

RESEARCH
ARTICLE

 **Serdar Aslan¹**
 **Serafettin Yazar¹**
 **Ahmet Kargi¹**
 **Eray Kurnaz²**
 **Dilek Sahin³**
 **Kemal Peker²**
 **Ibrahim Astarcioglu¹**
 **Kamil Yalcin Polat¹**

¹ Memorial Bahçelievler Hospital Transplantation Center, İstanbul, Türkiye

² Düzce University Faculty of Medicine, Department of General Surgery, Transplantation Center, Düzce, Türkiye

³ Düzce University Business Administration Faculty Health Management Department, Düzce, Türkiye

Corresponding Author:

Eray Kurnaz

mail: eraykurnaz52@hotmail.com

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konuralptipdergi@duzce.edu.tr

konuralptipdergisi@gmail.com

www.konuralptipdergi.duzce.edu.tr

The Results of Liver Transplantation Performed In a Single Center Due To Hepatocellular Carcinoma

ABSTRACT

Objective: Hepatocellular cancer (HCC) is the most common malignancy of the hepatobiliary system. There are significant differences in the global spread of HCC. It is the major cause of death in patients with cirrhosis. Its molecular pathogenesis is highly complex and heterogeneous. Major risk factors for the development of HCC are chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection and alcohol-related liver cirrhosis. Hepatocellular cancer is rarely seen in the first 4 decades of life, except in communities where HBV infection is hyperendemic.

Methods: The study was conducted by retrospectively scanning the files of 204 patients diagnosed with HCC who applied to Organ Transplantation Center between 21.09.2014 and 13.04.2019. Patients were transplanted liver by being classified according to Milan criteria, San Francisco [University of California San Francisco (UCSF)] criteria, and Barcelona Clinic Liver Cancer (BCLC) criteria.

Results: The median age of the patients was 58.03 (range 31 to 72). 170 of the patients were men and 34 of them were female. Liver transplantation (LT) was performed from cadaveric donors to 31 patients and from living donors to 173 patients. There is a significant relationship between the life span of the patients and their gender. Female patients have a longer life expectancy [t (202) = 2.963, p = 0.003]. A significant relationship was found between life expectancy and surgical classification [F (3) = 3.008, (p = 0.031)].

Conclusions: In patients diagnosed with HCC and undergoing LT; the gender being female and the classification method before transplantation affect life expectancy.

Keywords: Transplantation, Liver, Hepatocellular Carcinoma.

Hepatosellüler Kansere Nedeniyle Tek Merkezde Yapılan Karaciğer Nakli Sonuçları

ÖZET

Amaç: Hepatosellüler kanser (HSK), hepatobiliyer sistemin en sık görülen malignitesidir. HSK'nin küresel yayılımında önemli farklılıklar vardır. Sirozlu hastalarda en önemli ölüm nedenidir. Moleküler patogenezi oldukça karmaşık ve heterojendir. HSK gelişimi için başlıca risk faktörleri kronik hepatit B virüsü (HBV) enfeksiyonu, kronik hepatit C virüsü (HCV) enfeksiyonu ve alkole bağlı karaciğer sirozudur. HSK, HBV enfeksiyonunun hiperendemik olduğu bölgeler dışında, genellikle hayatın ilk dört dekadı içerisinde görülmez.

Gereç ve Yöntem: Çalışma, 21.09.2014-13.04.2019 tarihleri arasında organ nakli merkezine başvuran HSK tanılı 204 hastanın dosyaları geriye dönük olarak taranarak gerçekleştirildi. Hastalara Milan kriterlerine, San Francisco [University of California San Francisco (UCSF)] kriterlerine ve Barcelona Clinic Liver Cancer (BCLC) kriterlerine göre sınıflandırılarak karaciğer nakli yapıldı.

