

MANAGEMENT OF HEPATOCELLULAR CARCINOMA IN THE AGE OF LIVER TRANSPLANTATION

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REZUMAT

Carcinomul hepatocelular este a treia cauză de deces prin cancer, având o creștere semnificativă a incidenței și mortalității în țările occidentale. Tratamentul său este foarte dificil, datorită prezenței cirozei, a tumorilor frecvent multifocale, precum și a tehnicilor imagistice actuale imperfecte. Abordarea "Barcelona Clinic Liver Cancer" (BCLC) ia în considerare numărul și mărimea leziunilor, prezența ganglionilor limfatici pozitivi și a metastazelor, severitatea cirozei, invazia portală și nivelul de performanță a pacientului, cuantificate într-un sistem ce îi permite clinicianului să aleagă terapia cea mai adecvată. Scopul tratamentului este de a îndepărta tumora, prezervând în același timp funcția hepatică. Există două criterii principale care determină abordarea terapeutică: severitatea cirozei și volumul tumoral global. Rezecția chirurgicală este indicată pacienților non-cirofici cu funcție hepatică păstrată și cu extensie tumorală redusă. Una dintre problemele importante după rezecție este frecvența crescută a recidivei tumorale. De aceea, este necesară o urmărire agresivă postoperatorie, cu menținerea opțiunii pentru transplant hepatic. Terapiile ablative sunt rezervate pacienților la care nu se poate efectua rezecția, datorită afectării hepatice grave; ablația cu radiofrecvență și injectarea percutanată de alcool sunt cele mai frecvent utilizate. Embolizarea transarterială prin injectarea unui agent chimioterapeutic poate fi realizată prin metode specifice radiologiei intervenționale. Transplantul hepatic are rolul său bine stabilit în tratamentul carcinomului hepatocelular, putând fi singura alternativă terapeutică pentru pacienții cu tumori nerezecabile. În acest sens, criteriile de la Milano, impuse în 1995, își păstrează valoarea prognostică. Rolul terapiilor premergătoare transplantului prin prisma modificărilor recente în politica de alocare a organelor pentru transplant trebuie reevaluat.

ABSTRACT

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths and has a steep increase in incidence and mortality in the Western world. Its management is very difficult, due to the presence of cirrhosis, the frequent multifocality, as well as the imperfection of the current imaging techniques. The Barcelona Clinic Liver Cancer (BCLC) approach computes number and size of lesions, presence of lymph nodes and metastases, severity of the underlying cirrhosis, portal invasion and patient performance status into a system that allows the clinician to choose the most adequate therapy. The goal of treatment is to remove the malignancy while preserving liver function. There are two main criteria dictating the therapeutic approach: the severity of underlying cirrhosis and the overall tumor burden. Surgical resections are reserved for non-cirrhotic patients and cirrhotics with well preserved liver function and low tumor extension. One of the important problems after resection is the high frequency of tumor recurrence. Therefore, a highly aggressive follow-up should be recommended, and it might be a wise approach to have these patients recommended for liver transplantation even after a "radical" resection. Ablative therapies are usually reserved for patients that are not candidates for liver resection, because of a more advanced degree of liver disease. Radiofrequency ablation and percutaneous ethanol injection are the most frequently used procedures. Transarterial embolization by injecting a chemotherapeutic agent can be achieved through interventional radiological approach. Liver transplantation has established its role in treating hepatocellular carcinoma, being the only viable therapeutic alternative for patients with non-resectable disease. The Milan criteria imposed in 1995 seem to maintain their prognostic value. The role of "bridging" therapies in the setting of recent changes in the organ allocation policy has to be re-evaluated.

INTRODUCTION

One of the most intriguing debates among physicians involved with liver diseases and liver transplantation is the therapy of hepatocellular carcinoma (HCC). There are about 8,500 - 11,500 new HCC cases diagnosed in the USA every year. HCC is the third leading cause of cancer-related deaths and has a steep increase in incidence and mortality in the Western

world, having doubled its incidence in the United States between 1985 and 1998.¹⁻³ The fact that about 95% of cases arise in the complex setting of cirrhosis makes the diagnosis of HCC and its therapeutical approach a challenging and versatile field.⁴

DIAGNOSIS AND SURVEILLANCE

The difficulty of management is further enhanced by the frequently encountered multifocality of the disease as well as by the imperfection of current imaging techniques in discriminating the malignant lesions from regenerative nodules. In a recent metaanalysis, Colli et al determined a pooled sensitivity of 60% for ultrasound studies, 68% for CT studies and 81% for MRI studies in diagnosing HCC. Lesions larger than 2 cm are more readily diagnosed and a typical appearance (rapid contrast uptake during arterial phase

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with washout during the venous phase) on CT or MRI precludes further diagnostic studies.

