

# IS RESECTION OF HEPATOCELLULAR CARCINOMA IN THE ERA OF LIVER TRANSPLANTATION WORTHWILE? A single center experience

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**ABSTRACT - Background** - Liver resection for hepatocellular carcinoma is a potentially curative therapeutic procedure that can be performed readily after its indication, without the need of a long waiting time and lower costs when compared to liver transplantation, being a good alternative in patients with preserved/good liver function. **Objective** - Evaluate long-term results of liver resection from a high volume single center for selected patients with hepatocellular carcinoma in a context of a long waiting list for liver transplant. **Methods** - One hundred and one patients with hepatocellular carcinoma, with a mean age of 63.1 years, and preserved liver function were submitted to liver resection. Clinical and pathological data were evaluated as prognostic factors. Mean follow-up was 39.3 months. **Results** - All patients had a single nodule and 57 (58.2%) patients were within the Milan criteria. The size of the nodule ranged from 1 to 24 cm in diameter. In 74 patients, liver resection was performed with the open approach and in 27 (26.7%) was done laparoscopically. Postoperative morbidity was 55.3% being 75.5% of the complications classified as Dindo-Clavien I and II and operative mortality was 6.9%. Five-year overall and disease free survival rates were 49.9% and 40.7%, respectively. After a log-rank univariate analysis, the levels of preoperative alpha-fetoprotein ( $P=0.043$ ), CA19-9 ( $P=0.028$ ), capsule invasion ( $P=0.03$ ), positive margin (R1-R2) ( $P=0.004$ ) and Dindo-Clavien's morbidity classification IV ( $P=0.001$ ) were the only parameters that had a significant negative impact on overall survival. On the odds-ratio evaluation, the only significant factors for survival were high levels of alpha-fetoprotein ( $P=0.037$ ), and absence of free margins ( $P=0.008$ ). **Conclusion** - Resection, for selected cases, is a potentially curative treatment with acceptable morbidity and mortality and, in a context of a long waiting list for transplant, plays an important role for the treatment of hepatocellular carcinoma.

**HEADINGS** - Hepatocellular carcinoma, therapy. Catheter ablation. Liver neoplasms. Liver transplantation. Neoplasm staging. Treatment outcome. Waiting lists. Survival analysis.

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the fifth most common malignancy worldwide<sup>(3,13,20)</sup>. Every year, 700.000 to 1.000.000 new cases are diagnosed and about 600.000 to 800.000 die from the disease, making HCC the third cause of death worldwide<sup>(20)</sup>. About 90% of cases occur in patients with chronic liver disease<sup>(5,13)</sup> and, in the last years, there is an increasing incidence especially in western countries, related to hepatitis C infection<sup>(10,31)</sup>. Curative therapeutic options available are resection and liver transplantation (LT) although; ablation techniques maybe appropriate to treat small tumors (<2 cm). The choice between transplantation and resection is controversial and there are no controlled

trials comparing these modalities. The ideal curative procedure is LT because of its potential to treat simultaneously the primary tumor and the underlying liver disease<sup>(26)</sup>. On the other hand, best results for LT are achieved in patients within a strict selection criterion as the Milan (one nodule up to 5 cm or 3 nodules up to 3 cm each)<sup>(26)</sup>. Moreover, due to a lack in liver grafts availability seen worldwide associated to an increase of incidence of HCC, the number of donors is not enough to meet the need for organs. The disproportion between the growing number of transplant candidates on waiting lists and the short number of donors, can lead to a long waiting list time. The risks of a long waiting time are tumor progression and liver function deterioration, resulting in a significant number of dropouts<sup>(25)</sup>.

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Thus, liver resection is a potentially curative therapeutic procedure that can be performed readily after its indication (without the need of a long waiting time) with lower costs when compared to liver transplantation, being a good alternative in patients with preserved/good liver function. Moreover, resection proved to be a safe procedure in the last years with good long-term results (50% to 70% 5-year overall survival) and mortality rates in specialized centers lower than 5%<sup>(15,27,34)</sup>. Better operative results can be achieved through laparoscopic liver resection that, especially when indicated for solitary, small and peripheral tumors in patients with preserved liver function, is safe and can lead to very good short and long-term results<sup>(19,35)</sup>. Recent meta-analysis have shown that laparoscopic resection was associated with shorter hospital stay, decreased blood loss, lower rates of postoperative morbidity (especially ascites) when compared to open liver resection<sup>(41,43)</sup>. On the other hand, the main drawback of resection is the high recurrence rate. Therefore, resection should be reserved for patients with preserved liver function and a close follow-up is needed for this group of patients.

