

Hepatocellular carcinoma in a high-complexity public center in Argentina: epidemiological characteristics and therapeutic outcomes

Carcinoma hepatocelular en un centro público de alta complejidad en Argentina: características epidemiológicas y resultados terapéuticos

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Abstract

Objective: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality globally. In our region, there is a scarcity of studies addressing its epidemiology and treatment. The aim was to characterize a cohort of HCC patients in a high-complexity public center in Argentina over a span of 10 years. **Method:** This study employed a retrospective observational and analytical cohort design. All patients aged 18 and above, diagnosed with HCC between January 2013 and December 2022 at Hospital El Cruce, were included. **Results:** The cohort comprised 380 patients, 75% being male, average age of 57 ± 10.14 years. Cirrhotic liver was evident in 94% of cases. Surgery was employed in 182 (138 hepatic transplants, 44 surgical resections), locoregional therapies in 121 (104 sole transarterial chemoembolization, and 17 in combination), and one radiofrequency ablation. Systemic treatment was administered to 34 patients, 17 of whom received it as monotherapy. Mortality within the series according to the Barcelona Clinic Liver Cancer (BCLC) staging: 0, 1/2 (50%); A, 92/220 (41.8%); B, 60/98 (61.2%); C, 21/23 (91.3%); D, 37/37 (100%). **Conclusions:** HCC emerges as a complex tumor with an unfavorable prognosis, underscoring the pivotal role of prevention and early detection in improving outcomes.

Keywords: Hepatocellular carcinoma. Epidemiology. Liver transplant. Hepatic resection.

Resumen

Objetivo: El carcinoma hepatocelular (CHC) es la tercera causa mundial de muerte relacionada con el cáncer. En nuestro medio existen pocos estudios sobre su epidemiología y tratamiento. Nuestro objetivo fue caracterizar una cohorte de pacientes con CHC en un centro público de alta complejidad en Argentina durante 10 años. **Método:** Estudio retrospectivo de cohorte observacional y analítico. Se incluyeron todos los pacientes mayores de 18 años con diagnóstico de CHC entre enero de 2013 y diciembre del 2022 en el Hospital El Cruce. **Resultados:** Se incluyeron 380 pacientes, el 75% eran hombres; edad promedio 57 ± 10.14 años. El 94% de los casos se asentaron sobre hígado cirrótico. Se empleó cirugía en 182 pacientes (138 trasplantes hepáticos, 44 resecciones quirúrgicas), terapias locoregionales en 121 (104 quimioembolización transarterial como terapia única y 17 asociadas) y una ablación por radiofrecuencia. Se administró tratamiento sistémico a 34 pacientes (en 17 de ellos como única terapia). La mortalidad de la serie según la Barcelona Clinic Liver Cancer Classification (BCLC)

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fue como sigue: 0, 1/2 (50%); A, 92/220 (41.8%); B, 60/98 (61.2%); C, 21/23 (91.3%) y D, 37/37 (100%). **Conclusiones:** El CHC es un tumor complejo con mal pronóstico, por lo que la prevención y detección temprana son claves para mejorar los resultados.

Palabras clave: Carcinoma hepatocelular. Epidemiología. Trasplante hepático. Resección hepática.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, the fifth in men and eighth in women in the United States, with a five-year survival rate of approximately 18%. It is expected that by 2030, approximately 41,120 people will die from this disease¹. The similarity between incidence rate and mortality (830,000 deaths per year) underscores the grim prognosis associated with this disease². The highest prevalence and incidence rates in the world are found in the Asian and African continents. In Argentina, it represents the ninth leading cause of cancer death in men and the tenth in women, with an adjusted mortality rate between 2007-2011 of 4.3 and 2.3 respectively².

HCC diagnosis peaks in people between 60 and 70 years of age, predominantly affecting men^{3,4}. Incidence rate varies according to geographical region and ethnicity, which is largely attributed to the prevalence (and the degree and time of exposure) of the main risk factors. Most patients with HCC have a history of chronic liver disease due to chronic infections associated with hepatitis B virus (HBV) or C virus (HCV), alcohol abuse or alcoholic steatohepatitis (ASH), and non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). Obesity, diabetes mellitus, and nicotine consumption have also been associated with an increase in HCC incidence rate, as have other less frequent diseases such as hemochromatosis or hereditary tyrosinemia type 1.

