

Management of Hepatocellular Carcinoma - Experience of a Single Center

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Rezumat

Managementul carcinomului hepatocelular - experiența unui singur centru

Introducere: Carcinomul hepatocelular (HCC) este a 5-a tumoră malignă ca frecvență pe glob și a 3-a cauză de deces prin cancer. Scopul acestui studiu a fost de a evalua opțiunile diagnostice și terapeutice ale carcinomului hepatocelular.

Metode: Am folosit metodele standard pentru diagnosticul HCC: proceduri imagistice și dozarea alfa-fetoproteinei (AFP). În studiu au fost incluși 190 pacienți diagnosticați cu HCC în perioada aprilie 2011 - mai 2012.

Rezultate: Stadiul HCC a fost clasificat conform BCLC și indicațiile de tratament au fost stabilite corespunzător. Studiul a inclus 43 de pacienți cu HCC în stadiu precoce, 58 pacienți cu HCC în stadiu mediu și 89 pacienți cu HCC în stadiu avansat. Majoritatea pacienților în faza precoce au fost tratați prin metode de ablație locală; 46 de pacienți în stadiu mediu au beneficiat de TACE. Terapia sistemică a fost preferată la pacienții în stadiu tardiv (48 pacienți), urmată de administrarea de Sorafenib (16 pacienți). 21 de pacienți cu boală terminală nu au primit tratament. Ratele de supraviețuire s-au corelat cu stadiul HCC: 2-18 luni în stadiul intermediar și 1-12 luni în stadiu avansat.

Concluzii: diagnosticul precoce al HCC este esențial pentru îmbunătățirea prognosticului pacienților, întrucât momentan există un număr mare de tratamente, clasice sau în dezvoltare, adresate acestor pacienți.

Cuvinte cheie: carcinom hepatocelular, alfa fetoproteina, transplant hepatic, ablație locală

Abstract

Background and aims: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer-related death. We aim to study the diagnosis and treatment options for HCC.

Methods: We used standard methods of diagnosis for HCC: radiology, determining serum alpha fetoprotein (AFP). We included 190 patients diagnosed with HCC between April 2011 and May 2012.

Results: All patients were classified and treated according to the BCLC staging. Our study included 43 patients with early stage HCC, 58 patients with intermediate stage HCC (Stage B) and 89 patients with advanced stage HCC (Stage C). Most patients in the early stage underwent local ablation, while TACE was preferred in 46 patients in the intermediate stage. Systemic therapy was the most frequent treatment for patients in the advanced stage (48 patients), followed by Sorafenib (16 patients). 21 patients with end-stage disease did not receive treatment. Survival rates depended on the HCC stage: 2 - 18 months in the intermediate stage and 1 - 12 months in the advanced stage.

Conclusion: Early diagnosis of HCC is essential in improving the patients' outcomes, as there are several classic therapeutic options and new emerging ones addressing patients with early stage disease.

Key words: hepatocellular carcinoma, alpha-fetoprotein, liver transplant, local ablation

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer-related death. Tumor incidence varies significantly, depending on geographical location. 80% of HCCs develop on underlying liver cirrhosis. 5 year overall survival rate is less than 10%. Despite current treatment, the five-year survival has remained 5%.

The timing of exposure to viral (hepatitis B and hepatitis C viruses) and chemical (alcohol and dietary aflatoxin) carcinogens influences the time of onset and progression of the molecular events that contribute to liver carcinogenesis. Chronic hepatitis leads to the development of cirrhosis. Progressively increasing loss of heterozygosity and aberrant DNA methylation lead to loss of tumor suppressor gene expression. Dietary aflatoxins cause specific p53 gene mutations that inhibit oncogene-induced apoptosis. Rb dysfunction and E cadherin inactivation occur later in the carcinogenic process. (1,2,3)

HCC diagnosis is performed by radiology (Ultrasound $\pm$ CEUS, CT scan, MRI), biopsy, levels of serum AFP. The prognosis depends on: the number and size of the nodule(s), the liver function at the time of diagnosis, the choice of treatment.

The Barcelona-Clinic Liver Cancer (BCLC) staging system (Fig. 1) uses variables related to: tumor stage, liver functional status, physical status, cancer-related symptoms and links the stages described with a treatment algorithm (4). Accordingly, patients may undergo resection, liver transplantation, tumor ablation (alcohol ablation, thermal ablation, cryoablation), transarterial chemoembolization (TACE), radiotherapy, systemic chemotherapy.

Material and Method

We used standard methods for diagnosis for HCC: radiology,

determining serum alpha fetoprotein (AFP). We included 190 patients diagnosed with HCC between April 2011 and May 2012. All patients signed an informed consent. They were all classified and treated according to the BCLC staging. They were treated according to the severity of the liver disease, using the BCLC protocols. The follow-up took place over a period of 18 months.

