

MANAGEMENT OF HEPATOCELLULAR CARCINOMA: A STUDY ON 240 PATIENTS IN A SINGLE REFERRAL CENTRE

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ABSTRACT

INTRODUCTION: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death globally. Our study aimed to provide an understanding of the risk factors, pattern and management of HCC in a real-life practice.

MATERIALS AND METHODS: Two hundred and forty consecutive patients with HCC were evaluated for an 11-year period (from 2006 to 2016). During the last 5 years the patients were followed up prospectively from the time of the diagnosis to their death.

RESULTS: A hundred and seventy-two males and 68 females (mean age 66.4 ± 10.3 and 62.4 ± 9.5 years, respectively) were included in the observation. Hepatitis B virus (HBV) infection accounted for 40.4% and hepatitis C virus (HCV) infection – for 25.8% of the aetiology of liver disease. Cirrhosis is a baseline condition in 82%. HCC was found to be a first complication of liver disease in 2/3 of the studied patients. Using Barcelona Clinic Liver Cancer staging system HCC can be categorised as: stage 0 (n=3); stage A (n=32); stage B (n=52); stage C (n=75) and stage D (n=103). Therefore, the prevalence of very early and early HCC was 13%. Radical therapy (resection or ablation) was recommended in 28% of the patients. Importantly, 18 of 55 (32.7%) patients after surgical resection were followed for more than 3 years without tumour relapse. The median survival, based on the main treatment was: 36 months after surgical resection; 24 months after ablation; 10.5 months for patients on Sorafenib; 9.5 months after TACE and only 3 months for palliative care.

CONCLUSION: Our study confirms the observed trends in underlying diseases, the heterogeneity of survival and underscores the need of early diagnosis of HCC.

Keywords: *hepatocellular carcinoma, hepatitis B, hepatitis C, surveillance, survival*

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INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for more than 80% of the primary liver malignancy. The main risk factors are well described: the chronic hepatitis B (HBV) and C (HCV) viral infections; severe and continuous alcohol consumption and fatty liver disease, related to insulin resistance. Cirrhosis is a premalignant condition in 80 to 90% of established HCCs (1,2). In our country there is no approved algorithm for surveillance of high-risk patients for development of HCC in order to improve early diagnosis. However, a well-organised programme for evaluation and treatment of chronic viral infections has been adopted in clinical practice, leading to excellent achievements using the antiviral therapy. The diagnostic approach in patients with suspected HCC usually combines the utility of both imaging and biopsy methods as the morphological confirmation of diagnosis is essential for the patients before starting systemic therapy, based on the National Oncology Algorithm. Decisions on management were taken after discussion conducted by the local Oncology Board. The treatment of HCC is dependent on the Barcelona Clinic Liver Cancer (BCLC) and TNM staging of the disease, as well as regional resources.

MATERIALS AND METHODS

This study involved patient data from a single referral centre in the St. Marina University Hospital and is a first report of the results of a project entitled Hepatocellular Carcinoma – a Current Diagnostic and Therapeutic Approach. We aimed to increase the percentage of patients with chronic advanced liver disease included in surveillance for HCC with regular ultrasound (US) exams at every 6 months. The other important goals were to assess the risk factors for established HCC, to characterise the baseline chronic liver disease and the diagnostic and therapeutic methods for HCC in clinical practice. Patients diagnosed with HCC in an 11-year period (from 2006 to 2016) were included in the study. During the last five years the patients were followed up prospectively from the time of the diagnosis to their death. US exams, including contrast enhanced US with SonoVue contrast agent (Bracco) were performed with Aloca α 7 Prosound machine. HCC was diagnosed based on at least one imaging contrast-enhanced investigation [contrast-enhanced ultrasound (CEUS), computed

tomography (CT) or magnetic resonance imaging (MRI)] with established typical intensive arterial hyperenhancement followed by slow and late washout and/or US or CT-guided liver biopsy. The stage was defined according to BCLC staging and allocation system (3). Treatment decision was taken by multidisciplinary discussion conducted by a local Oncology Board. The liver resection and local ablation were considered to be potentially curative or radical treatment methods. The main modalities for monitoring were US, including CEUS, level of alpha-fetoprotein and contrast-enhanced CT. The survival was calculated from the date of diagnosis. All patients' data were registered in the Access-based data system.

