REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

**Title:**
**Characteristics and outcome of incidental hepatocellular carcinoma after liver transplantation: a cohort study**

Authors:
Raquel Ríos León, Eugenia Sánchez Rodríguez , Antonio Martínez Ortega, Enrique Rodríguez de Santiago, Natalia Marcos Carrasco, Javier Graus Morales, Miguel Ángel Rodríguez Gandía, Jose Luis Lledó Navarro, Francisco Gea Rodríguez, Javier María Nuño Vázquez Garza, Agustín Albillos Martínez, Miguel García González

DOI: 10.17235/reed.2021.7744/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:
Ríos León Raquel, Sánchez Rodríguez Eugenia, Martínez Ortega Antonio, Rodríguez de Santiago Enrique, Marcos Carrasco Natalia, Graus Morales Javier, Rodríguez Gandía Miguel Ángel, Lledó Navarro Jose Luis, Gea Rodríguez Francisco, Nuño Vázquez Garza Javier María, Albillos Martínez Agustín, García González Miguel. Characteristics and outcome of incidental hepatocellular carcinoma after liver transplantation: a cohort study. Rev Esp Enferm Dig 2021. doi: 10.17235/reed.2021.7744/2020.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

**OR 7744**

# Characteristics and outcome of incidental hepatocellular carcinoma after liver transplantation: a cohort study

Raquel Ríos León[1], Eugenia Sánchez Rodríguez[1], Antonio Martínez Ortega[1], Enrique Rodríguez de Santiago[1], Natalia Marcos Carrasco[1], Javier Graus Morales[1,2], Miguel Ángel Rodríguez Gandía[1,2], Jose Luis Lledó Navarro[1,2], Francisco Gea Rodríguez[1,2], Javier María Nuño Vázquez Garza[3], Agustín Albillos Martínez[1,2] and Miguel García González[1,2]

[1]Servicio de Gastroenterología y Hepatología. Hospital Universitario Ramón y Cajal. Universidad de Alcalá. Madrid, Spain. [2]Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS). Madrid, Spain. [3]Unidad de Patología Hepática. Servicio de Cirugía General y del Aparato Digestivo. Hospital Universitario Ramón y Cajal. Universidad de Alcalá. Madrid, Spain

**Received:** 28/12/2020

**Accepted:** 23/02/2021

**Correspondence:** Raquel Ríos León. Servicio de Gastroenterología y Hepatología. Hospital Universitario Ramón y Cajal. Ctra. Colmenar Viejo, km 9,100. 28034 Madrid, Spain

e-mail: raquelriosleon@gmail.com

*Conflict of interest: the authors declare no conflict of interest.*

**ABSTRACT**

**Introduction:** despite advances in imaging diagnostic modalities, hepatocellular carcinoma is sometimes incidentally diagnosed on histological examination of the liver explant. The objectives of the study were: a) to compare the characteristics between incidental and known hepatocellular carcinoma; and b) to estimate survival and tumor recurrence after liver transplantation.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

**Material and methods:** a retrospective, single-center study was performed. The inclusion criteria were: a) cirrhotic patients, age ≥ 18 years; b) liver transplantation between 1998 and 2018; and c) hepatocellular carcinoma diagnosed via histopathologic examination of the explanted liver. Cholangiocarcinoma and patients with early retransplantation were excluded. Multivariate analysis was performed using binomial logistic regression to assess the factors associated with incidental hepatocellular carcinoma. Kaplan-Meier curves were plotted to explore the impact on overall survival and recurrence free survival.

**Results:** two hundred and sixty-nine patients were enrolled. The prevalence of incidental hepatocellular carcinoma was 4.18 % (95 % CI: 2.89-6.01 %) of all liver transplants performed in cirrhotic patients. The median diameter of the main nodule was smaller in incidental hepatocellular carcinoma (20 *vs* 27 mm, p = 0.004), although they were more likely to be beyond the Up-to-Seven criteria on explant examination (22.2 % *vs* 7.5 %, p = 0.001), with no differences in any other histological features. No differences were found in overall survival rates (incidental 70.2 % *vs* 70.4 %, p = 0.87) or recurrence-free survival (incidental 100 % *vs* 83.8 %, p = 0.07) at five years.

**Conclusion:** incidental hepatocellular carcinoma are smaller in size and are more frequently found to be beyond the Up-to-Seven criteria. However, no differences were found in overall survival rates or recurrence-free survival, although there was no tumor recurrence in the incidental hepatocellular carcinoma group.