Despite the debate between resection *versus* transplantation, several specialized centers in both procedures advocate the resection for the treatment of solitary HCC in patients with preserved liver function in the context of long waiting list time (6 to 9 months or more). Moreover, it has been shown that for patients within the Milan criteria, the long-term results for patients listed for LT (intention to treat analysis) with a waiting list time longer than 9 months, was similar when compared to patients who underwent resection<sup>(28)</sup>. Resection does not preclude future transplantation (rescue LT) and offers the advantage of a surgical specimen for histological and molecular evaluation, useful to understand the biology and aggressiveness of the tumor.

The aim of this study was to evaluate long-term results of liver resection from a high volume single center for selected patients with HCC in a context of a long waiting list for liver transplant.

## METHODS

From a prospective databank, 141 patients submitted to HCC resection were identified from August 2000 to July 2014. Exclusion criteria were fibrolamellar HCC (28 cases) and hepato-cholangiocarcinomas (12 cases).

One hundred and one cases, being 66 men and a mean age of 63.1 years (mean 27 to 83 years) were evaluated.

Beside liver function tests, serum levels of alpha-feto-protein and CA19-9 were also evaluated. All patients were classified according to the Child-Turcotte-Pugh (Child) and Model for End-stage Liver Disease (MELD) scores.

Diagnosis of HCC was based on computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen. No preoperative biopsies were necessary. All patients were submitted to upper GI endoscopy and chest CT scans.

All cases were discussed in a multidisciplinary weekly meeting before surgery. The selection criteria for resection adopted by our group were: solitary nodule;

preserved liver function (preferably Child-Turcotte-Pugh Class A and MELD <10); platelet count of >100,000/mL. Patients with portal hypertension and esophageal varices Grade 1 or 2 (with platelet count higher than 100,000/mL) in Child A patients were not excluded. In patients where a major liver resection was expected, a liver remnant volume of 40% was aimed in patients with chronic liver disease and 30% for those without chronic liver disease. In cases where the expected remnant volume was inferior to the former volumes, a selective portal vein embolization was performed and, after four weeks, a new volume evaluation was carried out.

Anatomical resection was preferred except in patients with small peripheral nodules. Laparoscopic approach was employed in patients with small tumors (<5cm) located on lateral or anterior segments (preferably up to two liver segments).

After surgery, all patients were followed at the outpatients' clinic and the mean follow-up was 39.3 months (range 12 to 133 months).

Preoperative data as tumor size, accordance to the Milan criteria, and etiology of the liver disease were evaluated. Liver resections were defined in non-anatomical or anatomical according to the Brisbane 2000 classification<sup>(36)</sup> and divided in open or laparoscopic. Per operative data included transfusions, postoperative complications, length of hospital stay, and mortality. Postoperative complications were classified according to the Dindo-Clavien classification<sup>(11)</sup>. Histological evaluation included surgical margins, presence of capsule, presence of capsule invasion, vascular invasion and presence of satellite nodules.

Postoperative follow-up was performed every 4 months during the first two years and every 6 months after that and included clinical, laboratory, and radiological evaluation. Data collected included disease recurrence and mortality.

Continuous variables were expressed as median (range) and were compared by means of the Mann-Whitney test. Categorical variables were compared by the chi-squared test or Fisher's exact test. Survival and recurrence-free survival were measured from the date of operation to the time of death or at the time when a recurrent tumor was first diagnosed, respectively. Survival analysis was estimated by the Kaplan-Meier survival method, and the differences in survival between the groups were compared by the log-rank test. Differences were considered as statistically significant when the *P* value was <.05.

## RESULTS

Regarding the etiology of liver disease: 34 patients (33.7 %) had hepatitis C, in 13 (12.9%) was due to alcohol ingestion, 11 (10.9%) patients had hepatitis B, 8 (7.9%) had nonalcoholic steatohepatitis (NASH), 14 (13.9%) had mixed etiology and 21 patients had other causes.