In tumors between 1 and 2 cm, coincident findings on both CT and MRI are required for diagnosis. Tumors smaller than 1 cm, being incompletely vascularised, very often elude radiologic diagnosis and should be monitored closely.⁵ A biopsy is only required in equivocal situations, but a negative finding will be regarded with suspicion, especially in small tumors.

The role of alpha-fetoprotein (AFP) in the diagnosis of HCC is limited and this study is no longer recommended for surveillance.⁶ However, values higher than 200 ng/ml are highly specific for HCC if found concomitantly with a liver mass.⁷

Currently, biannual ultrasound surveillance is considered sufficient for the cirrhotic patient without HCC, but any suspicious lesion should warrant further investigations until the diagnosis of malignancy is confirmed or infirmed, and surveillance after a positive diagnosis should be done more frequent and by high-specificity studies (CT, MRI) rather than by ultrasound, to avoid overlooking of further tumor development. The preoperative staging of the malignant growth is a very important prognostic factor and is frequently suboptimal.

STAGING SYSTEMS

Several staging systems have been developed for HCC. While the TNM classification is still the most popular for its ease of use, the Barcelona Clinic Liver Cancer (BCLC) approach computes number and size of lesions, presence of lymph nodes and metastases, severity of the underlying cirrhosis, portal invasion and patient performance status into a system that allows the clinician to choose the most adequate therapy and to accurately predict the outcome for each stage.⁸ (Fig. 1)

THERAPEUTIC APPROACH

The goal of treatment is to remove the malignancy while preserving liver function. There are two main criteria dictating the therapeutic approach: the severity of underlying cirrhosis and the overall tumor burden as evaluated by the number of nodules, their size and vascular invasion.

The therapeutic armamentarium offers a broad array of possibilities, which can be summarized as:

- Liver resection;
- Ablative procedures: percutaneous ethanol injection, radiofrequency ablation (RFA), cryoablation;

