# CIRUGÍA ESPAÑOLA

## Original article

# Surgical treatment of liver cancer: experience of the A Coruña UHC (Spain)

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ARTICLE INFORMATION

ABSTRACT

*Introduction:* Liver cancer (LC) is one of the most frequent tumours, in which the potentially curative treatment is surgery: partial surgical resection or liver transplant.
*Objectives:* To determine the morbidity and mortality, survival, and their associated factors in patients with LC, according to the type of surgical treatment: partial surgical resection or liver transplant.
*Material and methods:* A retrospective, observational follow-up study of LC patients diagnosed and treated from June 1994 to December 2007. A descriptive analysis of the variables was performed, as well as a Kaplan- Meier survival analysis and Cox regression.
*Results:* The incidence of tumour recurrence in the 150 transplant patients was 13.3%, with a survival at 1, 3, and 5 years of 89.3%, 73.1% and 61.4%, respectively. The multivariate analysis showed that only the histological grade/differentiation was an independent risk factor. In the 33 patients with partial surgical resection, the incidence of tumour was 51.5%, with a survival at 1, 3, and 5 years of 90.9%, 60.2%, and 38.6%, respectively. A significantly higher mortality was observed in patients with higher tumour and TNM staging.
*Conclusions:* The survival throughout follow-up was higher in liver transplant, and tumour recurrence was more frequent in patients with partial surgical resection. The survival results in transplanted patients are consistent with the Spanish and European Liver Transplant Register and with the United Network for Organ Sharing register.

### Tratamiento quirúrgico del hepatocarcinoma: experiencia del CHU A Coruña

RESUMEN

*Introducción:* El hepatocarcinoma (HCC) es uno de los tumores más frecuentes, y su tratamiento potencialmente curativo es la cirugía: resección quirúrgica parcial o trasplante hepático.

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Tratamiento ablativo
Supervivencia

*Objetivos:* Determinar la morbimortalidad, la supervivencia y sus factores asociados en pacientes con HCC según tipo de tratamiento quirúrgico: trasplante hepático o resección quirúrgica parcial.

*Material y métodos:* Estudio observacional de seguimiento retrospectivo de HCC diagnosticados y tratados de junio de 1994 a diciembre de 2007. Se realiza un análisis descriptivo de las variables, análisis de supervivencia Kaplan-Meier y regresión de Cox.

*Resultados:* En los 150 pacientes trasplantados, la incidencia de recidiva tumoral es del 13,3%, con supervivencias a 1, 3 y 5 años del 89,3, el 73,1 y el 61,4% respectivamente; el análisis multivariable demuestra que sólo el grado de diferenciación histológica es factor de riesgo independiente. En los 33 pacientes con resección quirúrgica parcial, la incidencia de recidiva tumoral fue del 51,5%, con supervivencias a 1, 3 y 5 años del 90,9, el 60,2 y el 38,6%. Se evidencia una mortalidad significativamente mayor en pacientes con estadio tumoral y TNM superiores.

*Conclusiones:* La supervivencia en el seguimiento es mayor con trasplante hepático y la recidiva tumoral es más frecuente en pacientes con resección quirúrgica parcial. Los resultados de supervivencia en pacientes trasplantados coinciden con el Registro Español y Europeo de Trasplante Hepático y el registro de la United Network for Organ Sharing.

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## Introduction

Liver cancer (LC) is one of the most frequent tumours. They comprise 90% of the primary malignant neoplasms of the liver are one of the most common tumours in the world.[1] They are the fifth most common type of cancer and the third cause of death in the world.[2]

Incidence varies greatly between geographical areas, so there are areas in which incidence is low (northern European countries, USA and Canada), medium (Spain and Mediterranean countries) and high (countries of south-eastern Asia, China, Japan and sub-Saharan Africa).[3-6] In Spain, the incidence is 6-8 cases per 100 000 inhabitants/year, and is more common in men than in women, with a ratio of 3-8:1.[7,8]

Ninety-five percent of LC occurs in patients with a cirrhotic liver. Tumour development is particularly common when the aetiology of the cirrhosis is hepatitis B or C virus, $\alpha_1$-antitrypsin deficiency or haemochromatosis, or when 2 or more epidemiological risk factors coincide.[9] In patients with cirrhosis of the liver, the annual incidence of LC is 3%-5%, this being the main cause of death in this group.[10]

The only potentially curative treatment is surgery (partial resection or liver transplant [LT]), but only 10%-20% of LC patients can receive this treatment at the time of diagnosis due to the advanced stage of the disease. In view of this, other treatment options for LC have been developed. These include local ablative therapy (radiofrequency ablation, percutaneous ethanol injection, etc.), transarterial chemoembolisation, radiotherapy, chemotherapy, and immunotherapy.

