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# Demographic, Clinical and Treatment Characteristics of Patients with Hepatocellular Cancer: 10 Years of Experience of a Single Center

## Hepatoselüler Kanser Tanılı Olguların Demografik, Klinik ve Tedavi Özellikleri: Tek Merkezin 10 Yıl Deneyimi

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**Öz**

Karaciğerin primer kanserleri, kansere bağlı ölümlerde 3. sırada yer almaktadır. Hepatoselüler karsinom (HSK), primer hepatik malignitelerin yaklaşık %80'ini oluşturur. Barcelona Clinic Liver Cancer (BCLC) sınıflaması HSK'yı 5 evreye böler ve tedavileri tahsis eder. Bu çalışmanın amacı merkezimizdeki HSK hastalarının aldıkları ilk tedavilerin incelenerek kılavuzlardaki yaklaşım ile karşılaştırmaktır. Çalışmamızda, 2006-2016 yılları arasında HSK tanısı almış hastaların verileri geriye dönük irdelendi. Hastaların yaş, cinsiyet, etiyoloji, Child-Pugh skoru, BCLC evresi, model for end-stage liver disease skoru, alfa fetoprotein düzeyi, tümör özellikleri, aldıkları ilk tedavi türü ve sağ kalım süresine bakıldı ve istatistiksel analizi yapıldı. Hastaların ortalama yaşı 61±10,5; 228'i erkek, 33'ü kadındı. Çalışmada yer alan hastaların 130'unun BCLC evresi değerlendirilebildi. Bu hastaların 77'sinin BCLC evre C olduğu saptandı. BCLC sınıflamasına göre hastaların ilk tedavilerini değerlendirdiğimizde, 22 hastaya sorafenib, 16 hastaya rezeksiyon, 15 hastaya TAKE, 14 hastaya Yitrium-90, 14 hastaya sorafenib dışı sistemik kemoterapi, 11 hastaya transplantasyon, 8 hastaya palyatif tedavi ve 4 hastaya ablasyon uygulandığı bulundu. Sağkalım süresinin 11.9 (8,1-15,9) ay ve bir yıllık sağ kalımın %32, üç yıllık sağ kalımın %19, beş yıllık sağ kalımın %16 olduğu saptandı. Merkezimizde HCC hastalarının yönetiminde BCLC kılavuzunun yanı sıra güncel literatür ve NCCN kılavuzundan da faydalanıldığı saptandı. Tedavi almayan hasta sayısının fazla olması da Evre D hastalara yeterli klinik ilgiyi göstermemiz gerektiğinin göstergesi olabileceğini düşündürdü.

**Anahtar Kelimeler:** Hepatoselüler Karsinom, Sağkalım, Tedavi Protokolleri

**Abstract**

Primary cancers of the liver are in the 3rd place in cancer-related deaths. Hepatocellular carcinoma (HCC) accounts for approximately 80% of primary hepatic malignancies. The Barcelona Clinic Liver Cancer (BCLC) classification divides HCC into 5 stages and allocates treatments. The aim of this study is to examine the initial treatments of HCC patients in our center and compare them with the approaches in the guidelines. The data of patients diagnosed with HCC between 2006 and 2016 were recruited retrospectively. Age, gender, etiology, Child-Pugh score, BCLC stage, model for end-stage liver disease score, alpha-fetoprotein level, tumor characteristics, type of first treatment and survival time were evaluated. There were 228 men and 33 women. The mean age was 61±10.5. Of the 130 patients 77 were found on BCLC stage C. The first treatment according to BCLC stage were sorafenib in 22, resection in 16, TACE in 15, Ytrium-90 in 14, systemic chemotherapy other than sorafenib in 14, transplantation in 11, palliative treatment in 8, and ablation in 4 patients. The median survival time was 11.9 (8.1-15.9) months. One-year survival was 32%, three-year survival was 19%, and five-year survival was 16%. The management of HCC patients was performed according to more than just BCLC guidelines in our center. The high number of patients who did not receive treatment may indicate that we need to show sufficient clinical attention to Stage D patients.

