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Hepatocellular Cancer and Liver Transplantation; Is There Any Novelty in Prognostic Factors for Survival and Recurrence?

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Abstract

Objectives: Hepatocellular cancer constitutes 75-85% of liver cancers, and its treatment requires a multidisciplinary approach. Milan criteria are golden standart candidate selection criteria that ensure excellent posttransplant survival and follow up with low recurrence rate. However, other classifications include histopathological features or biological behaviors may vary survival and recurrence. We examined the parameters that may have prognostic value in our study.

Material and Methods: 217 patients for recurrence, 226 patients for overall survival, 48 patients for disease free survival, whose explant pathology is hepatocellular carcinoma and data information can be obtained were evaluated. Recurrence and overall survival and disease free survival were statistically analyzed in terms of age, gender, living and cadaveric transplanted patient groups, blood group, BMİ, MELD and Child scores, Milan criteria and pathological parameters. All survival rates were evaluated in terms of recurrent organ location, number of organ recurrence, and survival rates.

Results: There were less recurrence rates in patients, with 0 blood group, inside milan criteria, with less total and maximum tumor diameter. It was also observed that the maximum tumor size affected the overall survival multivariately It was observed that survival was worse in early recurrence and recurrence in the first 24 months.

Conclusion: İt is observed that being inside the milan and tumor diameter affect the recurrence and survival, surgery to be performed in localized recurrences and additional systemic treatment will affect survival positively.

Keywords: Hepatocellular Carcinoma, Survi, Liver, Transplantation

Özet

Amaç: Hepatoselüler kanser, karaciğer kanserlerinin %75-85'ini oluşturur ve tedavisi multidisipliner bir yaklaşım gerektirir. Milan kriterleri, mükemmel posttransplant sağkalımı ve düşük nüks oranı sağlayan altın standart hasta seçim kriterleridir. Ayrıca, histopatolojik özellikleri ve biyolojik davranışları da içeren diğer sınıflamalar da hayatta kalma süresi ve nüksü değiştirebilir. Çalışmamızda prognostik değeri olabilecek parametreleri inceledik.

Araç ve yöntem: Eksplant patolojisi hepatosellüler karsinom olan ve veri bilgisi alınabilen 217 hasta nüks, 226 hasta genel sağkalım, 48 hastalıksız sağkalım için değerlendirildi. Yaş, cinsiyet, canlı ve kadavra nakli yapılan hasta grupları, kan grubu, BMİ, MELD ve Child skorları, milan kriterleri ve patolojik parametreler açısından nüks ve genel sağkalım ve hastalıksız sağkalım istatistiksel olarak analiz edildi. Tüm sağkalım oranları, tekrarlayan organ yerleşimi, organ nüksü sayısı ve hayatta kalma oranları açısından değerlendirildi.

Bulgular: 0 kan grubu, milan kriterleri içinde, total ve maksimum tümör çapı daha az olan hastalarda daha az nüks oranları vardı. Ayrıca maksimum tümör boyutunun genel sağkalımı çok değişkenli etkilediği gözlendi. İlk 24 ayda erken nüks ve nükste sağkalımın daha kötü olduğu gözlendi.

Sonuç: Milan kriterleri içi olmanın ve tümör çapının nüks ve sağkalımı etkilediği, lokalize nükslerde yapılacak cerrahi ve ek sistemik tedavinin sağkalımı olumlu etkileyeceği gözlenmiştir.

Anahtar Kelimeler: Hepatosellüler, Kanser, Sağkalım, Karaciğer, Nakil

Introduction

Hepatocellular cancer (HCC) constitutes 75-85% of liver cancers (1), and its treatment requires a multidisciplinary approach (2). Transplantation is the most curative treatment option because it provides both oncological resection and eliminate the diseased tissue that prepares the ground for the development of new tumors (2-4). It is known that, the Milan criteria are golden standart candidate selection criteria that ensure excellent posttransplant survival for patients with HCC, although growing experience of liver transplantation for HCC raised concerns about the Milan criteria as being too restrictive and far from satisfying the increasing candidate list. The other expanded classifications include histopathological features such as tumor differentiation / grade, tumor size and number, presence of vascular invasion or tumor markers. Therefore, survival times and the presence of recurrence may vary depending these classifications (2-6). We aimed to present our experience regarding predictive and prognostic factors for recurrence and survival rates after liver transplantation (LT) in HC.