No prospective, randomised studies (level 1 evidence) have been performed comparing the two surgery options (partial resection or LT), so the choice of the treatment is based on retrospective series and the opinions of experts.

Liver transplants are considered the best treatment for LC because they not only treat the tumour, but also the underlying disease that led to LC. However, mainly because of the shortage of organs and the long waiting lists, during which tumour progression may occur, the criteria and technique for surgical resection have been improved.[11]

Most transplant groups follow the Milan criteria established by Mazzaferro et al in 1996.[12] The long-term outcome of LT with the Milan criteria, like in transplant patients with incidental LC, is the same as that obtained with benign diseases, with a 5-year survival rate ranging between 60% and 75%,[12-15] and 5-year recurrence rates of between 10% and 15%.[16,17]

The best candidates for surgical resection are patients with good liver function (Child-Pugh A), without portal hypertension (hepatic pressure gradient <10 mm Hg), and with single tumours which are well-defined, peripheral and with a diameter <5 cm.[18-20] Cirrhotic patients with more advanced Child-Pugh stages or with portal hypertension suffer higher rates of perioperative mortality.[21]

## Material and methods

An observational, retrospective follow-up study was conducted on LC patients diagnosed in the A Coruña University Hospital between June 1994 and December 2007. We collected and updated the data until December 2008.

The diagnosis of LC was made following the consensus recommendations reached at the conference in Barcelona in 2000: a compatible liver biopsy, 2 compatible imaging tests for lesions >2cm, or an imaging test together with an alpha-fetoprotein (AFP) level >100 UI/l in cirrhotic patients.[22] The preoperative studies included an analysis of liver function, AFP, viral serology, an abdominal ultrasound, and a thoracic-abdominal CT scan; and MRI scans of the liver were performed on selected cases.

Patients were included who were diagnosed with LC and treated with partial surgical resection or LT, and patients who underwent a LT without a preoperative diagnosis of LC,

but this was revealed in an anatomical-pathological study of their liver (incidental LC). Like most transplant teams, we performed LT in patients with LC who fulfilled the Milan criteria defined by Mazzaferro et al[12]: single tumour nodule <5 cm, or less then three nodules with the biggest not exceeding 3 cm in diameter, and no evidence of tumour thrombosis of the portal and suprahepatic veins or distant metastases. Liver resection was indicated in patients with good liver function (Child-Pugh A), provided that tumours were accessible, and in selected cases with Child-Pugh stage B who met the criteria for LT. A rescue LT was indicated in 3 liver resected patients with tumour recurrence that fulfilled the criteria for a LT, in accordance with what has been reported in the literature.[23-25]

The following variables were studied: sex, age, underlying disease, AFP level, Child-Pugh stage, tumour-node-metastasis (TNM) staging, Cancer of Liver Italian Program (CLIP) classification, number of nodules, location, vascular involvement, degree of differentiation, metastases, type of treatment (liver transplant or partial surgical resection), and follow-up variables (disease-free interval, stage, survival, cause of death).

In the statistical analysis, a descriptive study was performed of all the variables. The qualitative variables are expressed as absolute values and percentages. The quantitative variables are expressed as means ± standard deviation.

The Student t test or the Mann-Whitney test was used as applicable for comparisons of means after testing normality with the Kolmogorov-Smirnov test. The chi-square statistic was calculated to determine the association between 2 qualitative variables. To calculate the likelihood of survival during follow-up we performed an actuarial analysis following the Kaplan-Meier methodology. To estimate survival and its associated variables, we performed a multivariate Cox regression analysis, adjusting for all the variables found to be associated with mortality or clinically relevant in the univariate analysis.

Confidentiality was assured by compliance with the Spanish data protection act RD 15/1999, and the study was authorised by the ethics committee for clinical research of the region of Galicia (record number 2009/166).

## Results

One hundred and fifty out of the 183 patients underwent a transplant and 33 underwent partial surgical resection. Table 1 shows the general characteristics of the patients.

