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Post-liver transplant HCC recurrence: patterns, treatment, and outcome

Mohamed Rabei Abdelfattah [1], Hussein Elsiesy [2]

[1] Department of Surgery, Faculty of Medicine, University of Alexandria, Egypt
[2] Organ Transplant Center, King Faisal Specialist Hospital and Research Center, Riyadh, Kingdom Saudi Arabia

Prof. Dr. Mohamed Rabei Abdelfattah. MD, Department of Surgery, Faculty of Medicine, University of Alexandria, AL Khartoum Square, Azzaritta, Alexandria, Egypt, PO BOX 21131

Phone: 0020102 306 1111 (mob.)
Em-ail: Mohamad.rabie@gmail.com

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Summary

The risk for recurrent hepatocellular carcinoma is still significant, and its overall prognosis is dismal. This study aims at reporting incidence of recurrent hepatocellular carcinoma (rHCC) cases following liver transplantation (LT), describing their clinical patterns, and current therapeutic modalities at our center. It also concerns potential risk factors related to HCC recurrence.

Materials and methods

A total of 148 patients underwent LT between August 2006 and December 2020 at our Center. Cases with rHCC were identified, and their clinical data were comprehensively collected.

Results

The mean post-transplant follow-up for the studied patients was 53±34.8 months. A total of 16 patients had HCC recurrence (8.9%). Majority of rHCC (68.8%) were observed within the first two years from LT. Vascular lymphatic invasion, poor tumor differentiation and RETREAT score were significantly related to HCC recurrence.

Conclusions

Early detection is an imperative for the use of more curative rHCC-managing options. The tumor volume-based criteria are insufficient to predict high risk patients for HCC recurrence. Risk stratification models for HCC recurrence should be employed to identify high-risk patients for HCC recurrence. Screening protocols should be tailored to the risk of HCC recurrence.

Keywords

Hepatocellular carcinoma, liver transplant, tumor recurrence.

Introduction

Since introduction of Milan criteria, an excellent outcomes of liver transplantation (LT) for hepatocellular carcinoma (HCC) were validated [1-3]. Unfortunately, this favorable outcome is not always achievable. The risk for recurrent HCC (rHCC) is still reported in approximately one-fifth of patients transplanted for presence of HCC. The occurrence of rHCC is a significant setback in the clinical course of affected patients with dismal prognosis reported in most instances [4-9].

Furthermore, the incidence of rHCC poses significant ethical concerns about current allocation system which favors transplantation of more HCC patients. The number of transplanted HCC patients has been reported to be steadily increasing over last two decades. The transplantation activity causes increased burden of already limited deceased donor pool, or provokes a debate over the living donation outcomes [10, 11].

It is therefore crucial to report the cases of rHCC following liver transplantation, to identify their clinical patterns, and to promote development of screening protocols for their early detection and treatment. Moreover, a comprehensive analysis should be made for identifying the risk factors associated with HCC recurrence.

This study aims primarily at reporting of the incidence of recurrent HCC following liver transplantation, to describe their clinical patterns, current therapeutic modalities at our center. It also addresses potential risk factors of HCC recurrence, by comparing them to the data reported elsewhere.

Materials and methods

A total of 178 patients diagnosed for having HCC approved the research consent and were subsequently included in the study. The clinical charts for those patients considered for liver transplant at our center were retrospectively reviewed. HCC at our center is diagnosed by contrast-enhanced computed tomography (CT) and/or abdominal magnetic resonance imaging (MRI). Staging was based on chest CT, cranial CT, and technetium-99m bone scintigraphy, to exclude extra-hepatic disease.

Current study was approved by our institutional Research Ethical Committee under the 8/11/09/02/2020 code. The ethical approval was obtained before conduction of this study. Patients were consented to use medical charts to obtain pertinent medical information for research purposes only. Extensive efforts to protect patients' identity were also ensured. In accordance with Declaration of Helsinki, all the patients were consented about their clinical management and were also informed that their decision to approve or disapprove the research consent will not influence their clinical management.

Our center currently adopts Milan Criteria (MC) as the standard criteria for LT for HCC. Any patient who is beyond MC is usually considered for a downstaging protocol using one or more locoregional therapies to downstage the tumor to within MC. LT for the down-staged patients is considered after further confirmation of the absence of extrahepatic disease. Pretransplant locoregional therapies included radiofrequency ablation (RFA), trans-arterial chemotherapy (TACE) and/or trans-arterial radiotherapy (TARE). Cases which were found unfit for liver transplantation were excluded from the study.

LT was performed using either deceased donor liver transplants (DDLT), or liver transplantation from a living donor (LDLT). The LDLT donors were first- and second-degree relatives of respective patients. Cases of pediatric LT or liver re-transplantation were excluded from this study.