**Keywords:** Incidental hepatocellular carcinoma. Liver transplantation. Survival. Tumor recurrence.

## INTRODUCTION

Liver transplantation (LT) is considered as the first-line treatment option for patients with hepatocellular carcinoma (HCC) who are not candidates for surgical resection (1,2). The overall five-year survival after LT of patients meeting Milan criteria ranges between 65 % and 80 % (2), with a recurrence rate of less than 10 % (3).

Non-invasive diagnosis of HCC is based on the vascular alterations that occur during hepatic carcinogenesis and the high pre-test probability of having HCC that cirrhotic

patients present (2). Ultrasound has a sensitivity of up to 84 % (4,5) and a specificity greater than 90 % (5). However, the sensitivity in early-staged HCC is 47 % and increases up to 63 % when combined with alpha-fetoprotein levels (4). A small size and well-differentiated HCC can be misdiagnosed as a regenerative or a dysplastic nodule, especially if ultrasound is the only technique performed (6).

The sensitivity of contrast-enhanced imaging techniques, multiphasic computed tomography (CT) and magnetic resonance imaging (MRI) for focal lesions smaller than 2 cm is low, even if they are both used in combination (2,6,7). In addition, it should be taken into account that HCC with a diffuse pattern might not be detected if the underlying hepatic parenchyma is very heterogeneous. On the other hand, small-sized and early hepatocellular carcinomas are usually composed of well-differentiated hepatocytes and their histological diagnosis on biopsy can be difficult, even for expert anatomopathologists (6).

Current data about both the incidence and prognosis of incidental hepatocellular carcinoma (iHCC) come from small series and is very heterogeneous among the different studies. The incidence of iHCC varies from 3.1 % to 30-40 % (8-11). Moreover, the results found in these studies regarding histological characteristics, recurrence rates and post-transplant survival of iHCC are often totally contradictory. These discrepancies do not seem to completely correspond to differences in the period of time when the data was collected. For all these reasons, it is difficult to extrapolate these results for clinical practice.

The primary objectives of the study were: a) to compare demographic, clinical and histological characteristics between iHCC and known hepatocellular carcinoma before transplant (kHCC); and b) to estimate survival and tumor recurrence after LT. The secondary objective was to determine the prevalence of iHCC in cirrhotic patients.

## MATERIAL AND METHODS

### Study design

A retrospective, analytical and unicentric study was performed. The inclusion criteria were: a) cirrhotic patients, age ≥ 18 years; 2) LT between January 1998 and January 2018 at Hospital Ramón y Cajal; and c) hepatocellular carcinoma

diagnosed via the histopathologic examination of the explanted liver. Patients with overlapping cholangiocarcinoma or early retransplantation (within the first seven days) were excluded.

The study protocol followed the principles of the Declaration of Helsinki (1975) and was approved by the Clinical Research Ethics Committee of our center (registration number: 065/18). The Ethics Committee determined that written informed consent was not required for this study due to its retrospective design. All patients signed an informed consent before liver transplant.

**Definition of main variables**

iHCC was defined as those tumors diagnosed via the histological analysis of the explant that had not been detected on any imaging tests performed prior to LT (8). If a patient had a previously known HCC and more nodules were found in the explanted liver analysis, they were categorized as kHCC.

Patients with a risk of recurrence after LT were defined as those with microvascular invasion, or satellitosis or who exceeded Milan criteria on liver explant examination (2,12).

Tumor recurrence was defined by the appearance of new suspicious nodules compatible with metastasis on imaging tests or by biopsy, either at the hepatic or extrahepatic level, within five years after LT. When the diagnosis was not anatomopathological, it was mandatory to prove no evidence of another primary tumor focus at diagnosis or during evolution.

**Data compilation**

Information on the clinical, analytical and histopathological characteristics was obtained from the clinical history. Alpha-fetoprotein levels were obtained from the last available blood test within the three months prior to transplantation. Tacrolimus blood levels (arithmetic mean) were obtained from the blood test performed within the first month post-transplantation. The presence of risk data (satellitosis, vascular invasion and low tumor differentiation according to the Edmonson-Steiner classification [13]) were recorded from the anatomopathological report of the explant.

**Procedures**

All patients were evaluated for LT following the pre-transplant protocol of our center. In our hospital, LT is performed with brain-dead donors. The initial study included a CT scan (with 1.5-mm slice thickness) and alpha-fetoprotein measurement. Those patients included on the liver transplant waiting list (LTWL) due to HCC also underwent a bone scintigraphy and a cranial scan.