The prevalence of risk factors varies globally, with a predominance of HBV in Asia, HCV in Japan, and NAFLD, NASH, and alcohol in Europe and North America. In most cases, the risk of developing HCC is multifactorial and includes demographic factors (age, sex, and ethnicity), severity and activity of underlying liver disease (stage and degree of fibrosis, inflammatory activity, and treatment), metabolic factors (diabetes and obesity), and factors related to exotoxin consumption (alcohol, tobacco, and other drugs). The global incidence rate of viral hepatitis-related HCC has decreased since the 2000s due to

the implementation of neonatal HBV vaccination programs and the availability of highly effective antiviral treatments for HBV and HCV^{5,6}.

It is well established that chronic liver disease predisposes to HCC formation; therefore, its prevention reduces the at-risk population. The effect of this strategy has been clearly demonstrated in Taiwan, where the introduction of a national HBV vaccination program for newborns in 1984 resulted in a 35.9% reduction in HCC incidence rate in those younger than 30 years⁷⁻⁹. Although there is no equivalent vaccine for HCV, the creation of direct-acting antivirals offers the possibility of eradicating HCV^{10,11}. Meanwhile, non-alcoholic liver diseases associated with obesity are emerging as dominant risk factors, making the implementation of public health policies to face this epidemiological transition urgent. Currently, there are few data to support the effectiveness of HCC surveillance programs in this subgroup of patients.

Unlike many other common tumor types, therapeutic options for HCC are mostly limited to cohort studies. Surgical approaches, such as liver transplant, liver resection, and radiofrequency ablation (RFA), have shown the best results in terms of long-term survival¹²⁻¹⁴. Regarding non-curative treatments, transarterial chemoembolization and systemic treatment are the only ones that have shown to improve survival^{15,16}. Epidemiological research related to HCC is crucial to understanding the distribution, causes, and risk factors of this pathology in our population. In Latin America, information on the prevalence, incidence, and risk factors of HCC remains limited due to the absence of national or regional databases. This approach is vital to establish preventive measures and generate control and surveillance strategies.

The objective of this study was to characterize a cohort of patients diagnosed with HCC at a public high-complexity center in Argentina over a 10-year period. Secondary objectives were to describe the demographic, etiological, and clinical characteristics of the population, diagnostic and therapeutic modalities implemented, survival, and HCC-related mortality.

Method

We conducted a retrospective study on a prospectively loaded observational and analytical cohort database. All patients older than 18 years diagnosed with HCC from January 2013 through December 2022 at *Hospital de Alta Complejidad en Red El Cruce* in Argentina were included. Cases with incomplete medical records or missing data that made HCC diagnosis impossible were excluded. Study data were uploaded and processed under strict confidentiality, as established by Laws 25.326 on Personal Data Protection and 26.529 on Patient Rights in their Relationship with Health Professionals and Institutions of the Argentine Civil Code. Approval was obtained from the Teaching and Research Committee of our institution. Cases with confirmed HCC and with follow-up or treatment at the institution were selected.

The data used were obtained from the Hospital Management System (SIGEHOS®) developed by the General Directorate of Information Systems of the Ministry of Health of the Autonomous City of Buenos Aires and the Galileo electronic inpatient medical record system (NOEMALIFE®). Electronic health records were manually reviewed for data collection, loading, and validation.

For HCC diagnosis, imaging modalities or anatomic-pathological analyses were used. The Liver Imaging Reporting and Data System (LI-RADS)¹⁷ was used for high-quality cross-sectional imaging studies (triphasic abdominopelvic multislice computed tomography [CT] or gadolinium-enhanced abdominal nuclear magnetic resonance imaging) in patients with underlying liver disease. Staging was completed with chest CT and bone scintigraphy in case of strong clinical suspicion. Liver cirrhosis was diagnosed according to liver tissue biopsy analyses or from clinical manifestations of its decompensation. The Child-Pugh and MELD (Model for End Stage Liver Disease) classifications were used to establish the prognosis of liver cirrhosis.

The Milan criteria¹⁸ were used for the selection of liver transplant candidates, and the Barcelona Clinic Liver Cancer (BCLC) stages¹⁹ were used to classify patients and guide the therapeutic approach.

All patients were discussed in an interdisciplinary panel. Following the clinical practice guidelines established by the BCLC guide, different therapeutic strategies were applied according to disease stages, underlying liver disease, and general patient conditions (curative, non-curative, or palliative intent). Overall survival was calculated according to BCLC stages.