The study was designed as a single center experience. 270 patients underwent liver transplantation due to HCC totally. 217 patients for recurrence, 226 patients for overall survival (OS), 48 patients for disease free survival (DFS), whose explant pathology is HCC and data information can be obtained were evaluated. Median range follow up was between 1-180 months. Patients with combined hepatocellular-cholangiocarcinoma or cholangiocarcinoma as a result of pathology of the surgical specimen or preoperative biopsy were not included in the study.

Preoperative Evaluation

Detailed biochemistry tests were routinely performed on the patients who applied to our clinic. AFP and other tumor markers were examined. Thorax and portal phase abdominal computer tomography (CT) and Abdomen magnetic resonans imaging (MRI) were performed to all patients for preoperative evaluation. HCC was diagnosed in patients with radiologically typical enhancement patterns (early arterial enhancement and late venous wash out). 18F-FDG-PET/CT was performed to evaluate biological behavior and extrahepatic involvement in patients diagnosed with HCC radiologically. Biopsy was performed for lesions with atypical radiological enhancement patterns or suspicious cholangiocarcinoma. TARE was applied to eligible patients with non-milan or high FDG uptake on PET-CT or with AFP >400 supporting poor biological behavior. Liver transplantation was performed in patients who were re-evaluated after 2 months and were thought to be inside milan radiologically and AFP <200. Also, patients who were evaluated as in milan radiologically after TARE but found to be outside milan in the explant pathology were evaluated in terms of recurrence in the study. Transplantation was performed to the patients whose all test results were evaluated in the liver transplantation council and deemed appropriate.

Postoperative Recipient Follow Up

AFP and thorax and abdomen CT and/or abdomen MRI were performed every 3 months in the first year after liver transplantation and then every 6 months. When recurrence was detected in routine follow-ups, options such as chemotherapy, surgery, locoregional therapy or radiotherapy were prefered and used according to location and tumor extent. Control 18 F-FDG-PET-CT was applied to assess treatment response. The treatment strategy was decided according to the result.

Investigated Parameters

Demographic data, age and gender, living and cadaveric transplanted patient groups, blood group, Child and MELD scores, etiology were stated in the study as a ratio (%). Hepatocellular cancer recurrence and overall survival and disease free survival were statistically analyzed in terms of age, gender, living and cadaveric transplanted patient groups, blood group, BMİ, MELD and Child scores, milan criteria, tumor number, maximum tumor diameter, total tumor diameter, microinvasion, macroinvasion/ invasion, multicentricity, grade, etiology. The average recurrence time was specified in months. Those with early recurrence in the first 6 months or recurrence within 2 years and those with recurrence 6 months or 2 years later were analyzed statistically in terms of survival time, separatelly. Primary recurrence locations were examined according to the number of patients and their rates were specified. Survival rates were evaluated in terms of recurrence organ location statistically. Besides, the numbers of all treatment methods related to recurrence were indicated and recurrent organ location evaluated in month and statistically. Also, single and multiple organ recurrence counts were included in the study and were studied in month and statistically. Patients with single or multiorgan recurrence were also statistically analyzed for survival. One, 3 and 5-year DFS and OS durations and rates were examined. DFS rates of patients in and out of Milan were analyzed separately. The patients were informed about the study and their consent forms were obtained. All procedures were conducted in accordance with the ethical standards of the respective committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This study was approved by the Human Experiments Ethics Committee with the ethics committee decision number 2020-242.

73% of within Milan had 1-year, 58% had 3-year and 47% had 5-year DFS. On the other hand, 68% of beyond

Statistical Methods

Nominal and ordinal parameters were described with frequency analysis, whereas scale parameters were described with means and standard deviations. Chi-Square Test and Chi-Square Likelihood tests were used for differences between categorical parameters. Kolmogorov Smirnov test was used for normality of scale parameters. Mann Whitney U test was used for difference analysis, since distributions were non-normal. Spearman's rho correlation and Cox Regression tests were used for relational analysis. SPSS 17.0 for windows was used at 95% Confidence Interval.