Results

Out of 190 patients, 113 had elevated AFP levels as follows: 23 patients with levels under 10 ng/ml, 39 patients with levels between 10 and 200 ng/ml and 51 patients with levels over 200 ng/ml. The values did not correlate to the severity of the disease or the prognosis.

The study included 43 patients with early stage HCC, 58 patients with intermediate stage HCC (Stage B) and 89 with advanced stage HCC (Stage C). Most patients in the early stage underwent local ablation, while TACE was preferred in 46 patients in the intermediate stage (Table 1). Out of these 46 patients, 3 underwent TACE with drug-eluting microspheres (DEB-TACE). Systemic therapy was the most frequent treatment for patients in the advanced stage (48 patients), followed by Sorafenib (16 patients). 21 patients with end-stage disease did not receive treatment.

Survival rates depended on the HCC stage: 2 - 18 months in the intermediate stage and 1- 12 months in the advanced stage. These rates demonstrate, as expected, the better outcome of patients diagnosed and treated in the early stages of the disease.

Discussion

The incidence of HCC varies considerably around the world with the highest rates in Southeast Asia and sub-Saharan Africa (areas where HBV infection is endemic and high). The United States have recently moved into the intermediate

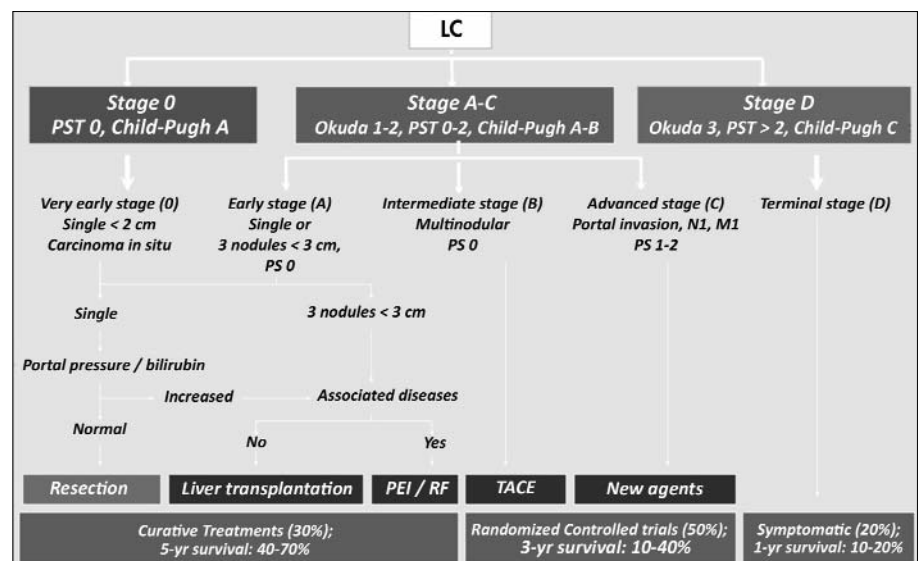


Figure 1. BCLC staging

Table 1. Treatment options used in patients with HCC according to the BCLC staging

Early stage	Intermediate stage	Advanced stage
Liver transplant (4)	TACE (46)	TACE + Sorafenib (3)
Resection (7)	TACE + RAF (9)	Sorafenib (16)
Local ablation (32)	TACE + Sorafenib (3)	Sorafenib + Bevacizumab + Erlotinib (1)
RAF (23)		Systemic therapy (48)
PEI (4)		
RAF + PEI (5)		

RAF: radiofrequency ablation, PEI: percutaneous ethanol injections, TACE: transarterial chemoembolization

incidence areas (age-adjusted incidence rates close to 4 per 100,000 person-years). (5)

A large study evaluated the age-adjusted incidence rates (per 100,000 person years in the underlying general population) of HCC patients diagnosed between 1975 and 2002. Cases were confirmed with histology or cytology. The data source is Surveillance, Epidemiology, and End Results (SEER) Population-based registries, which included information from 12 registries (14% of the US population). HCC is rare below age 40, but increases progressively thereafter. As the incidence of HCC has increased in the United States (during 2000-02), the age distribution curve has shifted to the left indicating that younger persons are becoming progressively more affected. Persons between 45 and 65 have been disproportionately affected with HCC (6,7).

Another study (8) aimed to evaluate the temporal changes in risk factors among patients with HCC. A total of 2,548 patients 65 years and older with HCC diagnosed between 1993 and 1999 were enrolled. HCC was diagnostically confirmed with positive histology, cytology, laboratory test/marker study, direct visualization, or positive radiology tests. All patients had continuous enrolment in Medicare for at least 2-years prior and up to 2-years following diagnosis (or until death). The proportion of hepatitis C virus (HCV)-related HCC increased from 11% during January of 1993 to June of 1996 to 21% during July of 1996 to December of 1999, whereas hepatitis B virus (HBV) - related HCC increased from 6% to 11% ($P < .0001$). No significant changes over time were observed for alcohol-induced liver disease, nonspecific cirrhosis, or non-specific hepatitis.