Among those patients with HCC, only those who met the Milan criteria were included for LT. In such cases, follow-up while on the LTWL consisted of a monthly abdominal ultrasound and alpha-fetoprotein measurement and an extension study every four months. When no suspicious lesion was identified on imaging tests, neither at the time of inclusion on the LTWL nor during the follow-up, quarterly ultrasounds were performed and alpha-fetoprotein measurements were performed every 1-3 months according to the frequency of the reviews determined by the biochemical MELD, until LT. A CT and/or a MRI study was performed if a nodule was detected on an ultrasound during follow-up. A biopsy was performed if there were doubts about its malignant nature. Those lesions in which the diagnosis of HCC could not be confirmed were followed-up and the study reassessed when any changes in size or in radiological characteristics were detected. Unless contraindicated, all patients with HCC received a locoregional ablative treatment. All radiological tests and interventional radiology procedures were performed by radiologists specialized in HCC and by gastroenterologist sonographers. Histological analysis of the liver explant was performed by anatomopathologists specialized in liver pathology. Liver tissue was sectioned every 0.5 cm.

After transplantation, patients received immunosuppression with corticosteroids (most of them withdrawn during the first six weeks), tacrolimus and mycophenolate mofetil. In some cases, tacrolimus was replaced by cyclosporine. In some patients with kHCC, the calcineurin inhibitor was combined or replaced by everolimus. Post-transplantation follow-up consisted of blood tests that included drug levels and an abdominal ultrasound every three months along with periodic alpha-fetoprotein measurements.

**Statistical procedures**

Continuous quantitative variables are provided as the median and range, since a significant number of variables did not show a normal distribution. The Shapiro-Wilk test and graphical methods were used to check the normality of quantitative variables. Qualitative variables are expressed as their relative and absolute frequencies. For the univariate analysis, the Chi-squared or Fisher's exact test were used as appropriate for categorical variables. The population confidence interval (CI) at 95 % for the proportion of iHCC patients was calculated by the Wilson method. Analysis of variance or Mann-Whitney U-test for independent samples were used for quantitative variables according to the data distribution. Variables showing a $p < 0.10$ in the univariate analysis were included in the multivariate analysis. The presence of factors predictive of iHCC were assessed by backward stepwise binomial logistic regression. The linearity of the quantitative variables and the presence of co-linearity were confirmed via the variance inflation factor. Regression model goodness-of-fit was assessed by the Hosmer-Lemeshow test and its discrimination capacity via the area under the ROC curve (AUC). The best model was selected according to the AUC and the principle of parsimony.

Kaplan-Meier curves (Log-rank test) and multiple Cox's regression analyses were used to explore the impact of iHCC on overall survival and recurrence free survival. The initial multivariate Cox' model was composed by those variables with a $p < 0.20$ in the univariate analysis. The elimination of covariates was performed in a stepwise backward process. Variables with a p value between 0.05 and 0.15 were screened to identify potential confounding factors, and further removed from the model if they did not behave as such. All tests were two-tailed and significance was set at $p < 0.05$. All statistical tests were performed using the software package Stata version 14.1 (StataCorp., Texas, USA).

**RESULTS**

**Study population**

From a total of 646 liver transplants that were performed between January 1998 and January 2018 in cirrhotic patients, 290 patients met the inclusion criteria. Eight patients were excluded due to overlapping cholangiocarcinoma, two patients due to early retransplantation and eleven patients due to incomplete pathological reports. Finally, 269 patients were included in the study. The median follow-up was 61.3 months (range 23.6-119.4).

Of the 269 patients with HCC in the explant, 27 were iHCC (10.04 %, 95 % CI: 7-14.2 %). The iHCC accounted for 4.18 % (95 % CI: 2.89-6.01 %) of all transplants performed in cirrhotic patients (non-cirrhotic patients and acute liver failure were excluded), with no differences between liver transplants prior to 2008 (n = 14) and after 2008 (n = 13). The time on the LTWL was 246 ± 256 days (*vs* 212 ± 253, p = 0.35). The kHCC characteristics are shown in table 1. All patients that had been on the waiting list for more than six months had their HCC treated.

The characteristics of iHCC main tumoral nodules were:

- < 1 cm, n = 4 (1/4 multinodular).
- 1-1.9 cm, n = 9 (4/9 multinodular).
- ≥ 2 cm, n = 14 (7/14 multinodular)

In the multinodular group, three patients had diffuse HCC with an alpha-fetoprotein level before LT between 3.72 and 1,261.5 ng/ml. No suspicious lesions could be found during follow-up of the patient with an alpha-protein of 1,261.5 ng/ml, despite performing several imaging tests as established in our protocol. In the iHCC group, 18.5 % (5/27) received everolimus at any time, four of which (14.8 %) started everolimus during the first post-transplant year.