Results

The average age was 57. 87% of the patients were male and 13% were female. BMI mean was 27.5. Living donor liver transplantion (LDLT) was performed in 83%, and decaesed donor liver transplantation (DDLT) in 17% of the patients. Blood groups were; 39% A group, 16% B group, 37% 0 group, 8% AB group. Child A ratio was 43%, Child B ratio was 23%, Child C ratio was 8%. The mean MELD score was 11.5. In etiology, 45% HBV, 1% HCV, 10% HBV + HDV, 8% NASH, 8% ethanol, 8% cryptogenic, 20% others (autoimmune hepatitis, Budd Chiari, PSC) were observed. Blood group difference between recurrence groups were significantly different ($p<0.05$), and O group was more common in non-recurrence group. Age, gender, transplant donor, etiology, CHILD and meld scores of recurrence group differences were insignificant (table 1), ($p>0.05$). Cox regression analysis for effects of etiology on recurrence with DFS and OS were insignificant ($p>0.05$). In addition, binary logistic regression analysis (with time independent) showed also insignificant results for effects of etiology on recurrence (table 2), ($p>0.05$).

TABLE 1: Demographic Variables, Child And MELD Scores and Spearman's rho correlation analysis results for factors effecting recurrence

	Recurrence	Non-recurrence	P
Age, mean ± SD	56.70±9.63	57.15±10.93	0.387[a]
Gender (n, %) Male Female	 142 (83.5) 28 (16.5)	 44 (91.7) 4 (8.3)	0.159[b]
Transplant donor (n/%) Cadaveric Living	 29 (17.1) 141 (82.9)	 141 (77.1) 42 (22.9)	0.644[b]
Blood Group (n/%) O A B AB	 54 (33.3) 70 (43.2) 27 (16.7) 11 (6.8)	 21 (46.7) 10 (22.2) 7 (15.6) 7 (15.6)	0.031[c]
Child Score (n/%) None A B C	 41 (24.1) 64 (37.6) 48 (28.2) 17 (10.0)	 14 (28.6) 23 (46.9) 9 (18.4) 3 (6.1)	0.346[c]
Etiology(n/%) HBV HCV HBV+HDV Ethanol Cyrptogenic NASH Other	 78 (47.3) 3 (1.8) 12 (7.3) 7 (4.2) 16 (9.7) 15 (9.1) 34 (20.6)	 21 (42.9) - 6 (12.2) 6 (12.2) 3 (6.1) 3 (6.1) 10 (20.4)	0.308[c]
MELD Score	11.91±4.22	11.39±4.92	0.253[a]

a. Mann Whitney-U Test, **b.** Chi-Square Test, **c.** Likelihood Ratio,
SD: Standard Deviation. **HCC:** Hepatocellular carcinoma;

	Recurrence	p	R
	Age	**0.059**	**0.388**
Gender		-0.095	0.161
Blood Group		-0.027	0.699
BMI		-0.129	0.139
MELD		-0.089	0.254
Milan Criteria		0.159	0.026
Tumor Number		0.139	0.056
Max Tumor Diameter		0.148	0.039
Total Tumor Diameter		0.189	0.008
Multicentric		0.084	0.248
Vascular Invasion		0.044	0.555
Microvascular Invasion		0.014	0.850
Macrovascular Invasion		0.085	0.254
Grade		0.172	0.056

TABLE 2: Etiology effects on recurrence by DFS, OS and multinomial variance analysis

	DFS Multivariate analysis			OS Multivariate analysis			Recurrence Multivariate analysis		
	HR	95,0% CI	p	HR	95,0% CI	p	HR	95,0% CI	p
HBV	Referent			Referent		0.415			0.455
HCV				0.729	.342-1.554	0.413	**0.915**	0.390-2.150	0.839
HBV+HDV	0.652	0.301-1.413	0.279			0.980			0.999
Etanol	0.367	0.121-1.116	0.077	1.154	.406-3.279	0.788	1.700	0.508-5.685	0.389
Cyriptogenic	0.464	0.151-1.425	0.180	1.728	.620-4.818	0.296	2.914	0.795-10.678	0.106
NASH	0.811	0.221-2.971	0.752	0.484	.133-1.762	0.271	0.638	0.154-2.639	0.534
Other	0.670	0.182-2.474	0.548	1.668	.455-6.112	0.440	0.680	0.163-2.830	0.596