The cutoff of AFP that would maximize the sensitivity and specificity has been highly variable in several studies. The sensitivity has ranged from 25% to 65%, and the specificity ranges from 79% to 96%. This is considered suboptimal to be utilized as a screening test. The problems with these studies are the variable sample size, which limits the power of the studies, and that in all studies more than 80% of the cases (i.e., patients with HCC) had advanced stage. Because the goal of surveillance is the detection of small tumors, studying patients with advanced tumors would not be helpful towards reaching the goal.

A series of prospective studies (9) were based on the follow up of cohorts of patients with compensated cirrhosis, tested with AFP and ultrasonography every 6 months. A variable proportion of patients developed HCC, and the

incidence of HCC was dependent on the sample size. The positive predictive values, the chances that a positive test is positive in patients with HCC, ranged from 12% to 46%; and the negative predictive value, the chances that a negative test is negative in patients without HCC, ranged from 82% to 99%. The cutoff used was 20 ng/ml. These studies highlight the poor performance of AFP as a surveillance test.

The performance characteristics of AFP based on cutoff level have been further analysed (10). For an AFP cutoff between 10-11 ng/ml the pooled sensitivity is about 80% but the pooled specificity is about 70%. For the AFP cutoff between 17 and 21 (clinically recommended is 20 ng/ml), the pooled sensitivity drops to 65% but the pooled specificity improves to about 85%. As the cutoff of AFP increases, the sensitivity drops and the specificity improves. This shows that AFP is not an adequate surveillance test for HCC. In our study, the AFP levels did not correlate statistically with the severity or the prognosis of the disease.

In noncirrhotic patients surgical resection is the gold standard of treatment for HCC; this therapeutic option is rarely available for patients with underlying cirrhosis, therefore most of the cases in the early stages in our study underwent local ablation, either by radiofrequency, percutaneous ethanol injections or both. Liver transplantation is theoretically the best option for HCC patients as it removes both primary tumor and underlying liver cirrhosis (11). In 1996 Mazzaferro (12) reported excellent outcomes in patients within Milan Criteria (5- year survival rate currently exceeds 70%). These criteria include: single tumor less than 5cm, maximum 3 tumors, less than 3 cm each, no vascular invasion.

Several options have been recognized as bridging therapy for liver transplantation. Chemoembolization (TACE) limits the drop-out rate and, therefore, improves the intent-to-treat results of liver transplantation for HCC. Radiofrequency ablation has also been proposed for control of HCC before transplantation with good results. Surgical resection may also be offered as a first-line therapy in selected patients with HCC, with the possibility of liver transplantation as a second-line therapy if the histology shows a high risk of intrahepatic recurrence (13,14,15).

Whole Graft LT (DDLT) is the best therapeutic option for early, unresectable HCC (16). Outcome of liver transplantation for hepatocellular carcinoma - a single center experience (15). The waiting time for DDLT is much longer than that for

LDLT and allows patient selection in time. However, it is limited by a shortage of deceased donor liver grafts. Live donor liver transplantation (LDLT) has been developed to overcome the shortage of liver grafts. The waiting time for DDLT is much longer than that for LDLT, therefore LDLT minimizes the time on the waiting list. Some authors suggest similar results as in DDLT (17,18). Alternative options are using marginal livers and domino liver transplantation. The major drawbacks of LDLT are the risk of donor's death (about 0.5%) and the increased risk of recurrence rate. The shorter waiting time means there is unknown tumor behavior.

Recurrence after LT is as high as 40%. Patients may present several forms of metastatic foci in distant organs, such as the lungs, brain, bone, and in the transplanted allograft, among which few are amenable to liver resection/ local ablation; most of them require palliative chemotherapy - Sorafenib.

A meta-analysis for the effect of neoadjuvant and adjuvant therapy for operable HCC (19) revealed no evidence for efficacy of any of the adjuvant protocols reviewed. Sorafenib has been described as the first agent to improve survival for patients with advanced hepatocellular carcinoma (20). Patients undergoing a liver transplant, with high-risk features on explant pathology may have prolonged disease-free survival with the use of Sorafenib in the adjuvant setting. Currently there are randomized studies evaluating the safety and efficacy of Sorafenib after curative resection (21).

In our study, the best outcome was noticed in patients with early stage disease who underwent surgical procedures. TACE has also proven to be very effective in patients in the intermediate stage. The low number of patients who underwent DEB-TACE does not leave room for statistical analysis.

Conclusions

Early diagnosis of HCC is essential in improving the patients' outcomes, as there are several classic therapeutic options and new emerging ones addressing patients with early stage disease. Our study shows that all stages of HCC may receive effective therapy, with results approaching the literature data. In perspective, the combination of molecular therapies is expected to improve the outcome benefits already obtained with Sorafenib.

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