Different demographic, etiological, and clinical variables related to HCC were analyzed. Data collection and tabulation were performed in Microsoft Excel 2019 (Microsoft Corporation, Redmond, Washington®). Statistical analysis was performed using the MedCalc Version 20.218 platform (MedCalc Software Ltd, Ostende, Belgium®).

HCC-related mortality rates were estimated using the Kaplan-Meier method for the different stages, calculating the Mantel-Cox test for comparison of the different curves. The chi-square test was used as needed to explore categorical variables (95% confidence interval [95% CI]; significance level [p] ≤ 0.05).

Results

A total of 572 electronic health records (EHRs) were analyzed, of which 71.7% presented HCC. After eliminating duplicate EHRs and those with insufficient or incomplete data to be included in the final sample, 380 patients were obtained.

A total of 75% of our population was male, with a mean age of 57 ± 10.14 years (range, 16-86, mode and median, 57). A total of 97.4% of patients were Argentine. A total of 94% of cases were based on cirrhotic liver. Demographic data and patient characteristics are shown in Table 1. Chronic HCV and HBV infection and alcohol abuse were the most frequent causes of liver disease (46.5 and 32.2%, respectively). The “cryptogenic” category (corresponding to the third cause in our series) was applied to cases without significant history of alcohol consumption, negative viral hepatitis markers, and without studies confirming other possible etiological factors. In 18 patients (5%), NAFLD/NASH was identified as the cause of cirrhosis. A total of 142 (40.3%) of the 353 patients with underlying liver disease were followed under a surveillance program and diagnosed under that strategy. The remaining patients were diagnosed based on clinical findings and/or imaging findings associated with the tumor or underlying liver disease (many of them referred from other centers to our center).

At the time of diagnosis, 203 (53.4%) were classified as Child-Pugh stage A, 116 (30.5%) as stage B, and 61 (16.1%) as stage C (Table 2). BCLC stages at diagnosis: 0, 2 (0.5%) cases; A, 220 (58.2%) cases; C, 23 (5.8%) cases, and D, 37 (9.7%) cases.

Of the 23 patients who did not have underlying liver disease, cases such as: a 30-year-old man with familial amyloid polyneuropathy (autosomal dominant

Table 1. Demographic and epidemiological characteristics of patients diagnosed with HCC between 2013 and 2022 (n = 380)

Characteristics	n = 380	%
M/F	286/94	75.3/24.7
Mean age (years)	56.7 ± 10.1	
National/Foreign	370/10	97.4/2.6
Underlying liver disease	357	93.9
Etiology of liver disease		
HCV	157	44
Alcohol	115	32.2
Cryptogenic	27	7.6
NASH	18	5
Autoimmune hepatitis	14	3.9
Primary biliary cirrhosis	10	2.8
HBV	9	2.5
Alagille syndrome	2	0.6
Secondary biliary cirrhosis	2	0.6
Hemochromatosis	2	0.6
Primary sclerosing cholangitis	1	0.3
HCV genotype		
Undetermined	92	58.6
1A	23	14.6
1B	16	10.2
1C	1	0.6
2A	3	1.9
3A	19	12.1
4A	3	1.9
Major comorbidities	242	63.7
Tumor size		
< 5 cm	139	
≥ 5 cm	53	
Alpha-fetoprotein		
< 8 ng/mL	158	41.6
≥ 8 ng/mL	222	58.4

NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B virus; HCV: Hepatitis C virus

hereditary amyloidosis characterized by systemic deposition of amyloid material in tissues, especially in peripheral nerves, caused by a mutated transthyretin variant, whose only effective treatment is liver transplantation, the organ of synthesis for this) in whose explant a well-differentiated 1 cm HCC was found; another 34-year-old man with hepatic adenomatosis who underwent videolaparoscopic segmentectomy VI, whose pathological anatomy revealed a well-differentiated 2 cm HCC and who refused to be placed on a waiting list for potential liver transplantation, and 2 patients with fibrolamellar variant HCC (2 women, one 18-year-old patient in advanced stage who underwent systemic therapy and another 16-year-old who underwent right hepatectomy for a large 10 cm x 12 cm tumor).