Spearman's rho correlation analysis results showed that Milan criteria, max tumor diameter and total tumor diameter parameters were positively correlated with recurrence ($p<0.05$). Max tumor diameter had positive or increasing effect on recurrence for DFS univariate analysis ($p<0.05$). However, its effect on recurrence at multivariate level was insignificant for DFS multivariate ($p>0.05$). Both max tumor diameter and total tumor diameter parameters had significant effect on recurrence for OS univariate analysis ($p<0.05$). However, only effect of max tumor diameter had significant on OS multivariate analysis (table 3), ($p<0.05$). Tumor number, multicentricity, microvascular and macro/vascular invasion, grade had no significant effect on recurrence or OS/DFS univariate and multivariate analysis ($p>0.05$).

TABLE 3: Cox regression analysis results for recurrence at DFS and OS with significant cofounders

	DFS Univariate			DFS Multivariate		
	HR	95,0% HR	p	HR	95,0% HR	p
Milan criteria	0.694	0.376-1.284	0.245	1.156	0.473-2.826	0.751
Max Tumor diameter	1.216	1.027-1.441	0.024	1.212	0.983-1.494	0.072
Total Tumor diameter	1.038	0.988-1.090	0.137	1.017	0.942-1.098	0.673
	OS Univariate			**OS Multivariate**		
	HR	95,0% HR	p	HR	95,0% HR	p
Milan criteria	0.560	0.309-1.015	0.056	1.469	0.567-3.805	0.429
Max Tumor diameter	1.288	1.105-1.501	0.001	1.246	1.016-1.529	0.035
Total Tumor diameter	1.081	1.027-1.138	0.003	1.069	0.896-1.158	0.105

Estimated Overall Survival time for inside Milan and for beyond Milan Criteria group was insignificant, statisticaly (respectively, median 31 and 15 months, p>0.05). Estimated DFS for Milan within the group was for Milan beyond group with a statistically insignificant difference (median months: not reached, p>0.05

Survival rates for different recurrent organ were, 36 months for liver (n: 2-71), 62 months for lung (n: 20-159), 66 months for bone (n: 21-177), 43 months for intraabdominal extrahepatic locations (n: 11-79), 89 months for other locations (n: 30-148), 34 months for multiorgan (n: 4-90). Among the patients treated for single organ recurrence, the average survival of those who underwent only surgery was 56 months, received surgery and chemotherapy 78 months, received only chemotherapy, 87 months received chemotherapy and radiotherapy, and 60 months for those who received TARE. Also, among the patients treated for multi organ recurrence, the average survival of those who underwent only surgery was 13 months, received surgery and chemotherapy 34 months, received only chemotherapy, 27 months, and 36 months for those who received TARE.

Survival average differences between 24 month and 6 month cut off groups were statistically significant, as expected (p<0.05). Patients with single organ recurrence had a higher mean OS with a median survival of 58 months, than patients with multiple organ recurrence with a median survival of 34 months, but the difference was statistically insignificant (p>0.05). OS average differences between different recurrent organs and recurrence treatment regime with single-multiple organ were statistically insignificant (table 4), (p>0.05).

TABLE 4: Evaluation of OS and recurrent patients for 24 and 6 months cut-off value

< 24 months (n: 91)	>24 months (n=136)		p value
11.38±7.06	66.88±36.55	**OS Average, months, mean ± SD**	0.000*
Single organ recurrence	**>1 organ recurrence**		
53.11±40.51	34.07±27.60	**OS Average, months, mean ± SD**	0.075*
< 6months (n: 28)	**>6 months (n: 199)**		
3.02±1.77	**50.49±38.76**	**OS Average, months, mean ± SD**	0.000*

*Mann Whitney U Test, SD: Standard Deviation.

