a solitary tumor without vascular invasion as stage I, a solitary tumor with vascular invasion as stage II, multiple tumors with or without vascular invasion as stage IIIA, a tumor with regional lymph node metastasis as stage IIIB, and a tumor with distant metastases as stage IV. In this system, tumor size is excluded from the T factor[54].

Prognostic Factors

Pattern of Growth

The macroscopic pattern of growth of the types of ICC (MF, PI, GI) reflects the different biological behaviors and the tumor spread. The MF type occurs in the 60-70% of cases. This type is associated with an early portal invasion in 45% of cases,

and satellite nodules are present in 36% of cases. About 30% of cases present with lymph node involvement. The 5-year survival rate reported in the literature ranges between 25% and 48%[54,56]. Among all cases of resected ICC, the IG type is found in 8% to 23% of cases. IG type presents as a papillary-like tumor, and in most cases it is well differentiated with a low incidence of lymph-nodal, vascular or perineural invasion. The long-term survival of patients with IG-ICC after surgical resection is good, with a 5-year survival of 40-80%. Patients with type IG ICC is significantly longer survival respect patients with the MF and PI types. It is also associated with the presence of lymph-node metastases[57].

The PI type has a worse prognosis than the other two types. PI form occurs in 15-35% of cases and is associated with biliary, vascular and lymphatic infiltration at the hepatic hilum. The 5-year survival rate in these patients is less than 40%[58]. The 25%-45% of patients present with the mixed form MF + PI. This has the worst prognosis. In fact, patients present, at the time of diagnosis, with a more advanced stage. These patients, more often have lymph node metastases and vascular invasion and intrahepatic metastases. The long-term survival is poor, with less than 10% of patients alive at 5 years[57].

Local Extension

The local extent of the tumor is related to size, multifocality, vascular invasion, and invasion of the common bile duct. The size of the tumor determines the prognosis. Indeed, the 5-year survival in patients with a mass less than 3 cm in size is 42%, whereas patients with a mass greater than 6 cm, have a survival reduced to 0%[59]. The presence of satellite nodules has been reported in 20-30% of patients, with a poor 5-year survival (0-7%)[59,60]. Portal infiltration is an important negative prognostic factor for patients with ICC, survival in patients without portal involvement has been significantly greater than in those with macroscopic portal infiltration; these patients have a 3-year survival of 46% and 0%, respectively[61].

Lymph node Involvement

Literature have reported lymph node metastases ranging from 7% to 73%. This is an important prognostic factor: patients with N+ have a 5-year survival between 0% and 20%[62]. Lymph node involvement in the IG form is significantly lower than in the other forms (less than 20%), while the frequency of lymph node involvement in the mixed type MF + PI is significantly higher, reaching the 80% of cases. Lymph node involvement is also related to the stage of disease, and according to some studies, it is present in 80% of patients with T4 stage disease[63]. The frequency of lymph node metastases is also related to the site of the tumor and is reported to be higher in tumors with hilar involvement respect those with peripheral growth (75% and 45%, respectively)[64].

Macro- and Microscopic Biological Pattern

The histological aspects related to the prognosis are the cell differentiation, the lymphatic and perineural vascular invasion. The well or moderately differentiated tumors have a better prognosis than those that are poorly differentiated. The 5-year survival rates are 50% for well differentiated, 39% for moderately differentiated and 0% for poorly differentiated tumors[64]. Lymphatic vessel invasion is a poor prognostic factor for survival according[65], and no patient with lymphatic involvement has survival rates exceeding 3 years. Conversely, the 70% of patients without lymphatic invasion has a 5-year survival[66]. According to some studies, patients with perineural invasion have a 5-year survival rate lower than 10%, while in patients without such involvement it exceeds 60%. Perineural invasion is also associated with a high frequency of lymph node metastases and presence of vascular invasion[65]. Several biological and molecular prognostic factors have been identified in ICC. A reduced expression of IL-6 and p27kip1, and mutations in k-ras, p53, E-cadherin, α-catenin and β-catenin are associated with advanced malignancies, poor differentiation and early recurrence[67]. Unfortunately, these molecular markers have no clinical application.