**Keywords:** Hepatocellular Carcinoma, Survival, Treatment Protocols

## Introduction

Primary liver cancers ranked in sixth place among all cancer types worldwide in 2020 and also ranked in third place on cancer-related deaths (1). According to the American Cancer Society, primary liver cancer ranked fifth in cancer-related deaths in males, and the estimated number of new primary liver cancer cases was reported to be 41210 in all sexes (2). Hepatocellular carcinoma (HCC) exists in approximately 80% of hepatic malignancies (1). Chronic hepatitis B virus (HBV) and HCV infections, aflatoxin-contaminated foods, heavy alcohol consumption, smoking, type 2 diabetes mellitus, and being overweight are the main risk factors for HCC (3).

Many scoring methods have been discussed for treatment selection in patients, regardless of the tumor node metastasis staging system. One of these is The Barcelona Clinic Liver Cancer (BCLC) classification system. BCLC classification allocates treatments by dividing the disease into five stages based on tumor size, number, vascular invasion,

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metastasis status, Child-Pugh Score (CPS), and patient performance score (4-6). The European Association for Study of Liver (EASL) reported the HCC management guidelines in 2000 and accommodated the usage of BCLC classification since 2012 (7-9). Today, ablation methods, liver resection, liver transplantation (LT), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), sorafenib, monoclonal antibodies, and palliative treatments can be applied in the treatment of HCC (6).

We aimed to compare the treatment approaches conducted in our center, which has high-level treatment facilities such as organ transplantation and interventional radiology, with guidelines by examining the applied first treatment modality in HCC patients with this study.

## Material and Method

We examined the data of 273 patients over 18 years old diagnosed with HCC in our center or referred to our hospital for treatment between 2006 and 2016. We excluded twelve patients from the study because of missing survival data. We collected the data of the remaining 261 patients retrospectively. We evaluated the data of patients' age, gender, etiology of HCC, CPS, BCLC stage, the model for end-stage liver disease (MELD) score, alpha-fetoprotein (AFP) level, metastasis, tumor specifications (location and dimension), portal vein thrombosis (PVT), first treatment modality, and survival time. We obtained ethics approval to conduct this study from the Akdeniz University Faculty of Medicine Ethics Committee (decision date: 01.03.2017 / decision number: 140).

*Statistical analysis*

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows version 20.0 (IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the distribution of the data. Parametric data were presented as mean and standard deviation (SD), and non-parametric data were presented with median and interquartile range (IQR). Categorical variables were shown as numbers and percentages. Survival analysis was performed by the Kaplan-Meier method, and statistical differences were confirmed by log-rank test. The p-value was considered as 0.05 to determine the differences in the analyses.

## Results

The mean age of all patients was 61±10.5 years. The majority of patients are men (87%, n=228) and cirrhotic patients (85%, n=221). The most common etiologic factor was HBV infection with 131 (50%) patients (Table 1).

**Table 1.** Demographic and clinical characteristics of the patients.

| | |
|---|---|
| Age, year ±SD | 61 ±10.5 |
| Gender, n (%) | |
| Female | 33 (13) |
| Male | 228 (87) |
| Ethiology, n (%) | |
| HBV | 131 (50) |
| HCV | 38 (15) |
| HBV + HCV | 3 (1) |
| HBV + HDV | 9 (3) |
| Alcohol | 32 (12) |
| Others | 76 (36) |
| BCLC, n (%) | |
| Stage 0 | 1 (1) |
| Stage A | 8 (6) |
| Stage B | 7 (5) |
| Stage C | 77 (59) |
| Stage D | 37 (29) |
| Child-Pugh score, n (%) | |
| Class A | 139 (63) |
| Class B | 66 (30) |
| Class C | 16 (7) |
| MELD score, n (%) | |
| <10 | 114 (51) |
| 10-20 | 99 (45) |
| >20 | 8 (4) |
| Patient with metastasis, n (%) | |
| Yes | 64 (25) |
| Abdominal lymph node | 17 (24) |
| Periton | 12 (17) |
| Bone | 13 (18) |
| Lung | 10 (14) |
| Lung + Bone | 3 (4) |
| Adrenal gland | 3 (4) |
| Kidney | 3 (4) |
| Other organs | 10 (14) |
| No | 197 (75) |
| Portal Vein Trombosis, n (%) | |
| Yes | 64 (29) |
| No | 154 (71) |
| AFP level, n (%) | |
| <20 ng/ml | 97 (40) |
| 20-200 ng/ml | 63 (27) |
| >200 (ng/ml) | 79 (33) |