RESULTS

Two hundred and forty consecutive patients (172 males, 68 females) were registered with hepatocellular carcinoma in Clinic of Gastroenterology in Varna for the period from 2006 to July 2017 (for 11.5 years). The mean number of 20 newly diagnosed cases were included per year, without any significant trend in the distribution. The male to female ratio was 2.6:1. The youngest patient with HCC was 36 years old. The average age at diagnosis of male and female patients was 66.40 ± 10.31 and 62.44 ± 9.55 years, respectively. The main reason for diagnostic evaluation was nonspecific complaints (53.56%), followed by decompensation of cirrhosis (30.12%) and lesion found on surveillance via conventional ultrasound (16.32%). During the last 5 years the part of occasionally diagnosed HCCs during monitoring with US has increased to 22.72%.

Overall, cirrhosis is a baseline disease in most of our patients: 196 out of 240 (82%). Decompensated liver disease at the time of HCC presentation was found in 136 out of 196 patients (69.4%).

Risk Factors for HCC and Aetiology of Chronic Liver Disease

Chronic HBV infection was registered in 40.4% of patients with HCC, chronic HCV infection – in 25.8%; 2 cases had HBV/HCV co-infection and 4 cases had HBV/HDV co-infection. Only 2 out of 97 patients with hepatitis B had positive HBeAg (2%), thus predominant HBeAg negativity was observed. The viral load in patients with HBV infection was notably high: 6 585 589 IU/mL. Most of patients with HBV-related HCC, 74 out of 97 (76.3%) had never

received antiviral treatment. Further, primary liver cancer was diagnosed in 19 patients on long-term (over 1 year) nucleoside (Lamivudine, Telbivudine, Entecavir)/nucleotide (Tenofovir) analogue therapy against HBV or were previously treated with interferon-alpha. Interestingly, 6 out of 18 (33%) patients on continuous antiviral therapy were registered with resistance to Lamivudine and additionally 4 patients failed to achieve complete viral suppression, defined as undetectable HBV DNA during treatment with Entecavir or Tenofovir. The patients with HCV infection were previously untreated (87%) or were non-responders to interferon-alpha therapy. One patient in our registry was followed up from the onset of the acute phase of HBV infection; he was treated with 3 cycles of interferon (IFN)-alpha, achieving HBsAg seroconversion; HCC developed after 20 years of HBV infection in an HBsAg-negative phase (probable occult HBV infection).

The prevalence of antibodies to HBV core antigen (anti-HBc total or IgG), as a marker for previous HBV exposure, in the subgroup of patients with negative screening for HBV and HCV (HBsAg negative, anti-HCV negative) was significant - 56.52%.

Table 1. Viral markers in patients with hepatocellular carcinoma

| Test | Number of positive patients/ Number of tested patients (%) |
|-------------------------|--|
| HBsAg | 97/224 (40.41) |
| Anti-HCV | 62/224 (25.83) |
| Anti-HBc total (or IgG) | 111/128 (86.72) |
| Anti-HDV | 4/80 (5) |

The prevalence of diabetes was 35%. Moderate to severe alcohol intake was registered in 23% of patients. The other rare aetiological factors for chronic liver disease in our cohort were: Wilson's disease in 3 cases; autoimmune hepatitis in 2 cases and non-alcoholic fatty liver disease (NAFLD) in 1 patient (Fig. 1). Unknown aetiology was registered in 28 patients, but 10 of them (36%) had a marker for exposure to HBV (anti HBc positive antibodies).