**Comparison between the iHCC group and kHCC**

This analysis is presented in table 2. The maximum diameter of the largest nodule was smaller in the iHCC group (p = 0.01). There were no differences in five-year recurrence-free survival or overall survival in the univariate or multivariate analysis (Figs. 1 and 2). No tumor recurrence was found in the iHCC. Table 3 shows the factors associated with tumor recurrence and survival. All patients with tumor recurrence (n = 21) died within the first five years after liver transplant, 71.4 % due to HCC.

**DISCUSSION**

In this study, we evaluated a 20-year experience in LT of patients with HCC. The proportion of iHCC was 4.18 % of all LT performed in cirrhotic patients. Patients with iHCC have excellent outcomes in terms of recurrence-free survival and a similar overall survival.

The distribution of the etiology of the hepatic injury was similar in both groups. Alcohol consumption and the coexistence of more than one etiology triggering liver damage were more likely to occur in iHCC than in kHCC. To the best of our knowledge, only one study (11) has found an etiology, specifically hepatitis C, to be more prevalent in kHCC (univariate statistical analysis) (8,14). Non-alcoholic fatty liver disease (NAFLD) is now ranked as the second-most common cause of LT and will likely overtake hepatitis as the number one cause of LT in the future (15). Furthermore, abdominal ultrasound is limited in NAFLD and half of the HCC cases arise in non-cirrhotic patients (15,16). CT and MRI may be indicated as the primary screening modality to reduce the incidence of iHCC in these patients (16).

There were no differences in the number of iHCC diagnosed during the two periods analyzed (1998-2007 and 2008-2018), established by the introduction of multislice computed tomography (16-slice detector) in our hospital. This suggests that radiologic diagnosis of pre-transplant HCC still persists as a pending subject, albeit the figures reported in the present study are among the lowest ever published in previous literature (8-11).

Regarding the histological characteristics, the main nodule in iHCC was smaller than in kHCC (11,17). However, some literature in this field argue that there are no differences in tumor sizes (14,17), while others report that they are smaller than 20 mm (8,11,18). Considering that all dynamic imaging techniques in our center were performed by radiologist's with a high grade of expertise and the technique used was protocolized, our results suggest that iHCC may not be incidental. This is due to their smaller size, since 51.9 % were ≥ 2 cm nodules, which is above the threshold where the imaging tests have a good sensitivity and specificity (2). This fact could be explained because these nodules might have a different radiologic behavior which could hide the

diagnosis. Like other studies (8,14,19), no differences were found when focusing on vascular invasion, satellitosis and grade of tumoral differentiation.

Up to 44.4 % of iHCC were multinodular, similar to kHCC, although they had not been detected on imaging tests. The proportion found by other studies is variable, between 15.2-54 % (10). There is only a radiological suspicion of HCC in the iHCC group (a patient with a 12 mm nodule, inconclusive for the HCC imaging-based diagnosis and alpha-fetoprotein level 1,261,5 ng/ml) that required up to three biopsies that were negative for malignancy. Elevated alpha-fetoprotein levels increase the risk of recurrence after LT, although no consensus has been achieved on alpha-fetoprotein thresholds that reliably predict poor prognosis (2). Moreover, its increase whist on LTWL is suggestive of the presence of an HCC, although alpha-fetoprotein levels did not increase in our patient during a five-month follow-up until LT.

The proportion of patients beyond Milan's criteria were similar in both groups (around 24 %). However, other authors (11) argue that iHCC are more likely to be within the Milan criteria (86 *vs* 67 %, univariate statistical analysis). Even though we found that iHCC were more likely to exceed the Up-to-Seven criteria (22.2 % *vs* 7.5 %), which has been previously associated to five-year recurrence rates as high as 49 % (20), there were no recurrences in our cohort. However, no significant differences were found in terms of recurrence, which could be due to the limited size of our cohort. Other studies have not reported differences in the proportion of patients exceeding the Up-to-Seven criteria or recurrence rates (8,19). Five-year recurrence rate is described to be 7-30 % among iHCC, in contrast to 15.4-39 % among kHCC (8,11,14,17,19). Despite the different recurrence rates in both groups, we could not prove any significant difference in alpha-fetoprotein. This significantly differs to previous studies where alpha-fetoprotein was higher in kHCC (19).