We evaluated 130 of 261 patients by BCLC stage and found that 77 (59%) were on Stage C. According to CPS, the number of patients with class A, B, and C were 139 (63%), 66 (30%), and 16 (7%), respectively. The MELD score was below 10 in 114 (51%), between 10 and 20 in 99 (45%), and above 20 in 8 (4%) patients. The AFP level was below 20 ng/ml in 97 (40%), above 200 ng/ml in 79 (33%), and between 20 to 200 ng/ml in 63 (27%) patients (Table 1).

The tumor was most frequently located in the right lobe (n=137, 55%), the tumor diameter was 5 cm or more in 52% (n=129) of the 246 patients whose tumor diameter could be determined, and 55% (n=137) of the 248 patients whose tumor number was determined had multiple tumors (Table 2). We found that 153 (57%) patients were diagnosed with HCC by biopsy, and 25 (10%) patients were diagnosed in an external center.

**Table 2.** Tumor features.

| Variable | n (%) |
|---|---|
| Tumor location | |
| Right lobe | 137 (55) |
| Left lobe | 21 (8) |
| Bilobar | 91 (37) |
| Tumor diameter | |
| <2 cm | 15 (6) |
| 2-5 cm | 102 (42) |
| >5 cm | 129 (52) |
| Tumor count | |
| Single | 111 (45) |
| Multiple | 137 (55) |

We found that PVT was diagnosed in 64 (29%) of 218 evaluated patients. Metastasis was found in 64 (25%) patients (Table 1). The most common metastasis locations were abdominal lymph node (n=17), peritoneum (n=12), bone (n=13), and lung (n=10) (Table 1).

We found the distribution of the first choice treatment modalities according to BCLC stage as sorafenib to 22, resection to 16, TACE to 15, yttrium-90 (y-90) to 14, non-sorafenib systemic chemotherapy to 14, LT to 11, palliative care to 8 and radiofrequency ablation (RF) to 4 patients. We found no treatment was administered to the remaining 26 patients (Table 3). Upon thorough analysis of the treatment methods per the guideline, we found that in Stage 0, a single patient underwent resection, whereas in Stage A, three out of eight patients underwent LT or RF. In Stage B, only one out of seven patients received TACE. Furthermore, in Stage C, sixteen out of seventy-seven patients received sorafenib; in Stage D, six out of thirty-seven received palliative treatment. Table 4 displays the treatment modalities that were administered to all patients.

**Table 3.** The administered first treatment modality counts according to BCLC stages.

| BCLC | LT | Resection | RF | TACE | Y-90 | Sorafenib | Palliative | No treatment | Chemotherapy |
|---|---|---|---|---|---|---|---|---|---|
| **0** | - | 1 | - | - | - | - | - | - | - |
| **A** | 1 | 2 | 2 | 2 | 1 | - | - | - | - |
| **B** | 1 | 2 | - | 1 | 2 | 1 | - | - | - |
| **C** | 4 | 8 | 2 | 10 | 11 | 16 | 2 | 12 | 12 |
| **D** | 5 | 3 | - | 2 | - | 5 | 6 | 14 | 2 |
| **Total** | 11 | 16 | 4 | 15 | 14 | 22 | 8 | 26 | 14 |

The median survival time was 11.9 (IQR=8.1-15.9) months. The 1-, 3-, and 5-year survival rates were 32%, 19%, and 16%, respectively. The survivals according to treatment modalities are shown in Figure 1.