All patients had a single nodule and fifty-seven patients (58.2%) were within the Milan criteria (up to 5 cm). The size of the nodule ranged from 1 to 24 cm in diameter (mean = 6.8 cm).

Ninety-eight patients were Child-Turcotte-Pugh A and three Child-Turcotte-Pugh B; all patients had a MELD score lower than 16 and eighty-six patients had a MELD score lower than 10.

In 14 patients a preoperative portal vein embolization was employed and in all patients hypertrophy was observed and met the needed expected future liver remnant volume.

In 74 patients, liver resection was performed with the open approach and in 27 (26.7%) patients resection was done laparoscopically. When we looked at two different periods of time (2000-2009 and 2010-2014) the number of cases of LLR presented a significant increase (Figure 1).

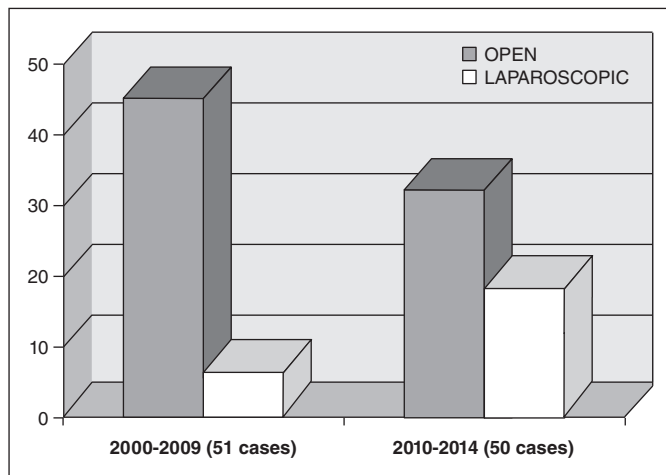


FIGURE 1. Hepatocellular carcinoma resection: open x laparoscopic approach in two different "eras".

In 69 (69.7%) patients resection was anatomical and blood transfusion was necessary in 18 patients (17.8%). Wedge resections and uni-segmentectomies were performed in 43 patients followed by 29 major hepatectomies (16 right, 10 left, 3 right extended), and 29 bi-segmentectomies.

Postoperative morbidity was 55.3% being 75.5% of the complications classified as Dindo-Clavien I and II, being the most common ascites, pleural effusion and biliary fistula. Reoperations were necessary in 6 patients (2 for bleeding, 4 for abdominal wall suture due to ascites leakage). Operative mortality was 6.9% (3 due to septicemia, 2 due to liver failure, 2 due to kidney failure leading to multiple organ failure).

At histological evaluation the presence of capsule was observed in 63 (64.3%) patients, capsule invasion in 11 (17.5%), vascular invasion in 52 (53.6%), and satellite nodule(s) in 13 (13.4%). Free margins (R0 resection) were obtained in 89 (92.7%) patients. Also based on histology, 77 (76.2%) patients had liver cirrhosis. Regarding tumor differentiation, patients were classified according to Edmondson-Steiner grading system<sup>(12)</sup> as follows: grade 1 (1.0%), grade 2 (25.5%), grade 3 (66.3%), grade 4 (6.1%).

Five-year overall survival (OS) and disease free survival (DFS) rates were 49.9% and 40.7%, respectively (Figure 2).

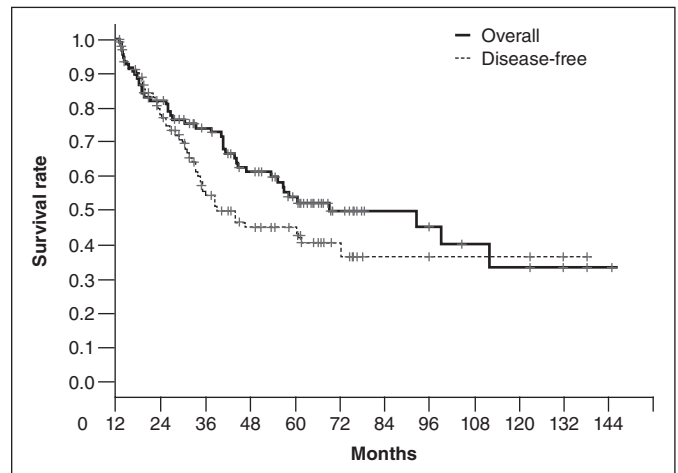


FIGURE 2. Overall and disease-free survival curves for patients submitted to hepatocellular carcinoma resection

The mean disease-free survival time was 27.9 months. Recurrence was observed in the liver in 40 patients, followed by lung (seven patients) and lymph nodes (four patients). From patients with liver only recurrence, 50% were within Milan criteria and were referred for liver transplantation. From the group of 20 patients referred to LT, eight were transplanted.