Five-year survival rates were similar in both groups (70 %), which concurs well with earlier studies (8,11,14,17). These similarities in survival rates might be due to the fact that, despite not having any recurrence among iHCC patients, their survival after LT was jeopardized by their impaired liver function (main indication for LT in this group) (21,22). In fact, 11.1 % of patients in this iHCC group died within the first 60 days after liver transplant, whilst only 3 % died among kHCC.

In addition, the more advanced liver disease in the iHCC group, although not significant in the multivariate analysis (MELD 21.1 ± 5 *vs* 18.1 ± 4), may suggest a heterogeneous liver parenchyma that does not allow the detection of an HCC. In the iHCC group, there were no differences in liver function between patients within or outside the Up-to-Seven criteria (MELD = 20 ± 4.5 *vs* 22 ± 5.5, respectively).

These findings are limited by the retrospective design, the wide recruitment period and the relatively reduced number of patients that were included in the iHCC subgroup. Notwithstanding these caveats, the strengths of this study are the existence of a pre-transplant evaluation protocol and the control of the possible confounding factors by performing a logistic regression.

In conclusion, iHCC appears to have different characteristics from kHCC, as main nodule tends to be smaller, almost half are multinodular and are more likely to exceed the Up-to-Seven criteria in the explant. However, despite these features, none of these incidental tumors recurred. Periodic dynamic imaging techniques (such as angio-CT) for patients awaiting liver transplantation, even if no suspicious lesion were detected at baseline, would be recommended to decrease the risk of iHCC, particularly in centers with prolonged waiting time for liver transplantation.

**REFERENCES**

1. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-14. DOI: 10.1016/S0140-6736(18)30010-2

2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.

3. Clavien PA, Lesurtel M, Bossuyt PM, et al. Recommendations for liver transplantation for hepatocelular carcinoma: an international consensus conference report. Lancet Oncol 2012;13:e11-22. DOI: 10.1016/S1470-2045(11)70175-9

4. Tzartzeva K, Obi J, Rich NE, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. Gastroenterology 2018;154:1706-18.e1. DOI: 10.1053/j.gastro.2018.01.064

5. Singal A, Volk ML, Waljee A, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocelular carcinoma in patients with cirrhosis. Aliment Pharmacol

Ther 2009;30:37-47. DOI: 10.1111/j.1365-2036.2009.04014.x

6. Forner A, Vilana R, Ayuso C, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology 2008;47:97-104. DOI: 10.1002/hep.21966

7. Sangiovanni A, Manini MA, Iavarone M, et al. The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. Gut 2010;59:638-44. DOI: 10.1136/gut.2009.187286

8. Pérez P, Rodríguez-Perálvarez M, Guerrero L, et al. Incidental hepatocellular carcinoma after liver transplantation: prevalence, histopathological features and prognostic impact. PLoS One 2017;12:e0175010. DOI: 10.1371/journal.pone.0175010

9. Klintmalm GB. Liver transplantation for hepatocellular carcinoma: a registry report of the impact of tumor characteristics on outcome. Ann Surg 1998;228:479-90. DOI: 10.1097/00000658-199810000-00005

10. Sotiropoulos GC, Malagó M, Molmenti EP, et al. Liver transplantation and incidentally found hepatocellular carcinoma in liver explants: need for a new definition? Transplantation 2006;81:531-5. DOI: 10.1097/01.tp.0000198739.42548.3e

11. Mourad MM, Algarni A, Aly MA, et al. Tumor characteristics and long-term outcome of incidental hepatocellular carcinoma after orthotopic liver transplant. Exp Clin Transplant 2015;13:333-8.

12. Perea Del Pozo E, Bernal Bellido C, Sendín Matín M, et al. Recurrent hepatocellular carcinoma after liver transplantation: analysis of risk factors. Transplant Proc 2016;48:2990-3. DOI: 10.1016/j.transproceed.2016.09.020

13. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954;7:462-503. DOI: 10.1002/1097-0142(195405)7:3<462::AID-CNCR2820070308>3.0.CO;2-E

14. Senkerikova R, Frankova S, Sperl J, et al. Incidental hepatocelular carcinoma: risk factors and long-term outcome after liver transplantation. Transplant Proc 2014;46:1426-9. DOI: 10.1016/j.transproceed.2014.03.010

15. American Association for the Study of Liver Diseases. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Clin Liver Dis (Hoboken) 2018;11:81. DOI:

10.1002/cld.722

16. Harris PS, Hansen RM, Gray ME, et al. Hepatocellular carcinoma surveillance: an evidence-based approach. World J Gastroenterol 2019;25:1550-9. DOI: 10.3748/wjg.v25.i13.1550