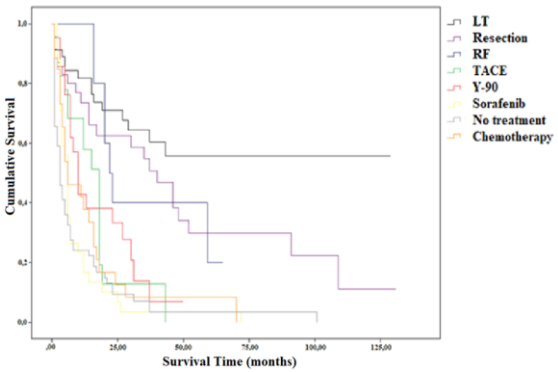


**Figure 1.** Survival of the patients according to the treatment modalities.

## Discussion

The most recent BCLC classification recommends ablation treatment as the first option in very early stage tumors. If the patient is a potential candidate for LT, resection and transplantation are recommended as first options according to liver functions. In early stage tumor, the first line treatment options resection, ablation and transplantation choice depend on liver functions. In intermediate stage tumor TACE, transplantation and systemic treatment can be administered according to tumor size, AFP level, portal flow, and tumor specifications. In advanced stage and terminal stage, only systemic treatment and palliative treatment is recommended, respectively (6).

**Table 4.** The administered treatment modality counts of all cohort.

| Treatment modality | n (%) |
|---|---|
| Liver transplantation | 46 (%22) |
| Liver resection | 35 (%17) |
| Radiofrequency ablation | 13 (%6) |
| Transarterial chemoembolisation | 23 (%11) |
| Y-90 | 21 (%10) |
| Sorafenib | 34 (%16) |
| Palliative | 10 (%5) |
| No treatment data | 53 (%20) |
| Systemic chemoterapy (non-sorafenib) | 26 (%13) |

According to previous and current guidelines, sorafenib treatment is recommended in BCLC grade C patients (6,8). We observed that sorafenib was preferred as first-line treatment in one patient at an out-center clinic instead of TACE because the tumor size was 8 cm and multiple. It was a conflicting treatment choice with the previous guideline. The current guideline recommends systemic treatment in Stage B patients if the tumor is diffuse, infiltrative, extensive, or bilobar (6). We found that the oncologists administered sorafenib treatment to 5 patients who were considered on Stage D. According to the National Comprehensive Cancer Network (NCCN), CPS is preferred over BCLC in treating

HCC (10). We found that these five patients in CPS class A or B who are not suitable for local treatment were considered as appropriate candidates for sorafenib by the oncologists.

The previous guideline recommended liver resection in Stage 0 patients (8). In our study, two patients on Stage A underwent liver resection. One had a 3 cm single tumor, and the other underwent resection at an out-center clinic. According to the current guideline, liver resection can applied to patients on Stage 0 if the performance score is 0 and potential candidates for LT, and on Stage A if the performance score is 0 and liver functions are well-preserved (6). We found two patients who underwent liver resection on Stage B. One underwent liver resection while waiting for LT, and the other was referred directly to a general surgeon from an out-center clinic for liver resection to an undiagnosed liver mass. We found that three of the eight patients underwent resection and then were administered sorafenib, who were on Stage C. It was reported that patients who underwent sorafenib treatment following liver resection had better survival than only sorafenib (11). This approach is different from the guidelines but compatible with the literature. There were three patients on Stage D who underwent liver resection. We found that all of them were diagnosed with HCC after resection and then referred to the oncologists by general surgeons.

Liver transplantation was performed in 10 patients who were not on Stage A, even though it was not recommended in the previous guidelines. In the current guideline, LT is a treatment option in selected patients with Stages A and B (6). One patient with a 6 cm tumor at Stage B underwent LT in compliance with University of California San Francisco criteria. According to the BCLC staging system, portal vein infiltration or performance score of ≥1 is classified as Stage C (6-8). Two patients with a performance score of 1 underwent LT despite being on Stage C. We considered that performance scores could have been interpreted differently according to a given anamnesis by a patient to a clinician. The remaining seven patients in Stages C and D underwent LT from a living donor.