Most of the 150 LT patients were men, and the most common underlying disease was alcoholism, followed by HCV. Most of the transplant patients presented with a single tumour nodule, and the most common Child-Pugh stage was A. The most common stages were T2 and TNM stage II. Most patients underwent transplantation as the only treatment for the LC, but 28.7% received neoadjuvant therapy before surgery. The most common adjuvant ablative therapy was transarterial chemoembolisation (35.6%), followed by alcoholisation (22.2%) and the combination of alcohol and radiofrequency ablation (22.2%). Only 3 patients underwent

liver transplantation as rescue surgery after a partial liver resection. The most common location of the tumour was the right hepatic lobe (RHL), with no vascular invasion in most patients. With regard to histological differentiation, we found that most tumours were moderately differentiated.

40% of the transplant patients died during follow-up. The most common cause of death was tumour recurrence (33.3%), followed by a relapse of the underlying disease (20%). The median disease-free interval was 41.5 months. At the end of the follow-up, 83.5% of the patients showed complete resolution of the disease.

| Table 1 – General characteristics of the patients included according to the treatment received | | |
|---|---|---|
| Variables | Liver transplant | Partial surgical resection |
| *Age, years* | 56.4±7.7 | 59.3±14.2 |
| *Tumour size, cm* | 3.1±1.4 | 5.7±3.6 |
| *Disease-free interval, months* | 51.7±42.8 | 23.9±19.6 |
| *Sex* | | |
| Male | 132 (88) | 26 (78.8) |
| Female | 18 (12) | 7 (21.2) |
| *Underlying disease* | | |
| HVC | 57 (38) | 17 (51.5) |
| HVC | 11 (7.3) | 0 |
| Alcoholism | 66 (44) | 4 (12.1) |
| *Child-Pugh* | | |
| A | 62 (41.3) | 25 (75.8) |
| B | 50 (33.3) | 6 (18.2) |
| C | 38 (25.3) | 2 (6.1) |
| *Tumour location* | | |
| RHL | 89 (59.3) | 20 (60.6) |
| LHL | 14 (9.3) | 8 (24.2) |
| Both | 47 (31.3) | 5 (15.2) |
| *Vascular invasion* | | |
| No | 109 (72.7) | 18 (54.5) |
| Microvascular | 26 (17.3) | 12 (36.4) |
| Macrovascular | 15 (10) | 3 (9.1) |
| *Current situation* | | |
| Resolution | 128 (85.3) | 13 (39.4) |
| Recurrence | 20 (13.3) | 17 (51.5) |
| *Stage* | | |
| Alive | 90 (60) | 14 (42.4) |
| Dead | 60 (40) | 19 (57.6) |
| *Cause of death* | | |
| Tumour recurrence | 20 (33.3) | 16 (84.2) |
| Underlying disease recurrence | 12 (20) | 1 (5.2) |
| *De novo* tumour | 7 (11.7) | 0 |
| Others | 21 (35) | 2 (10.5) |

HBV indicates hepatitis B virus; HCV, hepatitis C virus.LHL, left hepatic lobule; RHL, right hepatic lobule.
Data expressed as mean ± standard deviation or n (%).