17. Castillo E, Pelletier S, Kumer S, et al. Incidental hepatocellular carcinoma after liver transplantation: population characteristics and outcomes. Transplant Proc 2009;41:219-21. DOI: 10.1016/j.transproceed.2008.10.053

18. Raphe R, Felício HC, Rocha MF, et al. Histopathologic characteristics of incidental hepatocelular carcinoma after liver transplantation. Transplant Proc 2010;42:505-6. DOI: 10.1016/j.transproceed.2010.01.034

19. Piñero F, Mendizábal M, Casciato P, et al. Is recurrence rate of incidental hepatocellular carcinoma after liver transplantation similar to previously known HCC? Towards a predictive recurrence score. Ann Hepatol 2014;13:211-8. DOI: 10.1016/S1665-2681(19)30884-1

20. D'Amico F, Schwartz M, Vitale A, et al. Predicting recurrence after liver transplantation in patients with hepatocellular carcinoma exceeding the up-to-seven criteria. Liver Transpl 2009;15:1278-87. DOI: 10.1002/lt.21842

21. Schlegel A, Linecker M, Kron P, et al. Risk assessment in high- and low-MELD liver transplantation. Am J Transplant 2017;17:1050-63. DOI: 10.1111/ajt.14065

22. Michard B, Artzner T, Lebas B, et al. Liver transplantation in critically ill patients: Preoperative predictive factors of post-transplant mortality to avoid futility. Clin Transplant 2017;31(12). DOI: 10.1111/ctr.13115

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

**Table 1. Characteristics of previously known hepatocellular carcinoma**

| | *Known hepatocellular carcinoma (n = 242)* |
|---|---|
| Treatment before LT* | 185/242 (76.4 %) |
| Time from the first treatment to LT* (days) | 315 (141-503) |
| Number of total treatments before LT* | 1 (0-2) |
| ≥ 1 Radiofrequency/microwave ablation | 57/242 (23.6 %) |
| ≥ 1 Transarterial chemoembolization | 136/242 (56.2 %) |
| ≥ 1 Percutaneous ethanol injection | 28/242 (11.6 %) |
| ≥ 1 surgical resection | 17/242 (7 %) |
| Everolimus initiated during the first year of LT* | 40/242 (16.5 %) |
| Everolimus initiated without tumor recurrence post-transplant | 66/242 (27.3 %) |

Continuous quantitative variables are provided as the median and range. LT: liver transplantation.

**Table 2. Comparison between incidental and previously known hepatocellular carcinoma**

| | *Incidental hepatocellular carcinoma (n = 27)* | *Known hepatocellular carcinoma (n = 242)* | *Univariate analysis* | *Multivariate analysis** |
|---|---|---|---|---|
| Age (years) | 60 ± 15 | 57 ± 11 | 0.55 | - |
| Male sex | 21 (77.8 %) | 198 (81.8 %) | 0.61 | - |
| Hepatitis C | 18 (66.7 %) | 159 (66 %) | 0.94 | - |
| Hepatitis B | 3 (11.1 %) | 24 (10 %) | 0.85 | - |
| Alcohol | 14 (51.9 %) | 75 (31.1 %) | 0.03 | - |
| Others etiologies | 2 (7.41 %) | 20 (8.3 %) | 1 | - |
| More than 1 etiology | 10 (37 %) | 36 (15 %) | 0.012 | *0.007* |
| HIV | 3 (11.1 %) | 16 (6.6 %) | 0.42 | - |
| Biopsy pre-transplant | 1 (3.7 %) | 91 (33.8 %) | < 0.001 | *0.01* |
| Waiting list time (days) | 246 ± 256 | 212 ± 253 | 0.35 | - |
| Alpha-fetoprotein (ng/ml) pre-transplant | 16.24 ± 54.11 | 8.37 ± 24.43 | 0.59 | - |
| MELD pre-transplant | 21.1 ± 5 | 18.1 ± 4 | < 0.001 | *0.08* |
| Main nodule diameter (mm) | 20 ± 15 | 27 ± 16 | < 0.001 | *0.004* |
| Number of nodules | 1 ± 3 | 1 ± 1 | 0.4 | - |
| Multinodular | 12 (44.4 %) | 100 (41.3 %) | 0.06 | - |
| Existence of any | 5 (18.5 %) | 52 (21.9 %) | 0.68 | - |