Milan had 1-year, 52% had 3-year and 41% had 5-year DFS. Differences of DFS distributions based on Milan groups were insignificant (p=0.201). 91% of within Milan had 1-year, 84% had 3-year and 77% had 5-year OS. On the other hand, 89% of beyond Milan had 1-year, 75% had 3-year and 66% had 5-year OS. Differences of OS distributions based on Milan groups were insignificant (p=0.214).

Discussion

Although Milan criteria provide low recurrence rate and high survival times; In order to increase the number of patients need to benefit from transplantation, different patient selection criteria have been established. İnspite of heterogen results, when those beyond Milan were compared with Milan Criteria, it was seen that OS and DFS results were better in patients within Milan often (3,7-9). İt is more frequently determined that the increase in maximum and total tumor diameter, multicentricity and tumor number reduce the disease-free and overall survival and rise recurrence (7,10-20). At the same time, patients with microvascular invasion have significantly poorer survival outcomes. These analysis show that microvascular or macrovascular invasion may be independent predictor of survival and recurrence (7,9,12,16,21-25). However, the results showing that macrovascular invasion is not predictive of survival and recurrence should not be ignored (26,27).

Therewithal, tumor grade may be a significant risk factor for both survival and recurrence. Patients with well-differentiated tumors had better OS and DFS rates compared to patients with moderate/poor-differentiated tumors. (3,22,23,25-29). However, there might be underlying several tumor features that lead to better survival outcomes after liver transplant even among poorly differentiated tumors (8,24,25,27-32).

For all that there are not many studies showing the predictive value of age, gender, and etiology, on survival and recurrence, several results that being over 60 years old, male gender, and HCV etiology might be remarkable to be poor prognostic factors for survival and recurrence (3,21,29,29-31,33,34).

In our study, it was observed that the differences among age, gender, MELD, Child scores, BMI and etiological factors did not affect recurrence. Also, tumor number, multicentricity, micro and macro vascular invasion, and increasing tumor grade did not make any difference in terms of recurrence. However, there were less recurrence rates in patients, with 0 blood group, inside milan, with less total and maximum tumor diameter. It was also observed

that the maximum tumor size affected the overall survival multivariately.

Most cases of recurrent HCC after LT have been reported to occur at extrahepatic (38.5 to 53%) or both extrahepatic and intrahepatic sites (31 to 38.5%). Also, tumour recurrence is frequently extrahepatic, particularly in the lungs and bones. Although lung recurrence is more common, it has been observed that the survival rates after bone recurrence is shorter, and longer survival in intrahepatic recurrence and other single organ recurrence (5,9,24). Therewithal, the timing of recurrence is important for survival. Many studies have observed longer survival in recurrence after 2 years. In addition, survival in the first 6 months of recurrence appears to be worse, which can be called early recurrence (1,9,23). İn our study, there was no statistical difference between the post-recurrence survival rates of different organs. İt was also observed that multiorgan recurrence did not differ significantly compared to single organ recurrence. However, it was observed that survival was worse in early recurrence and recurrence in the first 24 months compared to the other groups.

İn patients who underwent surgery and systemic treatment for recurrence, surgical treatment has longer survival times than other treatments with a median survival of 28-65 months. It can also be said that this is due to localized disease or good tumor biology. Methods such as TARE, TACE and RFA, radiotherapy and systemic chemotherapy treatments will also contribute somewhat to survival (35). In our study, while the mean survival after surgery for single organ recurrence was 55 months, it was seen that survival time was 78 months after the addition of chemotherapy. However, there was no significant difference in survival among patients who underwent surgery for recurrence treatment, received systemic therapy, and other local ablative treatment methods.

Conclusion

Although liver transplantation is the best treatment option for selected HCC patients, it is important to examine tumor-related factors that may affect recurrence and survival. Morphology or biological behavior of the tumor may also be important determinants of survival after LT. Being inside the milan and tumor diameter affect the recurrence and survival, surgery to be performed in localized recurrences and additional systemic treatment may affect survival positively.

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