The liver explants were studied for presence of HCC lesions. Size, number, tumor grade, and lymph vascular invasion were reported by an experienced liver transplant pathologist. Triple immunosuppression protocol was utilized for LT recipients including calcineurin inhibitors (CNI) corticosteroids and mycophenolate mofetil.

İn addition to routine liver transplant follow-up protocol, the patients transplanted for HCC were followed up by liver ultrasound, α-fetoprotein (AFP), and liver function tests at six-month intervals for the rest of their lives. The cases with new focal liver lesion were further diagnosed by contrast-enhanced dynamic study to characterize this lesions, and liver biopsy was also taken to diagnose uncertain cases. The recurrent HCC (rHCC) cases were identified, and their clinical data were comprehensively collected.

Demographic data, pretransplant variables, transplant-related variables as well as characteristics of malignancies (number of lesions, tumor size and grade, lymph vascular invasion) were retrieved from the patient charts. Additionally, risk estimation of tumor recurrence after transplant (RETREAT score) was calculated [12], and these data were correlated with HCC recurrence. The data were analyzed by means of t-test and chi-square test. P-value of <0.05 was considered statistically significant. Kaplan-Meier curves were used to express survival outcomes and its significance was determined by log-rank test.

Results

A total of 178 patients presenting with HCC agreed to participate in the study. Fig. 1 shows their distribution as regards liver transplant, downstaging locoregional therapy (LRT) and incidence of recurrent HCC.

148 adult patients underwent LT due to presence of HCC at our institution between August 2006 and December 2020. They included 93 males (62.8%) and 55 females (37.2%), ninety-six of them were within Milan criteria. The mean post-transplant follow-up for the studied patients was 53±34.8 months, range from 24.3 to 160.1 months. The overall 5-year survival of patients, grafts, and tumor-free survival were 72.7%, 90.8% and 87.7%, respectively (Fig. 2).

A total of 16 patients had HCC recurrence during the follow-up period (8.9% of transplanted HCC patients). Of them, eleven rHCC cases were registered in males. Nevertheless, gender factor did not differ significantly between patients with HCC recurrence compared to those with no rHCC (P=0.6). The mean age at HCC recurrence was 60.8±4.1 years. The current study demonstrated that most HCC recurrencies (68.8%) were observed within two years from liver transplant. Moreover, elevated AFP and distant metastases (mainly, lung lesions) dominated in clinical pattern in 87.5% and 56.3% of rHCC patients, respectively (Table 1).

Table 1. Clinical, and laboratory characteristics for cases of rHCC

Clinical and laboratory profile		Number (%)
Time to HCC recurrence	≤ 2 years	11
	>2-5years	5
	>5 years	0
Location of HCC recurrence	Liver only	6
	Distant	9
	combined	1
AFP at HCC Recurrence	≤10 ng/dL	2
	>10-200	4
	>200-≤1000	5
	>1000	5

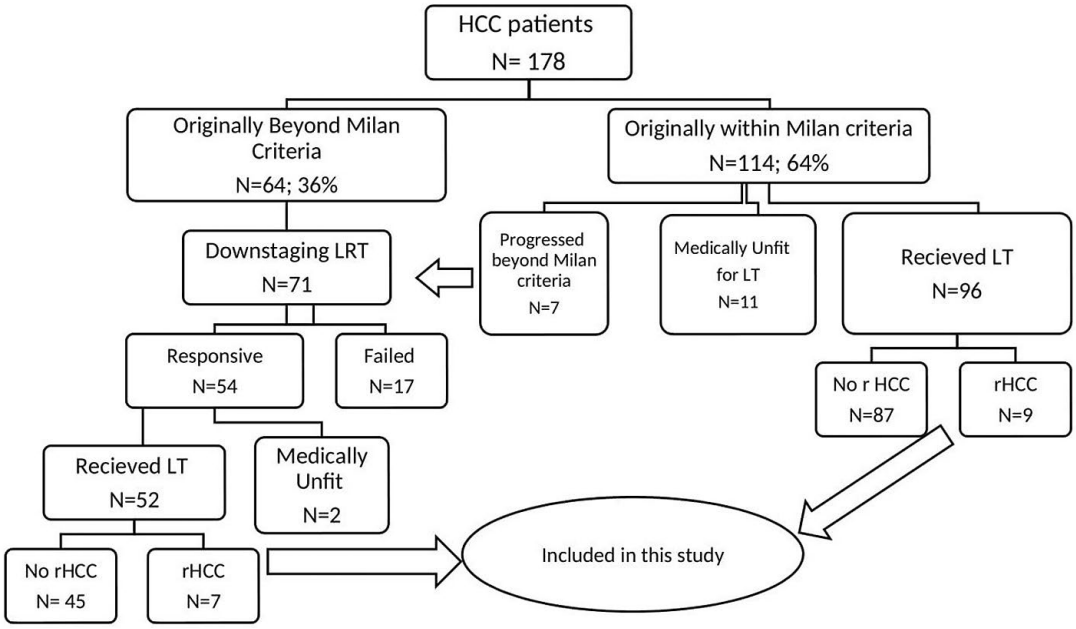

Figure 1. Distribution of HCC patients according to LT, LRT, and incidence of rHCC