Surgical Treatment

For a correct preoperative assessment of the resectability of a tumor, the performance status of the patient, liver function, the volume of the future remnant liver, the presence of lobe atrophy, the extension of the tumor, the vascular involvement, the lymph node involvement, and the presence of distant metastasis must be considered[68]. The resectability of tumors in patients with ICC ranges from 20%-70%[69], and depends on the presence of intrahepatic or distant metastases, vascular invasion or peritoneal carcinomatosis. Radical surgical resection (R0) is the treatment of choice and the only one achieving a long-term survival. A

major hepatectomy is often required to achieve radical resection. Furthermore, the resection of the extrahepatic bile duct, hilar vascular structures, the vena cava and the diaphragm may also be necessary[68,69]. Major hepatic resection can be performed with low morbidity and mortality because ICC usually arises in non-cirrhotic livers. The complication rate depends to the extent of liver resection and varies between 35% in minor hepatectomies and 55% in major liver resections. It is also associated with vascular or diaphragmatic resection[60]. Most authors report a mortality lower than 5%. Mortality is frequently related to major liver resections or is associated with vascular or bile duct resections. R0 is the only factor allowing a satisfactory long-term survival; it has a reported 5-year survival and, in selected patients, it can achieve 40%-60%[68,69]. The five-year survival for patients undergoing non-radical resection (R1) ranges between 0% and 25%[68].

Liver Transplantation (OLT)

A regimen of preoperative staging and neoadjuvant chemoradiation treatment followed by OLT for hilar cholangiocarcinoma has demonstrated excellent long-term, recurrence-free survival of patients[70], but the role of OLT in the treatment of unresectable ICC remains controversial. Despite at first, poor survival (28% at 5 years) and high recurrence rates (up to 78%) have been reported, recently promising results have been described in the literature, in particular when neoadjuvant and adjuvant therapies have been given. In fact, the reported survival rate in the patients receiving these treatments has been ranging from 33% to 46% in earlier series[71]. Nevertheless, a small case series and a short follow-up cannot allow for definitive conclusions.

Chemotherapy

Several clinical trials have been conducted on many chemotherapy treatments for patients with ICC. Most trials had significant limitations such as lack of a control arm, small sample size, and inclusion of heterogeneous tumor types. Presently, the most widely used therapy is based on gemcitabine and cisplatin because the response rate to a single-agent 5-fluorouracil-based or gemcitabine-based systemic chemotherapy is only 10% to 30%[72]. This approach, compared with gemcitabine alone, has demonstrated an improved progression-free survival and overall survival (11.7 months *vs.* 8.1 months)[73].

Disease Recurrence

Recurrence is common even after R0 resection and arises in 40-80% of cases, and it generally occurs early (within 2 years in 86% of patients). The most frequent sites of recurrence are the liver (74%), the peritoneum (22%), lymph nodes and bone (11%)[63]. In the literature, the following factors are identified and are related to recurrence: hilar involvement, size of the tumor, portal involvement, presence of lymph node metastases, high serum levels of Ca 19-9[63]. Another factor that is related to the onset of a high rate of recurrence is the gross macroscopic type of growth. The frequency of recurrence is significantly higher in the PI form compared to the MF form. The macroscopic type of growth also determines the site of recurrence. The MF form of ICC is particularly associated with an increased frequency of intrahepatic recurrences (68% of all recurrences), while lymph-nodal recurrence is more frequent in the MF + PI and PI forms of ICC. The treatment of recurrent tumors varies and is dependent on the location and extension of the tumor; in most cases, treatment is only palliative. In isolated cases, it is possible to reach a long-term survival after resection of an intrahepatic recurrence[74]. In very selected cases, surgical treatment including transplantation, has offered good results with regards to long-term survival[65,75]. However, the clear indications of the proper treatment of recurrent tumors, both surgical and palliative, have not yet been clearly established in the literature.