**Overall survival of the transplant patients**



**Overall survival of the patients undergoing partial surgical resection**
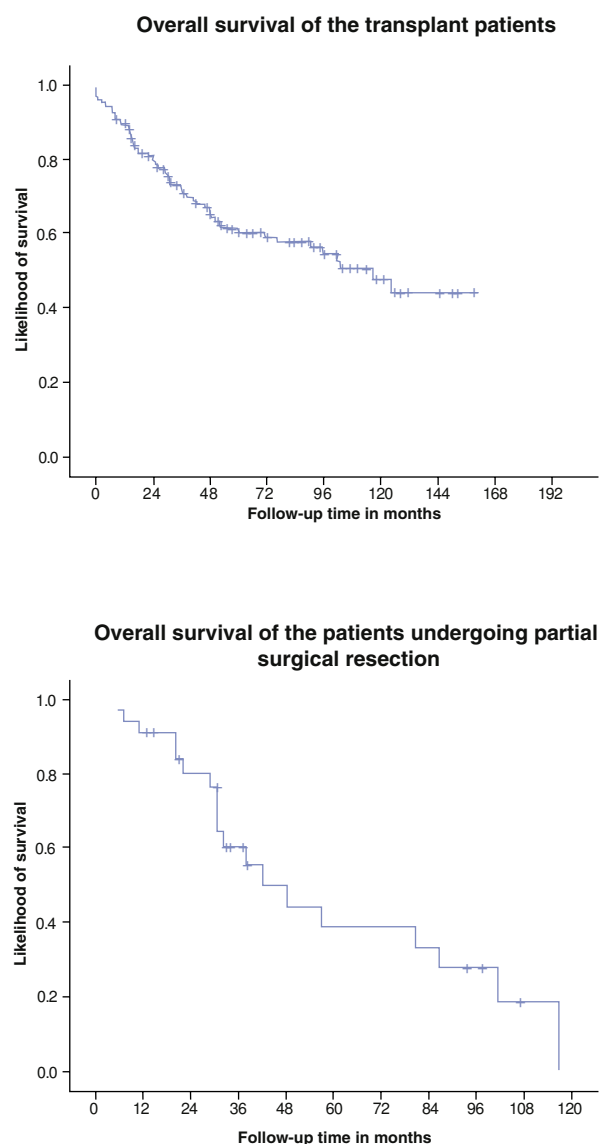


**Figure – Overall patient survival depending on the type of treatment.**

The incidence of tumour recurrence was 13.3%. Survival at 1, 3, 5, and 10 years was 89.3%, 73.1%, 61.4%, and 47.8%, respectively (Figure).

In the univariate analysis, we found no statistically significant differences between living and dead patients with regard to the following variables: age, AFP, size of nodules, number of nodules, incidental diagnosis, underlying disease, and Child-Pugh stage. No differences were found with regard to the T, TNM, or CLIP stages, or in relation to the variables ablation therapy, surgery and treatment category, tumour location, and the presence or absence of metastasis. The univariate analysis did show differences with regard to sex, with higher mortality rates among women than men, and in relation to vascular involvement and the degree of histological differentiation. The patients who died had more macrovascular involvement and lower degrees of histological differentiation.

Adjusting for the covariables age, sex, vascular involvement, and degree of histological differentiation, the variable having an independent effect for predicting mortality in transplant patients was the degree of histological differentiation, with significantly worse survival rates when histological differentiation was poor. The patients with poorly-differentiated LC are 4.03 times more likely to die. Macrovascular involvement, in turn, also increases the risk of mortality (relative risk [RR]=2.23), on the limit of statistical significance (Table 2).

In the group of 33 patients undergoing partial surgical resection we detected a predominance of men, and the most common underlying disease was HCV. Most had one single tumour nodule, and the most common Child-Pugh stage was A. The most common stages were T3 and TNM stage II. Half of the patients received other treatment besides surgery. The most commonly associated therapy was radiofrequency ablation, followed by embolisation. The most common location was the RHL. Half of the patients presented with no vascular involvement, and just over half presented with moderately-differentiated carcinomas in the histological analysis.

During follow-up, 57.6% died and the most common cause of death was tumour recurrence. The incidence of tumour recurrence was 51.5%. Survival at 1, 3, and 5 years among these patients was 90.9%, 60.2%, and 38.6%, respectively (Figure).

In the univariate analysis, the patients who died had higher AFP levels, bigger tumours and more nodules, although these differences were not significant. Mortality was significantly higher in patients with higher tumour and TNM staging. We did not perform multiple comparisons or Cox regression models due to the lack of statistical power to detect differences between the groups, as the only variable that was statistically significant between the patients who died and those who survived was the staging.

Table 3 shows the prognostic variables according to the different treatment procedures.

## Discussion

In agreement with the results of other authors,[9] most patients in the transplant group had LC in a diseased liver, as only 1.3% of the cases had no underlying disease. As in other series in western countries,[26,27] alcohol is the main causal agent (44% of the cases), followed by HCV (38% of cases). The incidence of incidental LC (not previously known) found in the literature varies greatly, ranging between 15% and 50%.[28-30] In our series the incidence was 14.7%.