| | | | | |
|---|---|---|---|---|
| recurrence data risk | | | | |
| Satellitosis | 2 (7.4 %) | 27 (11.2 %) | 0.75 | - |
| Microvascular invasion | 2 (7.4 %) | 25 (10.3 %) | 1 | - |
| Low tumor differentiation | 0 | 15 (6.3 %) | 0.38 | - |
| Within Milan criteria | 20 (74.1 %) | 188 (78 %) | 0.64 | - |
| Within Up-to-Seven criteria | 21 (77.8 %) | 223 (92.5 %) | 0.02 | *0.001* |
| Tacrolimus level (arithmetic mean) in the first month (ng/ml) | 8.16 (5.57-11.64) | 9.4 (6.78-12.74) | 0.43 | - |
| Everolimus started without tumor recurrence | 5 (18.5 %) | 66 (27.3 %) | 0.93 | - |

Continuous quantitative variables are provided as the median and range. *****Non conditional binomial logistic regression. P-Hosmer Lemeshow = 0.49. AUC = 0.84.

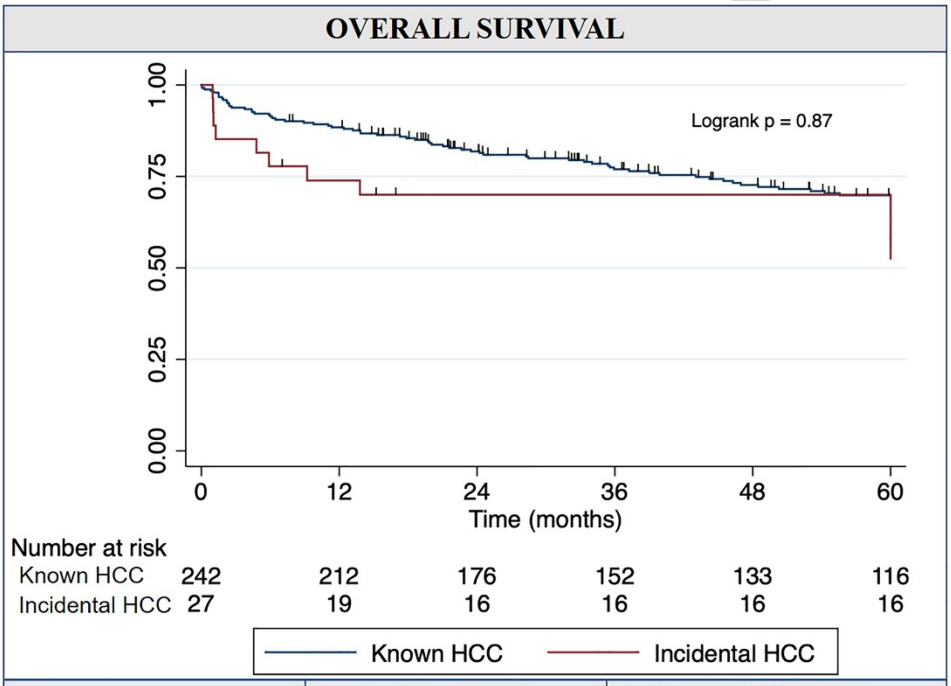
REVISTA ESPAÑOLA DE ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

**Table 3. Factors associated with recurrence-free survival and overall survival five years after liver transplantation**