After applying a log-rank univariate analysis, the levels of preoperative alpha-fetoprotein ( $P=0.043$ ) and CA19-9 ( $P=0.028$ ), capsule invasion ( $P=0.03$ ), positive margin (R1-R2) ( $P=0.004$ ) and Dindo-Clavien's morbidity classification IV ( $P=0.001$ ) were the only parameters that had a significant negative impact on overall survival. The disease's etiology (viral or non-viral) had no influence in the prognosis as there were no significant difference regarding OS ( $P=0.450$ ) or DFS ( $P=0.087$ ). The presence of cirrhosis also did not have no influence in the prognosis as there were no significant difference regarding OS ( $P=0.296$ ) or DFS ( $P=0.671$ ) neither the Edmondson-Steiner grading (OS,  $P=0.765$ ). On the odds-ratio evaluation, the only factors that significantly had impact on survival were high levels of alpha-fetoprotein ( $P=0.037$ ), and absence of free margins ( $P=0.008$ ).

## DISCUSSION

Resection remains one of the most effective treatments for HCC with five-year survival rates ranging from 50% to 70%, and figures as an attractive approach in the scenario of a concerning long waiting list for liver transplantation.

Chronic liver disease or cirrhosis composes the background for 80% to 90% of the patients who develop HCC, making the assessment of liver function mandatory for therapeutic decision. The Child-Turcotte-Pugh score is a very simple, reproducible and straightforward method to evaluate liver function, based only on clinical and laboratorial data<sup>(30)</sup>. Those patients classified as Child A, would tolerate a liver resection however, it is not a precise tool to predict postoperative liver failure<sup>(16)</sup>.

The MELD score, initially developed for prediction of survival in patients with portal hypertension submitted to transjugular intrahepatic portosystemic shunt, has become a good method to determine liver resection risk and, in patients with a MELD score <10 resection can be performed safely<sup>(37)</sup>. The Child and MELD scores are useful tools however, are not the most accurate way to evaluate liver function; in the Far East, the indocyanine green clearance test (ICG) is used as a routine before liver resection. The ICG test is considered in Asia the most refined and precise method to evaluate liver function and 15 minutes after IV injection, a retention <14% allows a major liver resection<sup>(14,22)</sup>. In Western countries this test did not become a routine. In our study, almost a quarter of the patients did not present cirrhosis on histological evaluation however when we compared the results of patients with and without cirrhosis, results were not significantly different. This can be explained by our selecting criteria where only patients with preserved liver function were submitted to resection; thus, patients with cirrhosis presented a good liver function and a satisfactory postoperative outcome.

Beside liver function tests, the evaluation of the liver remnant volume for patients scheduled for a major liver resection has become a routine. A liver remnant volume of 40% is aimed in patients with chronic liver disease and 25%-30% for those without chronic liver disease to avoid postoperative liver failure<sup>(18)</sup>. In cirrhotic patients, with preserved liver function, where a right hepatectomy is planned and a remnant left lobe liver volume is lower than 40%, a selective right portal vein embolization can lead to a compensatory hypertrophy of the left lobe to achieve 40% of the total liver volume. Moreover, if a hypertrophy is observed, this is an indirect sign of the liver's capacity of regeneration (functional test). In our series, from 16 patients where a major right liver resection was indicated, 14 had a small expected liver remnant and were submitted to a right portal vein embolization, having all achieved the expected compensatory hypertrophy after 4 weeks.

Another important point of discussion is if the presence of portal hypertension precludes liver resection. Despite recommendations not to resect in the presence of portal hypertension<sup>(4)</sup>, many groups<sup>(7,15,33)</sup>, with whom we are in accordance, are in favor of resection in the presence of mild portal hypertension in patients with small esophageal varices and platelet count higher than 100.000U/mL.