According to the guidelines, TACE is recommended for Stage B (6,8,9). In Stage A, TACE was preferred over RF for one patient due to tumor proximity to the diaphragm, and the other patient received initial treatment at an out-center clinic. Ten patients in Stage C received TACE instead of sorafenib. One of these patients received treatment in an out-center clinic. Since the number of tumors in four patients was only one, TACE might have been preferred over sorafenib. The remaining five patients received this off-label treatment, according to EASL. Since sorafenib treatment is not contraindicated after TACE treatment, NCCN applies this treatment in cases deemed clinically appropriate (10). Chen et al. (12) reported that patients who received TACE + sorafenib combination had a better disease control rate, survival, and disease progression time than those who received only sorafenib. It is stated that lesions larger than 5 cm that cannot be resected should be evaluated for arterial therapy (TACE/TARE) or sorafenib, according to NCCN. In addition, arterial treatments are relatively contraindicated in patients with bilirubin >3 mg/dl, portal vein thrombosis, and CPS class C if selective segmental injection is not performed (10). Transarterial chemoembolization was performed on two patients in Stage D. We believe that this situation, which does not comply with the EASL guideline, is an unnecessary preventive treatment approach, as the survival of these patients in the follow-up is not even one month.

Fourteen patients in our study received systemic chemotherapy. It was observed that 12 patients in Stage C and two patients in Stage D were given systemic chemotherapy other than sorafenib. Non-sorafenib systemic chemotherapy is not recommended in EASL (8). On the other hand, NCCN mentions that it can be applied within the scope of clinical trials (10). Ten of the twelve patients on Stage C were administered sorafenib after the non-sorafenib chemotherapy protocol. We observed that this type of treatment modality, which is not considered in the guidelines, was applied because sorafenib was reimbursed only for patients resistant to non-sorafenib chemotherapy. Only two patients received non-sorafenib chemotherapy at an out-center clinic on Stage D.

The previous guideline recommends RF for Stage A patients (8). There were two patients on Stage A and two patients on Stage C who received RF. One of the patients on Stage C underwent RF at an out-center clinic. The other patient was considered Stage C by general surgery because of suspicious invasion on dynamic computed tomography; however, the patient was reconsidered by gastroenterology, and RF was applied as a treatment. Also, this patient was considered a candidate for LT and underwent TACE as a bridge therapy on the waitlist. With this information, we assumed that the radiology report had been reconsidered in the multidisciplinary council.

There were 14 patients who received y-90 treatment. Of these patients, 11 were found on Stage C. This treatment modality was not covered in the previous EASL and American Association for the Study of Liver Disease guidelines (8,13). However, recent guidelines recommend y-90 for HCC treatment (6,9). The other patients in Stages A and B underwent y-90 treatment as bridge therapy while waiting for LT. We found that this treatment type was compatible with the guidelines.

Two patients received palliative treatment in BCLC Stage C according to their wishes, and six patients in Stage D received palliative treatment. It was determined that 26 patients in Stages C and D

did not receive treatment. Based on research findings among patients diagnosed with cirrhosis, it has been observed that only 17% of them followed through with their regular follow-up appointments, and a worrying 38% had an inconsistent attendance record (14). Another study demonstrated that just 20% of cases with HCC received consistent clinical follow-up (15). We thought that those who did not receive treatment in our study did not come up to follow-up after the diagnosis or refused treatment.

Alacacioglu et al. (16) reported that the median survival time of the HCC patients was 4 (1-50) months. In our study, the survival time was 11.9 months, 1-year survival was 32%, 3-year survival was 19%, and 5-year survival was 16%. It was reported that the overall survival time of 394 patients with HCC was 14.2 months in an 8-year follow-up period (17). Also, 5-year survival ranged from 23 to 44% in patients with hepatocellular carcinoma (18-20). In other studies, 5-year survival between 2002 and 2008 was reported as 15% in the United States and 12% in Europe between 2000 and 2007 (21). Our survival rates were lower because patients were diagnosed at a more advanced stage of BCLC.

## Conclusion

The management of HCC patients was performed according to more than just BCLC guidelines in our center. Even in out-of-extended criteria patients, liver transplantation was performed, and NCCN guidelines or literature knowledge were followed for HCC treatment. Non-sorafenib chemotherapy was administered because of the Social Security reimbursement protocol in our center. However, the high number of patients who did not receive treatment may indicate that we need to show sufficient clinical attention to Stage D patients.

## Conflict of interest statement

The authors have no conflict of interest to declare.

**Ethics Committee Approval:** Akdeniz University Faculty of Medicine Ethics Committee/decision date: 01.03.2017/decision number: 140).

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