OTHER PRIMARY LIVER CANCERS

Fibrolamellar Hepatocellular Carcinoma

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare variant of HCC. The incidence rate is about 0.02 per 100,000 in the U.S. (approximately 100 times less frequent than other HCCs)[49]. FL-HCC differs from HCC in most pathological and clinical characteristics. FL-HCC typically affects younger patients, aged from 14 to 33 years in most series, making it one of the major primary liver tumors in young patients. The majority of patients are not affected by underlying liver disease; in fact, a recent review of the literature has reported that only 3% of patients has underlying cirrhosis, while only 2% presents with hepatitis B infection and in 1% of patients has hepatitis C[76]. The alpha-fetoprotein serum level is elevated in approximately 10% of cases. The patients present with a few non-specific symptoms, such as fatigue or weight loss. The di-

agnosis is made by ultrasound. FL-HCC often appears as a large nodular mass, up to 20 cm in size and it is associated with a high rate of lymph node metastasis. The best treatment option is surgery, either aggressive liver resection or liver transplantation. Hilar lymphadenectomy should be performed because the high rate of lymph-node involvement at presentation. The reported 1-, 3- and 5-year overall survival ranged from 82% to 100%, 58% to 100%, and 58% to 82%, respectively, after liver resection[77] and 63% to 100%, 43% to 75%, and 29% to 55%, respectively, after liver transplantation[78]. The impairments to overall and disease-free survival are older age, resectability, impaired liver function, larger tumor size, multiple tumor foci, presence of co morbidities and advanced stage of disease (lymph nodal or distant metastases and vascular invasion). Despite the advanced stage at diagnosis, FL-HCC seems to have a fairly good prognosis, with a 5-year survival rate that is twice as high as that of HCC[79]. However, it has been recently reported that the long-term outcome in patients with FL-HCC does not differ from the outcome of non cirrhotic patients with HCC[80,81].

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EH, Figure 4) is a primary liver cancer originating from the endothelial tissue. Its incidence is less than one in one million and the male:female ratio is 1:2. Even if some possible etiologic factors of EH have been described, including oral contraceptives, vinyl chloride, exposure to asbestos or thorotrast, major trauma to the liver, underlying liver disease, primary biliary cirrhosis, and alcohol consumption, there has not been described any clear etiological correlation. Its presentation is either asymptomatic or, in 25% of patients, is associated with non-specific symptoms (e.g., pain in the upper right abdominal quadrant, weight loss, anorexia)[82]. The laboratoristic serum values or tumor markers are within the normal range or slightly elevated. CT or MRI findings often display one or more masses in the liver with hypervascularization, but the diagnosis still poses a challenge, therefore almost all cases, requires a histopathologic analysis with a biopsy for a definitive diagnosis. EH is multifocal in 87% of cases at presentation, with an extrahepatic spread, such as to the lung, lymph nodes or peritoneum, in almost 37% of patients[82]. Because of its rarity, heterogeneous status, and variable clinical outcome no generally accepted strategy for the treatment this disease is available. The management options include liver resection when the tumor is technically resectable, even in cases of multinodular bilobar spread, liver transplantation, chemotherapy, and radiotherapy. In a recent case series, liver resection demonstrated a 1-, 3- and 5-year overall survival of 100%, 86% and 86%, respectively, and a disease-free survival of 78%, 62% and 62%, respectively[83]. Liver transplantation showed good results despite the limited outcome data that are available from single-institution studies. Long-term survival data have demonstrated a 1-year survival rate of 80% or higher, and 5-year survival rates ranged from 54.5% to 83%[83,84]. The experience with systemic or locoregional chemotherapy, TACE, and radiotherapy is low and usually of limited value, particularly as a first-line therapy[82].