Bulgular: Hastaların medyan yaşı 58.03 (31-72 aralığında) idi. Hastaların 170'i erkek, 34'ü kadındı. Kadavra vericisinden 31 hastaya, canlı vericiden ise 173 hastaya karaciğer nakli yapıldı. Hastaların yaşam süreleri ile cinsiyetleri arasında anlamlı bir ilişki olduğu görüldü. Kadın hastaların yaşam beklentisi daha uzundur [t (202) = 2.963, p = 0.003]. Yaşam beklentisi ile cerrahi sınıflandırma arasında anlamlı bir ilişki bulundu [F (3) = 3.008, (p = 0.031)].

Sonuç: HSK tanılı olup karaciğer nakli yapılan hastalarda; cinsiyetin kadın olması ve nakil öncesi yapılan sınıflandırma yöntemi, yaşam beklentisini etkilemektedir.

Anahtar Kelimeler: Transplantasyon, Karaciğer, Hepatosellüler Karsinom.

INTRODUCTION

Hepatocellular cancer (HCC) is the primary tumor of the liver that can be seen frequently in chronic liver diseases that occur due to various etiological reasons, especially viral infections such as chronic hepatitis B or hepatitis C. Hepatocellular carcinoma (HCC) is originating from hepatocytes and it is the most common primary malignant tumor of the liver. 250 thousand to 1 million people died because of it annually worldwide (1-4). The biggest risk factor of the hepatocellular carcinoma is cirrhosis. In our country are viral hepatitis (HBV, HCV) and alcohol are the most common causes of cirrhosis. Other causes which increasing the risk of hepatoma are male gender, nonalcoholic fatty liver, diabetes mellitus, smoking, hemochromatosis, alpha-1-antitrypsin deficiency (5). According to new epidemiological data, the incidence of HCC is constantly increasing (1-3). Incidence of HCC is increasing in the Western population because of the high prevalence of HCV. This increase is related to frequency of HCV infection, the increased incidence of a migraine from HBV endemic countries, and the increase in the incidence of non-alcoholic fatty liver disease. HCC is rarely seen in the first four decades of life, except in communities where HBV infection is hyper endemic (3). The incidence of HCC is higher in men. The most valid reasons for this are high testosterone level, low estrogen level, and the fact that liver diseases are more common to men. The widespread use of HBV vaccination can reduce the HCC incidence in some regions.

Early diagnosis is very important for curative treatment approaches, and in developing countries, it is only possible with a good surveillance program (1). It is quite important to determine accurately whether the nodules detected in the liver are pre-neoplastic or early HCC. In the follow-up of dysplastic lesions with imaging methods, the malignant phenotype can be observed in approximately one-third of the lesions (2,3). Ideally, all treatment alternatives can be used if tumors are detected when they are 2 cm or less. However, one or more imaging methods are usually required to diagnose tumors in this size (4,5). Since small tumors do not have pathognomonic symptoms, the diagnosis is usually made in the more advanced stages of the disease and the patient loses the treatment options that can be curative (6). The median life span of patients diagnosed with HCC is approximately 6-20 months. Great tumor diameter, vascular invasion, poor functional status, lymph node, and/or distant metastasis are bad prognostic indicators (7-9).

MATERIAL AND METHODS

Our study was approved by Hospital Ethics Committee's decision dated 23.02.2021 and

numbered 7. The study was conducted by retrospectively analyzing the files of 204 patients diagnosed with HCC who applied to Organ Transplantation Center between 21.09.2014 and 13.04.2019. Patients which performed liver transplantation (LT) were classified according to Milan criteria, San Francisco [University of California San Francisco (UCSF)] criteria, and Barcelona Clinic Liver Cancer (BCLC) criteria. The information in the files and hospital resources were analyzed. The survival status of the patients was learned from the file information, from the automation system, and by accessing with phones when necessary. Overall survival was determined as the time elapsed from the time of diagnosis to death or to the last control date and it was calculated in months.