Abbreviations used in Fig. 1: HBV (hepatitis B virus); HCV (hepatitis C virus); WD (Wilson's dis-

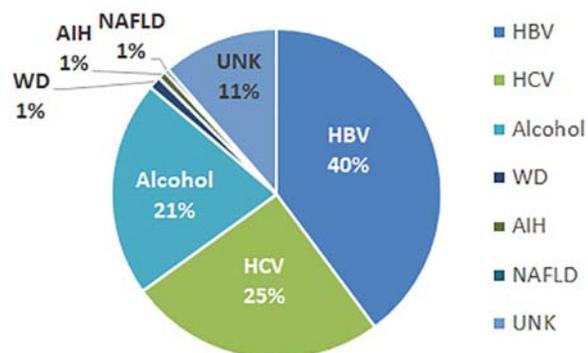


Fig. 1. Risk factors and aetiology of chronic liver disease in the cohort of patients with hepatocellular carcinoma (n=240)

ease); AIH (autoimmune hepatitis); NAFLD (non-alcoholic fatty liver disease); UNK (unknown).

Characteristics and Severity of Underlying Liver Disease

HCC was associated with cirrhosis in 196 patients (82% of the studied cohort). A hundred and forty-six cases (75%) can be defined with clinically significant portal hypertension, based on the presence of oesophageal varices (n=91) or ascites (n=121), or both (n=67) at time of HCC diagnosis. HCC was found to be a first complication of chronic liver disease in 2/3 of cases (n=156). The prevalence of oesophageal varices was 63%. Table 2 summarised the clinical and laboratory characteristics of chronic liver disease in the involved 240 patients.

Remarkable trends in laboratory results in the studied cohort of 240 patients can be synthesised as: mild but present liver synthetic function dysfunction; platelet count higher than expected for the severity of liver disease; predominant cholestasis than cytotoxicity; disturbed glucose metabolism (fasting glucose ≥ 6 mmol/L) in 44% of the cases. However, the conclusion could not be proved due to absence of comparison to other similar cohort of patient with cirrhosis without malignant transformation.

Twenty-one HCC patients had a liver stiffness measurement, with mean value of 27.85 kPa (ranged from 4.4 to 75 kPa, with the lowest value in a patient on a long-term antiviral therapy with Tenofovir and the highest value in a patient with severe portal hypertension, respectively).

Table 2. Clinical and laboratory data of 240 studied patients with hepatocellular carcinoma

| Characteristics | Results |
|--|--------------------------------------|
| Child-Turcotte-Pugh class of the chronic liver disease: A/B/C; n (%) | 90 (37.5%) / 73 (30.4%) / 77 (32.1%) |
| Performance status: 0/1/2/3/4 (n) | 29 / 117 / 52 / 36 / 3 |
| Oesophageal varices: small/large, n | 29 / 62 |
| Portal hypertensive gastropathy, n (%) | 99 (68.3%) |
| Ascites: mild/ moderate/ severe (n) | 45 / 35 / 46 |
| Bilirubin, mcg/L (mean ± SD) | 55.4 ± 77.6 |
| Prothrombin index, % (mean ± SD) | 68 ± 23.2 |
| Albumin, g/L (mean ± SD) | 32.2 ± 7.3 |
| Haemoglobin, g/L (mean ± SD) | 122.9 ± 20.1 |
| Platelet count, x10 ⁹ /l | 172.8 ± 34.8 |
| AST, IU/L (mean ± SD) | 113.1 ± 121.8 |
| ALT, IU/L (mean ± SD) | 67.2 ± 70.4 |
| GGT, IU/L (mean ± SD) | 241.6 ± 288.5 |
| AP, IU/L (mean ± SD) | 327.7 ± 414.7 |
| Cholinesterase activity, IU/l (mean ± SD) | 3887.3 ± 3047 |
| Glucose, mmol/L (mean ± SD) | 6.4 ± 2.7 |

Methods for Diagnosis of HCC

The primary diagnosis of HCC was based on at least two imaging methods in 133 cases (55.4%); in all other patients the imaging method was combined with at least one US or CT-guided biopsy of the hepatic lesions (Fig. 2). The fine needle aspiration biopsy (FNAB) was a morphologic method in 92 patients (86% of all performed biopsies) and the core biopsy for histology – in 15 patients. The false negative rate of biopsy investigation for malignancy in our cohort was 14%.