Hepatoblastoma

Hepatoblastoma is the most common primary liver cancer in childhood, but it is extremely rare in adults. A recent review of studies published in English[85] reported only 40 patients who were affected by hepatoblastoma since 1958. The median age of presentation is in the fourth decade, but the majority of patients were in the second decade of life. It presents as a single, large nodule in the liver in almost 80% of cases. The symptoms and laboratory tests are non-specific, and radiological imaging has a limited valueTherefore, a biopsy-proven histological examination often leads to a definitive diagnosis. There is no standardized management of adult hepatoblastoma. Radical surgical excision appears to be the 'gold standard' for curative therapy. Chemotherapy can be used as neo- or adjuvant, and it is based on platinum, adriamycin, irinotecan and pirarubicin. The prognosis of hepatoblastoma is extremely poor. The median survival is only 4 months with a 1-year survival of 29.6%. Younger patients had significantly better prognoses than older patients[85].

Sarcoma

Primary sarcomas of the liver account for less than 1% of all hepatic malignancies. Based on the most prevalent cell type in the nodule, they are called angiosarcoma, embryonal sarcoma, leiomyosarcoma, epithelioid hemangioendothelioma, fibrosarcoma, or malignant fibrous histiocytoma. Diagnosis can be performed in patients of all ages, and frequently, these malignancies are discovered during a routine ultrasound. The treatment of choice is radical resection, with a 39 months median survival[86].

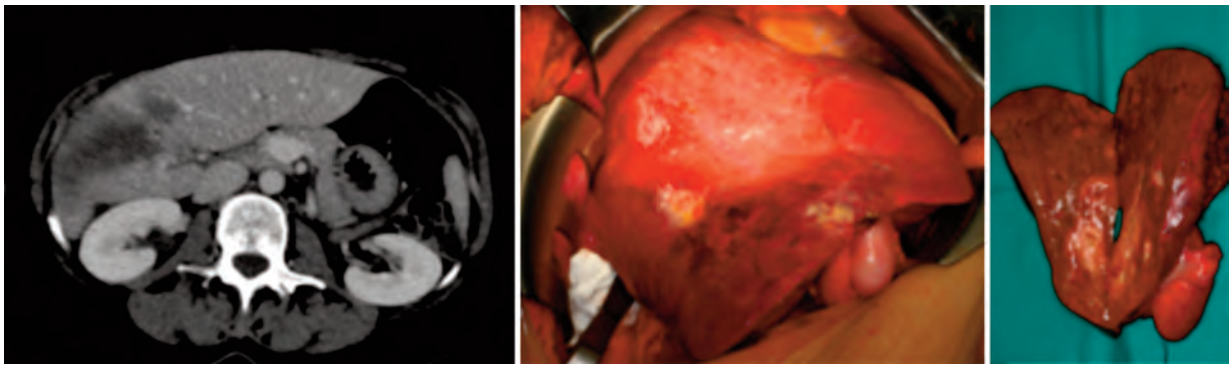

Figure 4. The onset of epithelioid hemangioendothelioma in a 19-year-old male patient. Right hepatectomy was performed with radical intent.

Primary Hepatic Lymphoma

The involvement of the liver in non-Hodgkin's lymphoma is common, whereas the occurrence of primary hepatic lymphoma is uncommon. In the literature no more than one hundred cases has been described. The majority of these cases are from autoptic studies. In the past three decades, the incidence of primary hepatic lymphoma has increased, mostly in immunosuppressed patients. With respect to the radiological findings, primary hepatic lymphoma often appears as a single nodule in the liver, but, especially in patients with immunodeficiency, multiple lesions can occur. A definitive diagnosis can be pursued only by histological-proven biopsy. Liver resection can offer good long-term results, especially in the case of solitary nodules. In patiens with advanced disease, chemotherapy can prolong survival[87].