Table 2. BCLC stage at diagnosis (n = 380)

Child-Pugh stage	BCLC stage
A: 53.4 (n = 203)	0: 0.5 (n = 2)
B: 30.5 (n = 116)	A: 58.2 (n = 220)
C: 16.1 (n = 61)	B: 25.8 (n = 98)
	C: 5.8 (n = 23)
	D: 9.7 (n = 37)

BCLC: Barcelona Clinic Liver Cancer Classification.

Table 3 illustrates all the treatments initiated. Surgical treatment was performed in 182 patients (including 138 liver transplants and 44 surgical resections). Locoregional therapies were initiated in 121 cases (104 under transarterial chemoembolization as sole therapy and 17 associated with different systemic treatments) and one RFA. Systemic treatment was administered to 34 patients (17 of them as sole therapy).

Of the 44 surgical resections, 36 (81.8%) were performed conventionally. A total of 31 procedures (70.5%) were minor resections (≤ 2 liver segments)¹⁰. Major hepatectomies were always performed on patients without underlying liver disease. The laparoscopic approach was used in 19 cases, with a conversion rate of 52%, with hemostatic control and vascular invasion being the main causes. There was a preference for this approach in cirrhotic patients with an applicability of 55.2% ($p = 0.026$). The most widely used diagnostic modality was multislice CT (70.5%). The mean alpha-fetoprotein (AFP) value at the time of resection was $424 \pm 1,126.2$ ng/mL (range, 1.3–5,404.6 ng/mL). A total of 84% had a single nodule with a mean size of 47.3 mm (maximum transverse diameter, range, 12–200 mm). Multivisceral resection was performed in only 1 patient: segment VI was removed along with the right colon due to invasion by contiguity (histopathological examination revealed a poorly differentiated HCC, histological grade 3). Almost all patients (97.7%) were Child-Pugh A, with a mean MELD of 11.6 ± 4.7 (range, 5–11). Half of the resected patients experienced disease recurrence, 86.4% (19/22) in the liver. The mean disease-free survival was 16 ± 16.6 months (range, 2.3–74 months). The overall mortality rate of the subgroup was 38.6%. Overall survival rates at 1, 3, and 5 years were 77.2%, 47.7%, and 13.6%, respectively. Early recurrence was related to lower cellular differentiation, vascular compromise by invasion or tumor thrombosis, and higher

Table 3. Treatments administered

Treatment	n = 380	%
Liver transplant	138	36.3
TAE/TACE	104	27.4
Resection	44	11.6
Systemic	17	4.5
RFA	1	0.3
Other	76	
Palliation	37	9.7
Lost to follow-up	22	5.8
TACE + sorafenib	14	3.7
TACE + sunitinib	1	0.3
TACE + lenvatinib	1	0.3
TACE + docetaxel + 5-FU	1	0.3

5-FU: 5-fluorouracil; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization; TAE: Transarterial embolization

nuclear grade ($p = 0.05$). According to the Dindo-Clavien classification, the morbidity of the series was 47.7%, being mostly minor complications (88%). Mortality at 90 days was 6.8%. In the group of cirrhotic patients, two patients died due to multiorgan failure, and one non-cirrhotic patient died due to hospital-acquired pneumonia.

Regarding patients undergoing liver transplant, 113 (81.9%) met the Milan criteria, with supplementary points granted on the waiting list. A total of 59.4% (82) of patients had preserved liver function (Child-Pugh A), 27.5% were Child-Pugh B, and 13.1% were Child-Pugh C. The mean MELD score at transplant for those patients who were granted supplementary points was 23.6 vs 25 points for those who did not meet the Milan criteria. The most widely used diagnostic modality for HCC diagnosis was CT (68%). The mean AFP value at the time of transplant was 62.4 ± 158.4 ng/mL (range, 0.8-1,100 ng/mL). A total of 61.6% had a single nodule with a mean size of 30.6 mm (maximum transverse diameter, range, 15-52 mm). The mean waiting time for transplant was 10.1 ± 11 months (range, 1.1-58.4 months). Broken down by subgroups, the waiting time for those with supplementary points was 10.6 ± 11.9 vs. 8.1 ± 4.8 months for those who did not receive them. The mortality rate of the group was 30.4% (42). A total of 8.7% (12) of patients presented recurrence (4 in liver, 4 in lung, and 4 in bones). The mean disease-free survival was 24.7 ± 20.3 months. Transarterial chemoembolization (TACE) was performed in 49 patients (35.5%) as bridge therapy to transplant, with a mean of 1.2 sessions. Overall survival rates at

1, 3, and 5 years were 76.8%, 53.6%, and 23.18% respectively. Downsizing or downstaging was achieved in 71.4% of patients. Of these, 54.2% were ultimately able to access liver transplant.