| | *No recurrence (n = 248)* | *Recurrence (n = 21)* | *Univariate/ multivariate analysis** | | *Survival (n = 195)* | *Death (n = 74)* | *Univariate/ multivariate analysis** |
|---|---|---|---|---|---|---|---|
| Age (years) | 57 ± 10 | 53 ± 11 | 0.2 | | 57 ± 10 | 59 ± 11 | *0.2/0.04* (HR = 1.02) |
| Male sex | 202/248 (81.5 %) | 17/21 (81 %) | 0.7 | | 162/195 (83.1 %) | 17/74 (23 %) | 0.7 |
| Hepatitis C | 160/247 (64.8 %) | 17/21 (81 %) | 0.6 | | 120/195 (61.5 %) | 57/73 (78.1 %) | 0.01/0.07 |
| Hepatitis B | 26/247 (10.5 %) | 1/21 (4.8 %) | 0.6 | | 24/195 (12.3 %) | 3/73 (4.1 %) | 0.05/0.1 |
| Alcohol | 83/247 (33.6 %) | 6/21 (28.6 %) | 0.6 | | 66/195 (33.8 %) | 23/73 (31.5 %) | 0.8 |
| More than 1 etiology | 42/247 (17 %) | 4/21 (19 %) | 0.9 | | 30/195 (15.4 %) | 16/73 (21.9 %) | 0.1/0.1 |
| HIV | 19/247 (7.7 %) | 0/21 (0 %) | 0.9 | | 17/195 (8.7 %) | 2/73 (2.7 %) | 0.5 |
| Within Up-to-Seven criteria | 225/247 (91.1 %) | 19/21 (90.5 %) | 0.02/0.7 | | 177/195 (90.8 %) | 67/73 (91.8 %) | 0.8 |
| Incidental hepatocellular carcinoma | 27/248 (10.9 %) | 0/21 (0 %) | 0.105/0.2 | | 19/195 (9.7 %) | 8/73 (11 %) | 0.9 |
| Multinodular | 102/245 (41.6 %) | 10/21 (47.6 %) | 0.01/0.2 | | 83/193 (43 %) | 29/72 (40.3 %) | 0.97 |
| Satellitosis | 20 /247 (8.1 %) | 9/21 (42.9 %) | < *0.001/0.02* (HR = 3.7) | | 18/195 (9.2 %) | 11/73 (15.1 %) | 0.3 |
| Low tumor differentiation | 12/244 (4.9 %) | 3/20 (15 %) | 0.06/0.06 | | 8/192 (4.2 %) | 7/72 (9.7 %) | 0.2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Microvascular invasion | 21/247 (8.5 %) | 6/21 (28.6 %) | 0.01/0.1 | *Tumor recurrence* | 0/195 (0 %) | 21/73 (28.8 %) | *< 0.001/< 0.001* (HR = 2.6) |
| Main nodule diameter (mm) | 25 ± 17 | 37.5 ± 25 | 0.001/0.7 | | | | |
| Alpha-fetoprotein pre-transplant (ng/ml) | 8.16 ± 17.23 | 112.37 ± 531.05 | *< 0.001/< 0.001* (HR = 1) | | | | |

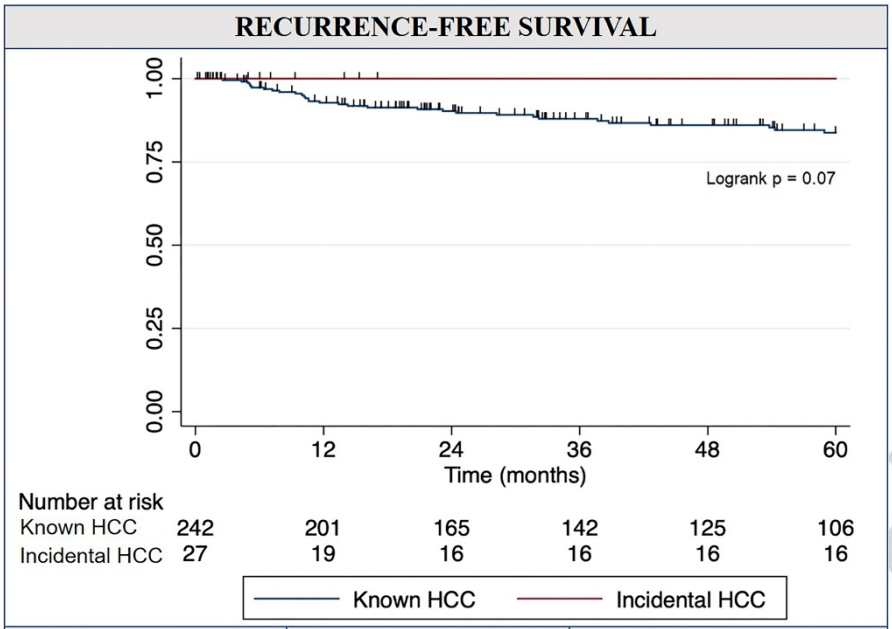
Continuous quantitative variables are provided as the median and range. *Cox-regression. HR: hazard ratio.




| | Know HCC | Incidental HCC |
|---|---|---|
| **Overall survival at 1 year** | 88% | 74.1% |
| **Overall survival at 3 years** | 77.3% | 70.2% |
| **Overall survival at 5 years** | 70.4% | 70.2% |

Fig. 1. Survival curves showing overall survival. One hash mark is placed at each censoring time. HCC: hepatocellular carcinoma.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology




| | Know HCC | Incidental HCC |
|---|---|---|
| Recurrence-free survival at 5 years | 83.8% | 100% |

Fig. 2. Survival curves showing recurrence-free survival. One hash mark is placed at each censoring time. HCC: hepatocellular carcinoma.