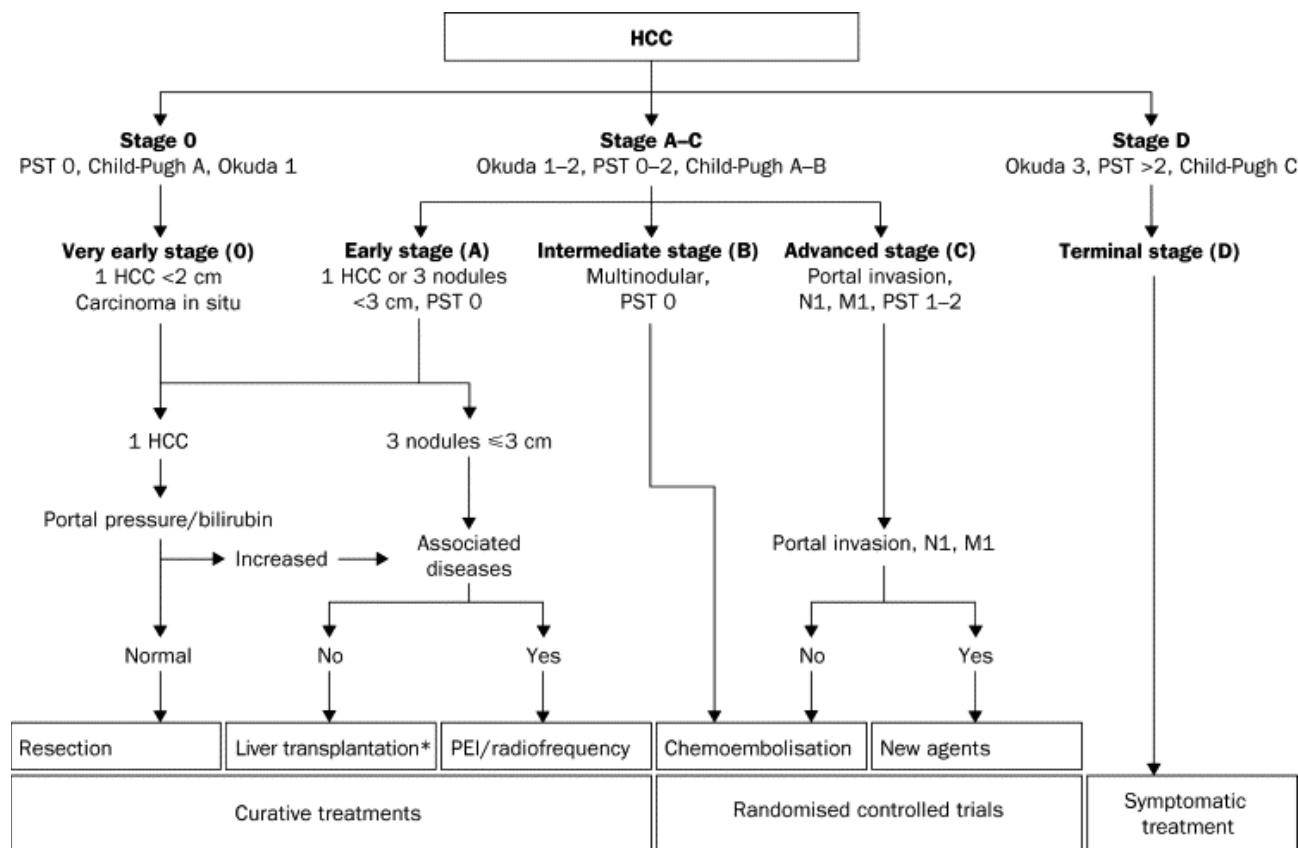


Figure 1. The Barcelona Clinic Liver Cancer staging protocol (PST = performance status test, N = nodules, M = metastases, PEI = percutaneous ethanol injection).

- Transarterial chemoembolization (TACE),
- Liver transplantation
- Systemic agents (all with limited efficacy): tamoxifen, doxorubicin, interferon, octreotide, anti-androgens;
- Selective internal radiation therapy (SIRT) is a novel, promising therapy featuring intra-arterial administration of microspheres coated with radioactive agents (Yttrium⁹⁰, Iodine¹³¹).

Surgical liver resection

Surgical resections are reserved for non-cirrhotic patients and cirrhotics with well preserved liver function and low tumor extension (ideally single tumor). The results of this therapy are maximized when performed in experienced centers. The selection of candidates is of paramount importance for the outcome. Bilirubin values of >1.1 mg/dl and portal hypertension with hepatic vein pressure gradient >10 mm Hg were shown to be predictors of postoperative hepatic decompensation.⁹ Even if the vein pressure gradient is not measured routinely, other signs of portal hypertension, such as oesophageal varices, ascites, splenomegaly or thrombocyte count <100.000/mm³ should preclude liver resection. Under ideal circumstances, a perioperative mortality of less than 3% and a 5 year survival rate higher than 50% can be achieved.¹⁰

One of the important problems after resection is the high frequency of tumor recurrence (either growth of micrometastases or de novo tumors), which can be as high as 70% at 5 years and is frequently multifocal. Repeated resection is feasible in only about 20% of these patients. Therefore, a highly aggressive follow-up should be recommended, and it might be a wise approach to have these patients recommended for liver transplantation even after a “radical” resection.

Ablative therapies

Ablative therapies are usually reserved for patients that are not candidates for liver resection, because of a more advanced degree of liver disease. According to local preferences and expertise, radiofrequency ablation (percutaneous, laparoscopic or open) and percutaneous ethanol injection (PEI) are the most frequently used procedures. According to the Barcelona staging, they can be used in patients with early stage disease. The best results are achieved in liver masses smaller than 3 cm, where the radicality of these procedures can be compared to that of liver resection.⁶ Compared to PEI, RFA can achieve a higher percentage of necrosis in tumors larger than 3 cm and, when performed

laparoscopically, RFA can offer access to difficult anatomical sites and completely destroy the tumor in more than 90% of ablated sites.^{11,12}

Transarterial chemoembolization

Injection of a chemotherapeutic agent (doxorubicin, cisplatin) and occlusion of the artery supplying the liver lobe that contains the mass can be achieved through interventional radiologic approach. The intervention can be used in patients that are not candidates for resections or ablative therapy, secondary to their higher tumor load and/or more advanced degree of cirrhosis. The procedure is inappropriate however for patients with advanced malignancy or decompensated cirrhosis (Child C or advanced Child B). Portal vein thrombosis, hepatofugal blood flow, and coagulation disorders are some of the other contraindications of the procedure. Careful selection of patients is required to avoid severe complications such as liver failure.

LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

The most ardent problem in liver transplantation is the shortage of available organs. Therefore, when deciding the allocation of organs to HCC patients, the survival chances have to outweigh the risk of dying from recurrent disease. Overall, an “acceptable” survival rate should be comparable to that of patients treated for non-malignant diseases.