Statistical Analysis: Statistical Package for Social Sciences 23 (SPSS for Windows 23.0) was used for statistical processes. The life expectancy (Survey) was calculated based on the time between transport and death for dead patients, and the time between transport and analysis (15.12.2020) for patients who are still alive. Independent samples t-test or one-way ANOVA was used to determine the difference between groups for variables showing normal distribution characteristics. Since the variables AFP and Mass size did not show normal distribution, the correlations were performed by Spearman Correlation Analysis. A bivariate logistic regression analysis was performed to determine the size of the mass and the survival status of the patient. Two-sided p-values less than 0.05 were defined as statistically as significant.

RESULTS

The median age of the patients was 58.03 (range 31 to 72). 170 of the patients were men and 34 of them were female. LT was performed from cadaveric donors to 31 patients and from living donors to 173 patients. There is a significant relationship between the life span of the patients and their gender. Female patients have a longer life expectancy [$t(202) = 2.963, p = 0.003$]. A significant relationship was found between life expectancy and surgical classification [$F(3) = 3.008, (p = 0.031)$]. There is a difference between mixed and Milan, patients with Milan have a longer life expectancy than mixed category. There was not a significant relationship between the survey and the etiological cause [$F(3) = 2.214; p = 0.088$]. Also, there was not a significant relationship between tumor differentiation and survey [$F(2) = 2.185; p = 0.115$], between perinodal invasion and survey [$t(200) = 0.552, p = 0.581$] and between the number of tumor focus in liver and survey [$t(202) = 0.656, p = 0.513$] (Table 1).

Table 1. Difference analysis of variables

Variable		N	%	Mean	SD	CI	p
Sex	Female	34	16.7	1.83	7.175	1.78-1.88	0.003
	Male	170	83.3				
Surgical Classification	Milan	131	64.2	1.49	0.797	1.38-1.61	0.031
	Beyond	47	23.0				
	UCSF	16	7.8				
	Mixed	9	4.4				
Etiological Cause	Autoimmune HCC	10	4.9	2.915 7	0.75065	2.80-3.02	0.088
	Cryptogenic HCC	32	15.7				
	HBV+ HCC	120	58.8				
	HCV+ HCC	39	19.1				
Tumor differentiation	Good	58	28.4	1.80	0.623	1.71-1.89	0.115
	Medium	105	51.5				
	Bad	20	9.8				
Perinodal invasion	Perineural invasion is absent	192	94.1	0.04	0.195	0.01-0.07	0.581
	Perineural invasion is present	10	4.9				
Number of focus	1 focus	124	60.8	1.83	0.380	1.77-1.88	0.513
	Foci more than 2	80	39.2				

No significant relationship was found between the survey and AFP level and age (Table 2). Tumor size affects survival chances of the patients. The predictor variable explains 0.4% of

the variance. One-unit increase in size decreases the chance of survival by 0.81 (p = 0.01) (Table 3) (Table 4).

Table 2. Spearman correlation results

			Age	Life expectancy day	AFP	Size 1
Spearman's rho	Age	Correlation Coefficient	1,000			
		P	.			
		N	203			
	Life expectancy day	Correlation Coefficient	-0.024	1.000		
		P	0.735	.		
		N	203	204		
	AFP	Correlation Coefficient	-0.123	-0.089	1.000	
		P	0.109	0.247	.	
		N	172	172	172	
	Tumor size	Correlation Coefficient	0.004	-0.094	0.066	1.000
		P	0.953	0.188	0.398	.
		N	198	199	167	199
Mean			58.03	1379.43	297.224	1.9284
Std. Deviation			7.175	894.525	2048.0211	1.9284

N: number; SD: standard deviation; CI: confidence interval; AFP: alpha fetoprotein

Table 3. Statistics and accuracies of logistic regression models

	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square	Hosmer and Lemeshow test		
LR	237.386 ^a	.031	.044	χ^2	df	p
				2.415	7	0.933

Table 4. Summary of multiple binary logistic regression analysis

Variable	B	Wald	Standard Error	p	Odds Ratio	95% CI	
						Lower	Upper
Tumor Size	-0.199	5.718	1	0.017	0.819	0.696	0.965
Constant	1.491	21.926	1	0.000	4.444		

DISCUSSION

The curative treatment options accepted for HCC are resection and LT (10). Advances in imaging methods and follow-up programs give a chance to patients with cirrhosis to surgical resection (7,8). Despite all these innovations, only a small group of patient with HCC can undergo hepatic resection (9,11).