Finally, of the 104 patients who received TACE as the sole treatment, the mean AFP before the start of treatment was $2,508.3 \pm 13,249.7$ ng/mL (range, 1.3-116,903 ng/mL). A total of 73.5% had preserved liver function (Child-Pugh A). None of the patients in the subgroup had severely impaired liver function (Child-Pugh C). The mean MELD score was 11 ± 3.6 . The preferred diagnostic modality was CT in 72.5% of cases. The mean number of LI-RADS V nodules per patient was 2.2, with a mean dominant nodule diameter of 53.5 mm and a mean sum of all lesion diameters of 77.2 mm. Tumor morphological follow-up and evaluation of treatment response for all patients were performed with CT. The mean number of therapeutic sessions was 1.7 (range, 1-7). The mortality rate of patients treated with TACE reached 85.6%. The mean survival was 11.2 ± 10.7 months.

Lastly, of the 17 patients who underwent systemic treatment exclusively, 64.7% (11) had extrahepatic metastases at the time of diagnosis (mainly in bones and lungs). The treatment of choice in most cases was sorafenib (76.5%, 12). In other cases, regorafenib or lenvatinib was used. All patients died, with a mean survival of 4.4 ± 4.9 months. According to the BCLC classification (and strictly analyzing case by case), 84.5% of patients (321 in total) received the recommended treatment, while 15.5% received another treatment option. Table 4 shows the treatment protocol administered according to the BCLC stage.

The mortality of the series according to the BCLC classification was as follows: 0, 1/2 (50%); A, 92/220 (41.8%); B, 60/98 (61.2%); C, 21/23 (91.3%), and D, 37/37 (100%).

The mean survival in months according to the BCLC classification and without considering the received treatment was: 0, 40 months; A, 32.9 months; B, 15.6 months; C, 5.9 months, and D, 1.7 months. Figure 1 illustrates the different survival curves according to the BCLC stages, complementing Table 5. Stage 0 is excluded because there were only two patients, so it cannot be extrapolated to the graph. Significant differences in survival were observed according to the stages ($p < 0.0001$).

Figure 2 shows the different survival curves according to the treatment initiated. RFA is excluded because there was only one patient, so it cannot be extrapolated to the graph. Significant differences in survival

were also observed according to the treatment initiated ($p < 0.0001$).

Discussion

In the present series of 380 HCC cases, the male sex was the most affected (75%), which is consistent with what was reported by Fassio²⁰ and Calderon Novoa²¹ in their 2 national series (72 and 71.4%, respectively). The age at diagnosis was 57 years vs the 62 and 64.7 years published by the previous authors. The main risk factor for HCC development continues to be underlying liver disease, present in 93.9% of cases (very similar to what was published by Fassio, 93%). Due to this, and as previously explained, current consensus recommends HCC screening by ultrasound every two years in patients with cirrhosis, HCV carriers with advanced fibrosis (F3-F4 of the METAVIR scale), and HBV carriers.

The main etiological factors in our cohort were viral hepatitis and alcohol abuse, which is consistent with the main causes of cirrhosis reported in Argentina. The percentage corresponding to cryptogenic/uncertain cirrhosis is intermediate between what is published in the references (5.2%²⁰ and 9.2%²¹). In 18 patients (5%), NAFLD/NASH was identified as the cause of cirrhosis. This percentage is striking, as it is very disparate from those published in the literature (close to 30%)²².

Surgical resection represents the main curative treatment option for patients with HCC. Surgical management of HCC patients with cirrhosis is complex (due to impaired liver function and the multiple comorbidities they generally present). HCC in a non-cirrhotic liver is less common than its counterpart in a diseased liver. In this population, liver resection should be the first-line treatment option if the tumor is technically resectable^{23,24}. The objective of liver resection is to completely remove the lesion with adequate margins (R0)²⁵⁻²⁷. Almost all resected patients (97.7%) had preserved liver function at the time of surgery. In our series, 29 resected patients were cirrhotic. The remaining 15 did not have cirrhosis; however, 3 of them had some degree of liver fibrosis associated with chronic HCV infection. The main disadvantage of resection is the high incidence of tumor recurrence in the liver, which occurs in up to 80% of patients²⁸. In our series, we reported a recurrence of 50% of resected patients, almost all of them (19 out of 22, 86.4%) in the liver. The mean disease-free survival was 16 ± 16.6 months (range, 2.3-74 months), similar