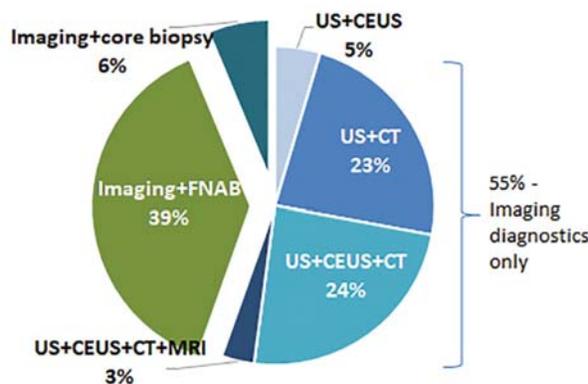


Fig. 2. Methods for diagnosis of HCC

Overall, contrast-enhanced US and CT were the principal imaging modalities in our practice. Regarding the staging of HCC we have got a small experience with PET/CT imaging in 7 patients. Data on diagnostic accuracy of used modalities will be presented in a future report.

Abbreviations used in Fig. 2: US (ultrasound); CEUS (contrast-enhanced ultrasound); CT (computed tomography); MRI (magnetic resonance imaging); FNAB (fine needle aspiration biopsy).

We analysed the level of tumour markers in the studied cohort. Overall, 77.5% of the patients diagnosed with HCC had elevation of alpha-fetoprotein (AFP); 95 patients with HCC (40%) had AFP serum concentration greater than 200 ng/mL and 85 patients (35.4%) - above 360 ng/mL. Interestingly, 70% of patients with elevated AFP had also increased carbohydrate antigen 19-9 (CA 19-9).

Tumour Burden and Staging

A solitary lesion (with mean diameter 5.2 cm) was registered in one third of the studied patients. A total of 50% of the patients had more than 3 lesions at the time of the diagnosis of the disease or were presented with poorly defined infiltrative pattern of malignancy (Fig. 3). A hundred and thirty-one cases (54.5%) had bilobar distribution of nodules. Sixty-

two cases had major vessel invasion (26%), predominantly malignant thrombosis of the portal vein and/or its main branches. Thirty-nine patients (16.2%) were diagnosed with regional lymph node enlargement and another 32 cases (13.2%) had distant metastasis in lungs, bones, suprarenal glands, pleura, abdominal wall and central nervous system.

Using the accepted Barcelona Clinic Liver Cancer (BCLC) staging system the disease can be categorised as: stage 0 (n=3); stage A (n=32); stage B (n=52); stage C (n=75) and stage D (n=103), Figure 4. The patients with very early and early HCC stage accounted for 13% of all HCCs; the tumour had been detected with ultrasound surveillance in 51%. In contrast, most HCCs were detected at stage D, mainly due to advance baseline liver cirrhosis.

Regarding the CLIP, scoring the patients can be assessed in seven categories: with score 0 (n=12); score 1 (n=41); score 2 (n=54); score 3 (n=34); score 4 (n=46); score 5 (n=25) and score 6 (n=10).

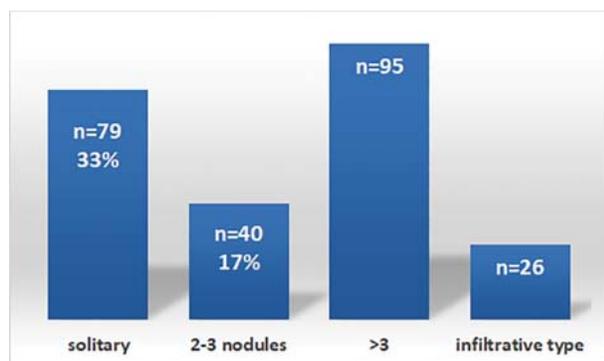


Fig. 3. Pattern of tumour lesions

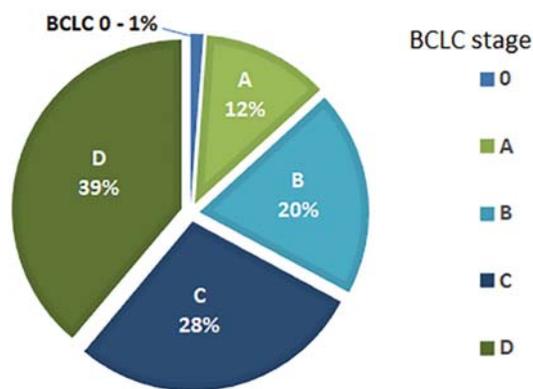


Fig. 4. Classification of HCC, according to the Barcelona Clinic Liver Cancer staging system (n=240)