In our day-by-day practice we employ the following criteria: preferably Child A and MELD <10 plus platelet count higher than 100.000/mL (for any kind of resection). Patients with portal hypertension and esophageal varices Grade 1 or 2 (with platelet count higher than 100,000/mL) in Child A patients were not excluded (minor resections).

It has been shown that besides serving as a screening and diagnosis tool for HCC, alpha-fetoprotein is also used as a prognostic factor<sup>(38,40)</sup>. Despite high serum levels of alpha-fetoprotein are related to bad prognosis<sup>(17,29)</sup>, it is not considered as a contraindication for resection. Indeed, in our study, higher serum levels of alpha-fetoprotein were related to a worse prognosis however did not contraindicate resection.

Anatomical resection, where entire segments and corresponding portal pedicles are resected, has been advocated as the ideal treatment for HCC because the main tumor spread pathway is through the portal vein; the en bloc resection of the tumor and its' portal vein territory may lead to better oncological results<sup>(9,45)</sup>. However, in patients with chronic liver disease and cirrhosis, parenchyma-sparing resection is mandatory to avoid postoperative liver failure and, in small peripheral and well-differentiated HCC there are studies showing similar results in anatomic and non-anatomic resections<sup>(6,45)</sup>. Thus, the choice between a non-anatomic wedge resection and an anatomic resection should be individualized. In our series, anatomical resections were preferred (70% of the cases) being wedge resections reserved for cases with small peripheral sub capsular nodules.

The optimal resection margin for HCC resection remains controversial. In a randomized trial comparing a wide 2 cm margin with a margin aiming 1 cm, Shi et al. found lower postoperative recurrence rates and better survival in the wide margin group<sup>(32)</sup>. However, it is accepted that a 1 cm clear margin is adequate for the majority of patients with HCC. Indeed, in our series; the absence of free margins (coincident margin or R1 resection) had a significant negative impact on prognosis.

It has been shown that tumor grading according to Edmondson-Steiner grading was able to raise the predictive efficiency of survival of patients with HCC<sup>(24)</sup>. In our series, the vast majority of patients were grade 3 with just a few patients grade 1 or 4; No significant differences were observed regarding survival probably due to a small number of patients with grades 1 and 4.

In the last years we noticed a distinct change in the type of procedure for HCC resection. From our entire series, 26.7% of the cases were submitted to a minimally invasive approach however, after 2009 when laparoscopic liver resection (LLR) became a routine in our group, 40% of HCC resections were performed laparoscopically. In the last 5 years, there was a clear shift from open to laparoscopic approach for HCC resection.

LLR presents the advantages of a minimally invasive procedure as less postoperative pain, fast recovery, and early return to work. It has also been shown that blood loss and transfusion, and length of hospital stay were significantly lower in the LLR group<sup>(21,41,43)</sup>. Moreover, lower incidences of postoperative ascites were consistently observed when compared with the open procedure, probably as a consequence of the preservation of the abdominal wall and umbilical round ligament collateral venous circulation<sup>(39,42)</sup>. Another advantage for LLR is that in cases of recurrence, there are fewer adhesions making liver transplant or even a re-resection easier<sup>(2,23)</sup>.

The major drawback of liver resection for HCC is the risk of recurrence, reaching 40%-50% in three years. Despite that, it has been shown that most patients who presented recurrence after resection can be subjected to salvage LT. Belghiti et al. showed that patients subjected to salvage LT present the same long-term results as those subjected to transplantation

as the primary treatment<sup>(1)</sup>. Indeed, in Cherqui et al. series, from patients with recurrent HCC following LLR, 77% were transplantable within the Milan criteria<sup>(7)</sup>. In our experience, 50% of patients who recurred were within the Milan criteria and were referred for transplant. The discrepancy between our numbers and European centers (50% vs 77%) is probably due to the fact that 42% of our patients were initially outside the Milan criteria with a more advanced disease than our European pairs that considered only initially transplantable patients.

HCC resection can lead to a 5-year global survival rate of 50 to 70% of the patients. In our study a global and disease-free survival at 5 years of 49.9% and 40.7%, were found, respectively. In our series, 41.8% of the cases were patients with large tumors out of the Milan criteria; it is important to point out that, for large tumors the only potential curative treatment is liver resection.