Early detected or small HCC, are defined as lesions smaller than 2 cm or lesions smaller than 4 cm, and even HCCs that are within the Milan criteria (12,13). In recent years, the postoperative risks have decreased, postoperative mortality rate has decreased to 0.7%, and postoperative major complication rate has decreased to 7.3% as a result of improvement of patient selection criteria, advances in surgical technique and technology, and improvement of postoperative care (12,14,15). Dependent to these developments, 5-year disease-free survival rates after resections have also increased up to 70% (11). The chance of success of hepatic resection is high in small HCCs (≤ 5 cm) (16,17). Although some authors emphasize that the results of hepatic resection are similar to small masses in terms of disease-free survival, especially in HCCs above 5 cm developing on a non-cirrhotic background, the 5-year disease-free survival rate after resection of masses above 5 cm ranges between 20% and 30% (6,7). In univariate analysis, the factors determining disease-free survival rates after resection were determined as tumor size, high MELD score, vascular invasion and high tumor grade (6). Risk of the recurrence after hepatic resection was depended on the size and degree of differentiation of the primary tumor, and it was concluded that portal vein invasion in the resected liver was the biggest risk factor for recurrence (18). In some studies, high telomerase activity of the tumor is also emphasized as an independent recurrence factor (19).

Recurrence generally occurs in postoperative 3 years, and unfortunately, there is not an effective neo-adjuvant or adjuvant treatment to reduce the recurrence (20,21). The most important factor that increases postoperative mortality and morbidity after hepatic resections is a possible decompensated liver failure. Considering the size and cell reserve, this risk is higher in right lobe resections than in left lobe resections (22,23).

The Child-Pugh staging system, does not completely show the liver reserve in HCC patients developing on the basis of cirrhosis. It has been concluded that normal serum bilirubin level and portal vein pressure below 10 mmHg is the most

important parameters for post-operative liver failure risk estimation regardless of Child-Pugh stages (23).

The factors determining the limits of hepatic resection are the degree of the underlying cirrhosis and size, location and the number of tumor respectively. While major resections (lobectomies) are at the forefront in masses larger than 5 cm, minor and non-anatomic resections gain significance in masses less than 5 cm (24). Major resections provide advantages such as complete oncological removal, removal of the portal vein branches together with the mass, and low recurrence rates, while minor resections offer advantages such as preserving liver reserve and low risk of hepatic failure that may develop after surgery (25).

LT became accepted worldwide as the definitive treatment of liver failure in the mid-1980s. With the effective use of immunosuppressive treatments, its success has gradually increased and nowadays 5-year survival rates have increased up to 85% (26). In patients with HCC, due to the advanced underlying liver failure and the inability to perform resection, LT is a good option.

CONCLUSION

In the first years, the debate on which patient should be transplanted was focused on the criteria known as Milan criteria (single nodule smaller than 5 cm or 3 nodules smaller than 3 cm) were put forward. These criteria were followed for many years and consequently, disease-free survival rates of LT are high. In the studies conducted, 5-year survival rates were found to be 70% and recurrence rates below 10%. As a result of increasing the experience and success in LT over the years, Milan criteria and expanded San Francisco criteria with successful results has also begun in patients have a single nodule smaller than 6 cm, or 3 or fewer nodules with the largest size smaller than 4.5 cm, and the total nodule sizes smaller than 8.5 cm and they are all limited in the liver (6,26-29).

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