The incidence of tumour recurrence among our patients was 13.3%, similar to the data found in the literature.[28,29,31,32] Survival at 1, 3, 5 and 10 years among this group of patients in our series was 89.3%, 73.1%, 61.4%, and 47.8%, respectively, similar to the data in the literature. The 1.5-, 5- and 10-year survival rate for 2600 LT for liver cancer (2001-2007) was 85.2%, 64.5% and 49.4%, respectively, on the *Registro Español de Trasplante Hepático* (Spanish liver transplant registry). Among 6000 cases of LT in the European Liver Transplant Registry (ELTR), survival at 1, 3 and 5 years was 82%, 70% and 60%, respectively, similar to that found in the registry of the UNOS

**Table 2 – Cox regression model to predict mortality in transplant patients, adjusting for the covariables age, sex, vascular involvement, and degree of differentiation**

| Variables | β | RR (95% CI of RR) | P |
|---|---|---|---|
| Age | −0.009 | 0.991 (0.96-1.023) | .564 |
| Sex | 0.494 | 1.639 (0.818-3.284) | .164 |
| Vascular | | – | .149 |
| Microvascular vs no involvement | 0.163 | 1.177 (0.561-2.468) | .667 |
| Macrovascular vs no involvement | 0.803 | 2.231 (0.987-5.045) | .054 |
| Differentiation | | – | .002 |
| Poorly vs highly differentiated | −0.19 | 0.827 (0.457-1.494) | .528 |
| Poorly vs moderately differentiated | 1.393 | 4.026 (1.61-10.066) | .003 |

CI indicates confidence interval; RR, relative risk.

**Table 3 – Prognostic variables in accordance with treatment procedures**

| Variables | Liver transplant | Partial surgical resection |
|---|---|---|
| *Recurrence, n (%)* | 20 (13.3) | 17 (51.5) |
| *Survival, %* | | |
| 1 year | 89.3 | 90.9 |
| 3 years | 73.1 | 60.2 |
| 5 years | 61.4 | 38.6 |
| *Most common cause of death* | Others | Tumour relapse |
| *Variables associated with survival in the univariate analysis* | Sex, degree of histological differentiation, vascular involvement | T stage, TNM |
| *Variables associated with survival after adjustment by Cox regression model* | Degree of histological differentiation, vascular involvement | Cox regression cannot be performed due to reduced sample size |

(United Network for Organ Sharing), which shows figures of 80%, 70%, 57% at 1, 3 and 5 years, respectively.[33]

Some authors consider the size of tumour nodules to be a predictor of tumour recurrence and survival,[29,34,35] while other series have not established this association, partly because of sample size problems.[36] In our series, we did not observe statistically significant differences among transplant patients with regard to the tumour size, probably due to the fact that the patients with LC who underwent liver transplantation were selected following the Milan criteria,[12] which are restrictive with regard to the size of nodules.

Macroscopic vascular invasion is the factor given the greatest prognostic value in most of the literature, both for predicting tumour recurrence and survival.[28,29,37-42] In our series, in agreement with results published in the literature, the patients with macroscopic vascular invasion had worse survival rates. The main limitation is that this is generally discovered by the pathologist during the histological analysis of the explanted liver, so we should aim to diagnose this preoperatively. The degree of histological differentiation is another factor that has been widely analysed in relation to LC survival and recurrence.[28,29,41,43,44] In agreement with the studies by Gouillat[43] and Pérez Saborido,[28] among others, in our series, the patients with tumours with a poorer histological differentiation showed significantly worse survival rates.

In the group of patients who underwent partial surgical resection, 57.6% died during the follow-up period, with a crude survival rate of 42.4% at the end of the study, and an actuarial survival rate at 1, 3 and 5 years of 90.9%, 60.2% and 38.6%

respectively, similar to the results in other series.[18,19,45,46] The main cause of death during the follow-up period was tumour recurrence (up to 84.2%), just as other authors have found.[47-49] Unlike the results of other authors,[50-52] we found no statistically significant differences with regard to vascular invasion, the degree of histological differentiation, and the presence or not of metastasis. Nevertheless, the small number of patients who underwent partial surgical resection, only 33 cases, may limit these findings. Like other studies in the literature,[53,54] statistically significant differences were found in our series with regard to the tumour staging and the pTNM classification (TNM study of the surgical piece), with higher mortality rates among patients with T3 and T4 tumours and in the advanced stages of the pTNM classification.

We would like to highlight the importance of analysing the results of the surgical treatment of LC in other hospitals, both for internal evaluation and for assessing their agreement with other groups.

## Conflict of interest

The authors affirm that they have no conflict of interest.

## Acknowledgements

(hepatobiliopancreatic surgery and transplant unit), the radiologists Dr. Marinii, Dr. Pérez Fontán and Dr. Lago Novoa, and the anaesthetists, nurses and auxiliary nurses who have collaborated in the treatment of the patients.

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