Treatment Methods

Overall, radical therapy (resection or ablation of HCC) was recommended in 28% of studied patients (Fig. 5). Surgical resection (anatomical/segmental or atypical resection) was performed in 23% of the cases (n=55). The perioperative mortality rate and short-term lethal evolution due to severe liver decompensation were registered in 7.3% of the treated patients by radical surgical intervention. Importantly, 18 out of 55 (32.7%) patients with radical resection were followed up for more than 3 years (median 4.2 years) without relapse of HCC. In all other cases a relapse of HCC was registered during the first 3 to 24 months after surgery, treated by further resection (n=3), local ablation (n=4), systemic therapy with Sorafenib (n=8) or palliation (n=15). Median survival of patients treated by surgical resection was 36 months. In 13 patients (5%) the first treatment method was the local ablation, mainly radiofrequency ablation. Complete ablation, confirmed by follow-up CEUS was achieved in 61% and there were no serious complications leading to death. The median survival of patients treated by local ablation was 24 months. No patient with HCC was treated by liver transplantation.

To summarise, radical treatment of HCC in our cohort was successful to achieve disease-free and overall survival in 26 patients; the carcinoma was established by US follow-up in 70%; all these cases had viral aetiology of chronic liver disease (in stage of compensated cirrhosis at a prevalence of 77%) and radical treatment of HCC was accompanied by continuous viral suppression in HBV-related carcinomas. Modern treatment with direct-acting antiviral agents (Sofosbuvir/Ledipasvir ± Ribavirin) was introduced to 4 patients with HCV cirrhosis and results on HCV eradication and HCC follow-up will be further evaluated.

We have small experience with TAE/TACE (mainly TAE) as a first-line therapy in 2% of studied patients with median survival of 9.5 months. Systemic therapy, predominantly with Sorafenib was introduced to 17% of involved patients and median survival was registered as 10.5 months. Most frequent method, however, was best supportive care (in 53%), including treatment of liver cirrhosis decompensation. Overall survival of these patients was 3 months.

In addition, antiviral treatment during and after treatment for HCC was recommended in 28 patients with viral cirrhosis.

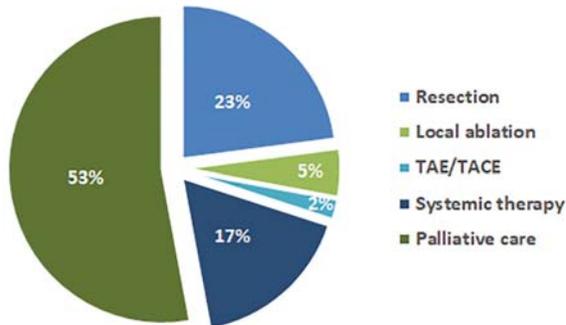


Fig. 5. First-line treatment method in a cohort of 240 patients with hepatocellular carcinoma

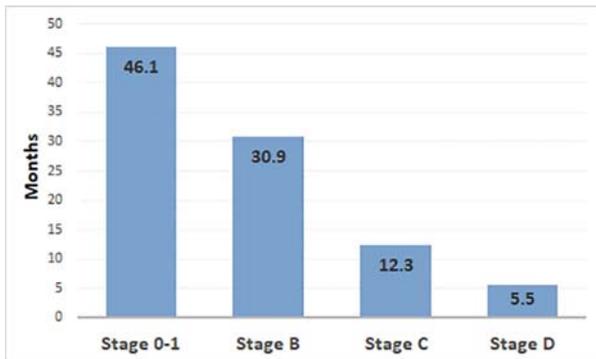


Fig. 6. Overall survival of 240 patients with hepatocellular carcinoma, according to the BCLC stage of disease

Finally, we tried to analyse the efficacy of interventions as a part of prospective surveillance and management of patients after 2012 and after inclusion in a project for HCC best care. Table 3 summarises the observed difference in tumour burden and stage of HCC and recommendation for potential curative treatment, according to application of US surveillance.