Patient selection

HCC is usually a slow-growing malignancy. However, the fact that it appears in the cirrhotic patient as well as its tendency to multifocality and to recurrence after therapy recommend liver transplantation as a logical way to deal with both malignancy and liver disease.

In the early 80's, as soon as liver transplantation became an accepted standard therapy for end-stage liver disease, the indication for liver replacement was extended, somehow indiscriminate, to patients with liver tumors. After initial poor results, the transplant community learned that recurrence and progression of malignancy are very rapid under immunosuppression and that the indication for transplantation should be limited to carefully selected patients. Number and size (>5 cm) of tumors, and vascular invasion were identified as poor prognostic factors and patients with extrahepatic disease were excluded from transplantation.¹³ In time, other factors that affect

survival and recurrence were identified, such as positive nodes and histologic grading.¹⁴ An accurate preoperative staging seems to have a beneficial effect on tumor recidive.¹⁵

In 1996, Mazzaferro et al. published a landmark study, imposing the so-called "Milan Criteria". This study showed that patients with up to 3 tumors, none larger than 3 cm, or 1 tumor < 5 cm had an excellent survival, while patients exceeding these criteria had a significantly worse outcome.¹⁶ Even though data from the University of California at San Francisco (UCSF) and from the Mount Sinai Medical Center in New York showed that acceptable survival and disease-free survival rates can be achieved in patients with slightly higher tumor load, there is still not enough information to impose the routine transplantation of patients with higher tumor burden.^{17,18} (Table 1) Multimodal approaches with preoperative downstaging via TACE and postoperative chemotherapy seem to benefit certain patients with tumor extension beyond Milan criteria.¹⁸

Table 1. The "Milan Criteria" defined by Mazzaferro in 1996 define the tumor load within which the survival rates are similar to those of patients without malignant disease. Some institutions like the University of California at San Francisco (UCSF) try to extend the indications to limits where the survival and recidive rates are still acceptable.

Milan Criteria (Mazzaferro et al, 1996)

- Single tumor ≤ 5 cm, or
- 2-3 tumors none exceeding 3 cm, and
- No vascular invasion and/or extrahepatic spread

UCSF Criteria (Yao et al, 2001)

- Single tumor ≤ 6.5 cm, or
- 2-3 lesions, none exceeding 4.5 cm, with total tumor diameter ≤ 8 cm
- No vascular invasion and/or extrahepatic spread

Organ allocation

Patients with HCC frequently have a well preserved liver function. Classically, they have longer waiting times and a higher chance of being removed from the transplant list due to progressive disease. Yao et al. found a 25% yearly drop-out rate from the waiting list in these patients.¹⁹

Table 2. The Model of End Stage Liver Disease (MELD) equation computes the three most important predictors of mortality on the waiting list: creatinine, bilirubin and the International Normalized Ratio (INR) for prothrombin time.

MELD Score = 0.957 x Loge (creatinine mg/dL) + 0.378 x Loge (bilirubin mg/dL) + 1.120 x Loge (INR) + 0.643

In 2002, the United Network for Organ Sharing (UNOS) introduced the Model for End-Stage Liver

Disease (MELD) score to prioritize patients awaiting liver transplantation. This is a score that accurately predicts the 90 days mortality risk of patients while on the waiting list. (Table 2)

Recognizing that the patients with HCC have a higher mortality risk than predicted by their MELD score, the current UNOS policy exceptionally attributes a MELD score of 24 (equivalent to a 15% mortality risk on the waiting list) to HCC patients that have solitary tumors between 2 and 5 cm or 2-3 tumors, none larger than 3 cm. This score allows transplantation within 6 months in most centers. The score can be upgraded every three months with an additional equivalent of 10% mortality risk. Patients with HCC smaller than 2 cm do not receive exceptional MELD scores after it has been observed that about 30% of these small tumors have been misdiagnosed, with no tumor being found in the explanted livers. The implementation of this policy led to a significant decrease of the waiting time and waiting list mortality of HCC patients and to a significant increase in the number of transplanted HCC patients.²⁰

In Europe, a new Eurotransplant policy implemented in 2005 allows HCC patients that fall within Milan criteria and have already been on the waiting list for one year to be upgraded to priority status T2 (equivalent to Child C cirrhosis), whereby most patients are transplanted within 6 months.

"Bridging" therapies

The progression of hepatocellular carcinoma can be sometimes unpredictable, and patients that seem ideal candidates for liver transplantation can present a few months later with multicentric progression of their malignancy. The time spent on the waiting list seems to be a very important predictor of tumor progression and drop-out from the waiting list. Therefore, before the MELD era, treating these patients with ablative procedures or TACE was a rational approach to maintain them in an active transplant status.