Table 4. Therapy implemented according to BCLC guidelines

BCLC stage (n)	Type of treatment
0 (n = 2)	1 RFA, 1 LT
A (n = 220)	128 LT, 40 TAE/TACE, 38 resection, 12 lost to follow-up, 1 TACE + sorafenib, 1 systemic
B (n = 98)	9 LT, 58 TAE/TACE, 1 systemic, 5 resection, 14 TACE + systemic, 11 lost to follow-up
C (n = 23)	3 TAE/TACE, 15 systemic, 1 resection, 1 TAE/TACE + sorafenib, 3 palliation
D (n = 37)	Palliation, 3 TAE/TACE

5-FU: 5-fluorouracil; RFA: Radiofrequency ablation; BCLC: Barcelona Clinic Liver Cancer Classification; TACE: Transarterial chemoembolization; TAE: Transarterial embolization; LT: Liver transplant

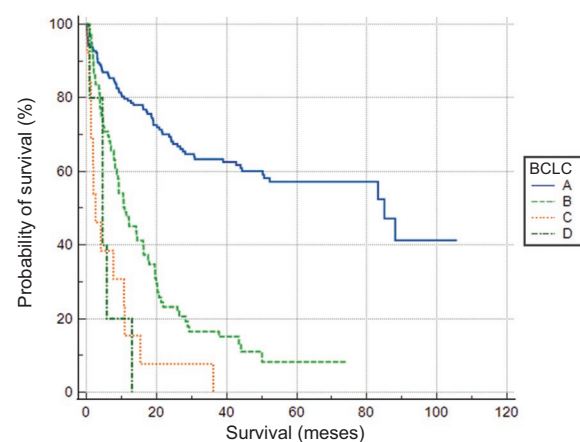


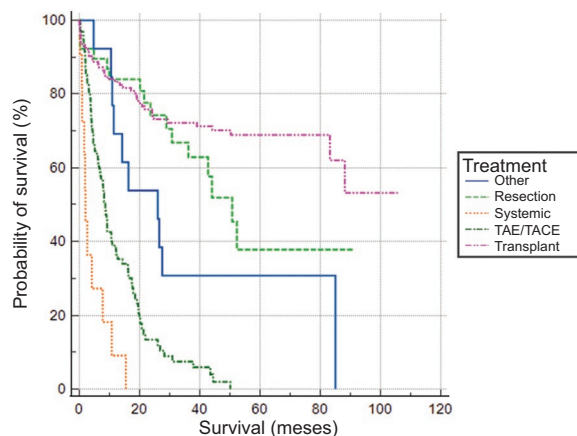
Figure 1. Survival of the different groups according to Barcelona Clinic Liver Cancer Classification (BCLC) stage.

to what is reported in the literature²⁸. On the other hand, in patients with HCC undergoing liver transplantation, a 5-year survival rate of 75-80% can be achieved with a low risk of recurrence (approximately 15%). Since the introduction of the Milan criteria in daily practice, survival rates after liver transplantation for HCC have significantly improved. Currently, the five-year overall survival of patients within the Milan criteria reaches rates similar to those for non-tumoral indications (65-70%)²⁹. The reason behind these superior results is that liver transplantation treats both HCC with wider surgical margins and the underlying liver cirrhosis (a key risk factor for tumor recurrence). The main limitation of this therapy is the scarcity of organs available for all patients who need it, so efforts have been made to select patients with the best expected outcomes after liver transplantation. On the

Table 5. Overall survival according to different BCLC stages

BCLC stage (n)	1 year	3 years	5 years
0 (n = 2)	100%	50%	50%
A (n = 220)	67.7%	44.1%	20%
B (n = 98)	46.9%	21.4%	11.2%
C (n = 23)	21.7%	12.3%	5.2%
D (n = 37)	5.4%	0%	0%

BCLC: Barcelona Clinic Liver Cancer Classification.