DISCUSSION

Epidemiology of HCC is changing globally and trends show an increasing morbidity in North, Central and Eastern Europe and North America but a slow decline in Japan, Korea and China. The burden of this important complication of the chronic advanced liver disease is expected to increase in the next 10 years (4). Several reviews were focused on a broad spectrum of clinical practice in HCC manage-

ment worldwide, including surveillance of patients with cirrhosis for HCC, establishing the diagnosis of HCC, and various therapeutic options for the treatment of HCC (5-11). Thus, we initiated a project to gather a real-life data from a large tertiary referral centre for patients with chronic liver disease in Bulgaria, including multidisciplinary team of specialists, involved in HCC management.

Our observation registered 240 patients with HCC for a 11-year period without significant increase of new cases in the last 5 years. Two important manuscripts on HCC management in Bulgaria were published recently (12,13). The study from St. Ivan Rilski University Hospital involved 65 consecutive HCC patients for an approximately 3-year interval (12). The report from Queen Giovanna University Hospital was focused on 450 patients with primary liver neoplasms for an 11-year period (1997-May 2017) (13).

It is well known, that male to female predominance is greater than 2:1 with HCC, and a 2.6:1 ratio is recorded in our cohort. Cirrhosis is a baseline disease in 80 to 90% of the cases in clinical series, as 82% registered in this study. Interestingly, the largest observation on HCC in Bulgaria showed even higher percentage of HCCs – 99.1%, based on liver cirrhosis (13).

The most common risk factor for HCC was HCV in North America, Europe and Japan, and HBV in China, South Korea and Taiwan (5). In contrast to data from Europe, in Bulgaria the principal aetiology for liver disease complicated with HCC was HBV. HBV infection accounted for 40.4% and HCV infection – for 25.8% of aetiology of liver disease in our observation. We may further speculate on the even more significant role of HBV (as occult or infection in the past) if we consider the high prevalence of positive HB core antibodies (56%) in persons with negative screening for active HBV and HCV infection. A vaccination programme in newborns against HBV infection in Bulgaria started in 1992 and its favourable impact on HBV-related HCCs is expected probably in the near future. Table 3 summarised general features of HCC, according to published literature.

The conclusion is that in our region we need to focus on early diagnosis of HCC, simultaneously with registration of HCC in patients with compen-

Table 3. Detailed analysis of studied cohorts of patients with HCC, according to application of US surveillance and studied period

| Patient's cohorts | % screened | % Tumour size < 3 cm | % Multifocal tumours | % Vascular invasion | % BCLC stage 0-1 | % Curative treatment | Median survival (months) |
|--|------------|----------------------|----------------------|---------------------|------------------|----------------------|--------------------------|
| Patients diagnosed with HCC from 2006 to 2011 (n=99) | 11 | 16 | 80 | 21 | 5 | 23 | 15.3 |
| Patients diagnosed with HCC from 2012 to July 2017 (n=141) | 20 | 40 | 59 | 28 | 21 | 31 | 21 |
| Patients diagnosed with HCC during US surveillance (n=39) | 100 | 59 | 36 | 5 | 46 | 80 | 42.5 |

*Only data for patients from European centres were registered in the table; **Percent cases with AFP>20 ng/ml

sated liver disease, mainly cirrhosis. This favourable “stage migration” can be achieved with surveillance with US and tumour markers like AFP among patients with advanced liver disease, particularly with HBV aetiology. Although the early stage of HCC is much lower (13%) than recorded in European and US registries we were able to recommend and perform curative treatment in 28% of patients. That applicability rate is in accordance with 25-40% use of curative therapy in Western series and leads to favourable survival rate.

Finally, the ultrasound monitoring of patients with advanced chronic liver disease registered an increased rate of BCLC 0-1 staged tumours (46%) and the applicability of potentially curable treatment approach, achieving best survival rate of median 42.5 months. Thus, our pilot study provided evidences, promoting systematic use of surveillance in the patients at risk of having HCC.

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