In patients with early HCC (<2cm), there is still a debate which treatment is the best: LT, resection or radiofrequency ablation. Despite some reports with very good results with radiofrequency ablation (RFA), for this group of patients, RFA provides a worse DFS as compared with hepatic resection, implicating in a greater need for retreatment<sup>(8,44)</sup>. In our treatment protocol RFA is indicated for small (<2cm) tumors centrally located within the liver parenchyma.

The mortality rate observed in our series (6.9%) is higher when compared with our 2% mortality rate for the resection of colorectal liver metastasis. This can be explained by the fact that about 80% of our patients had cirrhotic livers and, moreover, 29 major resections (more than three segments) were performed.

In conclusion, HCC treatment should be in a multi-disciplinary fashion and, resection, for selected cases is a potentially curative treatment (five-year overall and disease free survival rates of 49.9% and 40.7%, respectively) with acceptable morbidity and mortality. In a context of a long waiting list for transplant, resection plays an important role for the treatment of HCC. To avoid HCC recurrence, the major drawback of resection, protocols for adjuvant treatment or even preemptive LT based on histological and molecular tumor evaluation should be considered. LT and liver resection should not compete but be complementary curative treatments for HCC.

#### Authors' contributions

Herman P did the study design. Herman P and Lopes FLM wrote the manuscript. Lopes FLM did the data collection. Kruger JAP, Fonseca GM, Jeismann VB, and Coelho FF did the revision.

Herman P, Lopes FLM, Kruger JAP, Fonseca GM, Jeismann VB, Coelho FF. Ressecção de carcinoma hepatocelular na era do transplante de fígado: vale a pena? Experiência de um único centro. *Arq Gastroenterol.* 2016;53(3):169-74.

**RESUMO - Contexto** - A ressecção do carcinoma hepatocelular é um procedimento terapêutico potencialmente curativo que pode ser realizado imediatamente após sua indicação, sem a necessidade de longo tempo de espera e com custos mais baixos quando comparado com o transplante hepático, sendo uma boa alternativa em pacientes com função hepática preservada. **Objetivo** - Avaliar os resultados a longo prazo da ressecção hepática em centro de alto volume cirúrgico para pacientes selecionados com carcinoma hepatocelular em um contexto de uma longa lista de espera para transplante de fígado. **Métodos** - Cento e um pacientes com carcinoma hepatocelular, com idade média de 63,1 anos, e função hepática preservada foram submetidos à ressecção hepática. Os dados clínicos e patológicos foram avaliados como fatores prognósticos. O seguimento médio foi de 39,3 meses. **Resultados** - Todos os pacientes apresentavam um único nódulo e 57 (58,2%) estavam dentro dos critérios de Milão. O tamanho do nódulo variou de 1 a 24 cm de diâmetro. Em 74 pacientes, a ressecção hepática foi realizada com a abordagem aberta e em 27 (26,7%) através de laparoscopia. A morbidade pós-operatória foi de 55,3%, sendo 75,5% das complicações classificadas como Dindo-Clavien I e II e a mortalidade operatória foi de 6,9%. As sobrevida global e livre de doença em 5 anos foram 49,9% e 40,7%, respectivamente. Depois de análise univariada log-rank, os níveis de alfa-fetoproteína no pré-operatório ( $P=0,043$ ), CA19-9 ( $P=0,028$ ), invasão de cápsula ( $P=0,03$ ), margem positiva (R1-R2) ( $P=0,004$ ) e classificação de morbidade de Dindo-Clavien tipo IV ( $P=0,001$ ) foram os únicos parâmetros que tiveram um impacto negativo significativo na sobrevida global. Na avaliação de risco relativo (odds-ratio), os únicos fatores importantes para a sobrevivência foram altos níveis de alfa-fetoproteína ( $P=0,037$ ), e ausência de margens livres ( $P=0,008$ ). **Conclusão** - A ressecção hepática em casos selecionados, é um tratamento potencialmente curativo com morbidade e mortalidade aceitáveis e, num contexto de uma longa lista de espera para transplante, tem um papel importante para o tratamento do carcinoma hepatocelular.

**DESCRITORES** - Carcinoma hepatocelular, terapia. Ablação por cateter. Neoplasias hepáticas. Transplante de fígado. Estadiamento de neoplasias. Resultado de tratamento. Listas de espera. Análise de sobrevida.

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