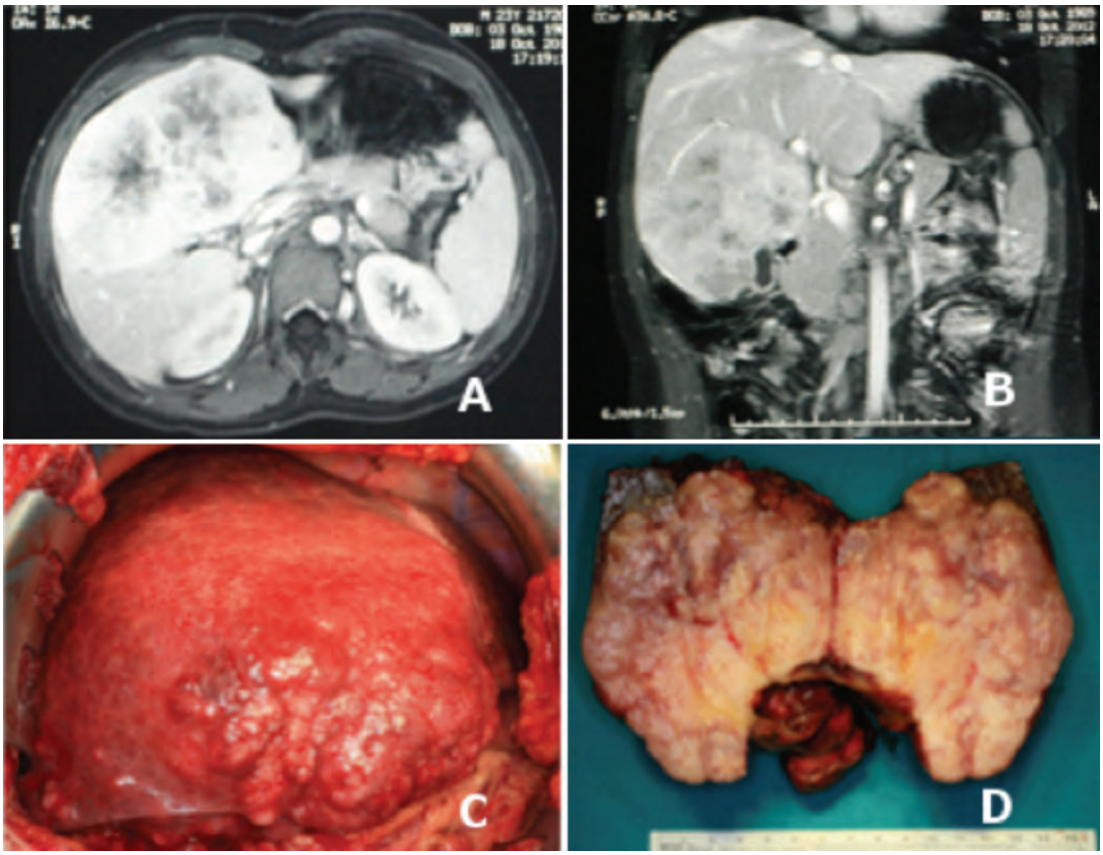

Figure 5. Hepatoblastoma in the right hepatic lobe.

Combined Hepatocellular and Cholangiocarcinoma

Combined hepatocellular and cholangiocarcinoma is a primary liver cancer that comprises the histological features of both HCC and ICC. It accounts for 0.4-14.2% of all primary liver carcinomas; it varies significantly with geographical location. Its risk factors are a combination of those of both HCC and CCC. Its presentation can mimic HCC or ICC and depends on the most prevalent cell type, therefore it can occasionally be misdiagnosed. As with ICC, 30% of cases present with a lymph-nodal spread. Liver resection that includes the hilar lymph node is the standard treatment. The reported median survival ranges from 20 to 47 months. Vascular and lymph node invasion and the presence of satellite metastases are predictors of poor outcome after resection. The recurrence rate is high, approximately 95% within 2 years after resection, accounting for the poor prognosis[88].

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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