**Figure 2.** Survival of the different groups according to established treatment. TACE: transarterial chemoembolization; TAE: transarterial embolization.

other hand, the survival results of our series are very disparate from the estimated medians made by the BCLC stages: BCLC 0-A, 3.3 and 2.7 years (in contrast to what has been published [more than five years]); BCLC B, 15.6 months (vs. approximately 20-30 months); BCLC C, 5.9 months (vs. approximately 8-10 months), and BCLC D, 1.7 (vs. approximately 3 months)²⁸⁻³⁰.

We believe that this may be due to various factors: for the most part, patients evaluated by our unit are referrals, which may delay their effective entry into the hospital system. In line with the above, patients started their treatment later, which directly impacted survival. And due to the pandemic we suffered from 2020, patient follow-up was severely affected.

To avoid tumor progression, patients receive treatment while on the waiting list, which is known as “bridge therapy.” Patients can also receive specific treatments to reduce tumor mass and meet a particular criterion for transplantation, which is known as

downsizing or downstaging (there is no literal translation in our language, it could be interpreted as “size reduction” or “stage reduction”)³¹. TACE was performed in 49 patients (35.5%) as bridge therapy to transplant, with a mean of 1.2 sessions. Overall survival rates at 1, 3, and 5 years were 76.8%, 53.6%, and 23.18%, respectively. Downsizing or downstaging was achieved in 71.4% of patients undergoing this strategy (49), of whom half were ultimately able to access liver transplantation. This demonstrates the usefulness and importance of this concept to allow these patients, outside the classic transplant criteria, a chance of cure. The most widely used modality as bridge therapy is transarterial chemoembolization (the only one used so far by our team), although ablation or radiation therapy can also be used.

Finally, systemic therapy is the preferred treatment modality for patients with advanced HCC, as well as for patients with intermediate-stage HCC who do not qualify for local therapies. The survival of patients treated with systemic agents has improved significantly since 2017 with the introduction of new agents.

To ensure that patients are treated with optimal therapy, clinical decision-making requires a multidisciplinary team to evaluate and adapt therapeutic strategies. Although local therapies remain the cornerstone of treatment in early stages of the disease, there has been a paradigm shift in patients with intermediate HCC. As a result of substantial progress in systemic treatments, a critical review of the indication for locoregional therapies is mandatory. Studies have provided evidence that mean overall survival with TACE is significantly worse in unselected patient populations (mean overall survival < 20 months) vs selected patients with maintained liver function and small tumors (30-45 months)³¹. Therefore, guidelines recommend TACE in patients with disease limited to the liver, tumor size < 7 cm, without macrovascular infiltration, preserved liver function, and good functional status according to the ECOG (Eastern Cooperative Oncology Group) scale. In addition to identifying optimal candidates for local therapies, the opportunity and appropriate timing to transition from local to systemic therapies should not be overlooked.

We believe this study has several strengths. It has a high number of patients, considering that it is a single center with few years of existence (from the beginning). Being a national reference and referral center, the care of these patients has been concentrated by a specialized team (considering the low prevalence of HCC in our region). Since its conception as a high-complexity unit, multidisciplinary and

interdisciplinary work of various specialties has been available, with the fortune of having a wide range of therapeutic options. On the other hand, its retrospective nature hinders data collection, which could generate systematic errors such as information or classification biases. Because of this, several patients were excluded for not meeting the necessary data for the sample or for having been lost during follow-up.

Conclusions

HCC is a complex and aggressive tumor with a poor prognosis due to the cirrhosis on which it generally develops, which limits therapeutic options and increases the chances of recurrence. Despite numerous studies, it still presents low chances of cure, so primary prevention of cirrhosis and early detection of HCC are key to improving outcomes.

This study comprehensively addresses all aspects of HCC, from its etiology to its treatment and follow-up, and highlights both positive aspects and areas that need improvement. It is necessary to create prospective databases, as well as health policies to reduce the incidence of cirrhosis and HCC. The evolution of non-viral risk factors requires innovative prevention and surveillance strategies, and despite challenges in treatment, more effective therapies and more precise predictive biomarkers are being developed for personalized treatment. HCC research continues to advance, and there are reasons to be optimistic about improving treatment outcomes in the future.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of people and animals. The authors declare that no experiments on human beings or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed the confidentiality protocols of their institution, have obtained informed consent from the patients, and have the approval of

the Ethics Committee. The recommendations of the SAGER guidelines have been followed, according to the nature of the study.

Statement on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

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