There are no conclusive studies to attest the superiority of one or another ablative procedure or TACE, but there is a general consensus that "bridging" procedures played an important role in avoiding the drop-out from the waiting list.^{12,21-27} Under current conditions, when HCC patients are transplanted with priority and have a significant shorter waiting time, the role of the bridging procedures needs to be re-evaluated. One argument in favour of continuing to treat the tumors before transplantation is that the waiting time can be prolonged by several other independent factors (medical or social) which can repeal the advantage

of the MELD exception. Also, there is clearly a role for these procedures in “downstaging” lesions that otherwise would exceed Milan criteria as well as in patients with borderline large tumor load that would otherwise be at risk for drop-out from the waiting list.

Outcome

When offering liver transplantation to HCC patients, survival rates comparable to those of patients transplanted with non-malignant diseases should be obtained. Failure to do so attracts the anthem of wasting valuable donor organs on patients that do not achieve sufficient survival benefit from transplantation. Survival in these patients is directly linked to recidive of malignancy, which is more rapid and aggressive under immunosuppression.

Several factors, mentioned earlier in this paper, were identified as predictors of recurrence and mortality. Among them, the number and size of tumors seem to be the most amenable to routine use and are incorporated in the various policies of organ allocation and patient selection. The overall five-year survival rate of patients that fall within the Milan criteria is situated at about 70%, while patients with higher tumor load, having more significant recidive rates, tend to do poorer. Recently, it was suggested that genotype analysis might identify gene alterations within the tumoral tissue that would predict post-transplant tumor recurrence.²⁸ Other markers, such as the presence of AFP mRNA expressing cells in the peripheral blood are also under evaluation for their predictive power in regard to tumor recurrence.²⁹ Identifying such predictors might allow a more accurate selection of transplant candidates among patients with hepatocellular carcinoma.

All these results should be interpreted keeping in mind that the outcome of this patient population depends on several other factors. The smaller degree of liver disease is a favourable prognostic sign. Burroughs et al. found that HCC was a predictor of favourable outcome within the first three months; however, this advantage is not maintained on medium and long term.³⁰ On the other hand, a quite frequent policy is to use organs from high-risk donors to transplant these patients; while this may reduce the mortality and drop-out rate on the waiting list, it also affects post-transplantation outcome.

Chemotherapy delivered intra- and postoperative (with Doxorubicin being the most popular agent) does not seem to improve outcome.³¹ The immunosuppression regimens used after transplantation may have a certain importance, with the

antiproliferative effect of sirolimus being postulated. Sirolimus in HCC patients has been used in practice in several centers around the world, based on clinical observations and favourable in vitro effects and is currently under investigation by randomized studies (the SILVER Study in Europe).

Living Donor Liver transplantation (LDLT) for HCC

LDLT emerged as a way to expand the donor pool, offering a chance to be transplanted to HCC patients that would not meet transplantation criteria based on their underlying liver disease. The main issue with LDLT is the mortality and morbidity that may occur in the donor even under the strictest precautions. Based on life-expectancy and cost-effectiveness analysis, LDLT is warranted if the waiting time for a liver graft is expected to exceed 7 months.³² Under the current prioritization policy in the USA, the role of LDLT for HCC has decreased; however, in areas of the world where cadaveric organ donation is not a routine practice, the procedure is still highly popular.

A controversial issue is LDLT for patients that exceed Milan criteria and therefore are excluded from the usual HCC exception. The Milan criteria maintain their prognostic accuracy in LDLT. The Japanese experience shows survival and disease-free survival of 78.7% and 79.1% respectively in patients within Milan criteria. When these parameters were exceeded, survival and disease-free survival rates were 60.4% and 52.6%; considering these results as being acceptable or not is rather a matter of experience and attitude of each transplant center and they have to be extensively discussed with the potential donors and recipients.³³

CONCLUSION

Liver transplantation has established its role in treating hepatocellular carcinoma. It is the only viable therapeutic alternative for patients with non-resectable disease. While priority criteria imposed by UNOS represent a significant step towards preventing drop-out and mortality while on the waiting list, setting the limits of transplantability is still an active, challenging field. The Milan criteria imposed in 1995 seem to maintain their prognostic value, but means to allow selection of those patients who would still have a favourable outcome beyond these limits are actively searched. The role of “bridging” therapies and of LDLT in the setting of recent changes in the organ allocation policy has to be re-evaluated.

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