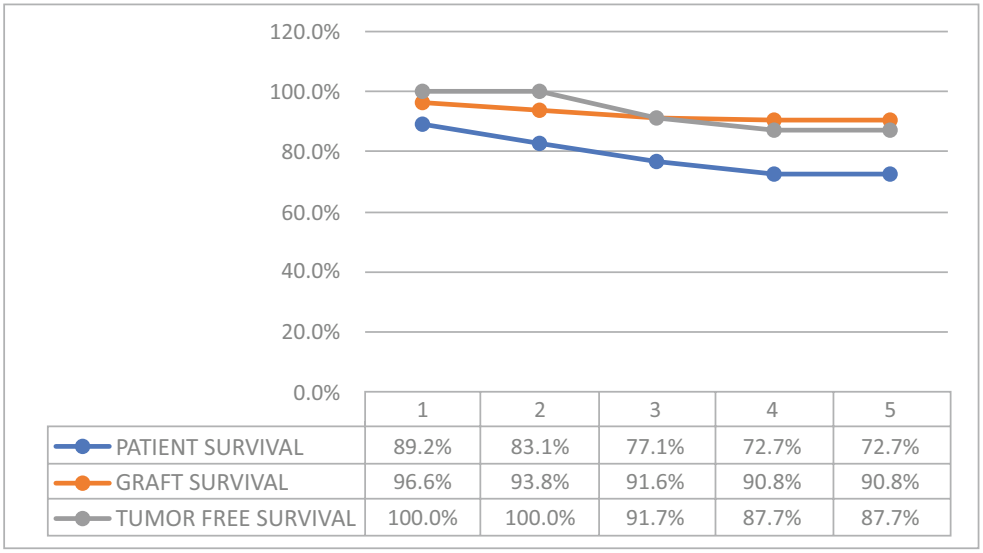

Figure 2. Overall patient, graft and tumor-free survival following LT for HCC patients

Vascular invasion, poor tumor differentiation and RETREAT score differed significantly between the patients with rHCC and patients with no HCC recurrence. On the other hand, transplant criteria, type of transplant and total tumor volume (TTV)>115 cm^3 showed no significant difference (Table 2). Correlation between RETREAT score, transplant criteria, and HCC recurrence is shown in Table 3.

Unfortunately, all rHCC cases in the current study were beyond surgical or locoregional therapy. Sorafenib was administered to these patients as a supportive measure. None of these patients were alive at the time of current report, their median survival following rHCC diagnosis was 135±11.5 days.

Discussion

The results of current study compare well with medical literature as regards the overall excellent outcome for transplanted HCC patients and the overall rate of rHCC [2, 3]. Filgueira et al., reported rHCC in 15-20% of transplanted HCC patients within a median of 12-16 months form liver transplant with around 75% occurring in the first two years. Timing of HCC recurrence in the current study was within two years following liver transplant in 68.8% of patients.

Filgueira et al. reported a poor prognosis for rHCC patients with median survival of 7-16 months from diagnosis of recurrence. They also claimed that HCC recurrence should be considered a systemic disease as only 30% of patients show isolated hepatic recurrence [4]. Chagas et al., reported 8% HCC recurrence rate and isolated hepatic recurrence in more than one-quarter of patients. Post-recurrence survival rates were 34% at 1 year compared to 0% in the current study [5].

Filgueira et al., reported that curative therapeutic modalities including reaction and ablative techniques are of value

Table 2. Transplant and tumor-related variables for rHCC following liver transplantation

Variables			Patients with no rHCC	Patients with rHCC	P value
Tumor characteristics	Transplant criteria	Within MC	87	9	0.45
		Beyond MC	45	7	
	Vascular Invasion N=10		4	6	0.00001
	Poor differentation N=8		3	5	0.00001
	TTV>115 cm^3 N=48		40	8	0.11
	RETREAT Score	<2 points	109	0	0.000
		3-5points	19	10	
		>5points	4	6	
Type of transplant	LDLT		80	11	0.53
	DDLT		52	5	

Table 3. Correlation between RETREAT score, transplant criteria and HCC recurrence

RETREAT Score Points	Patients with no rHCC		Patients with rHCC		Total
	HCC within MC	HCC beyond MC	HCC within MC	HCC beyond MC	
0	25	9	0	0	34
1-2	49	26	0	0	75
3-5	12	8	3	6	29
>5	1	2	3	4	10
Total	87	45	6	10	148
P value	0.45		1		–

specially in cases where a smaller number and size of lesions is detected provided the disease is strictly confined to the liver. They quoted significantly longer median survival (22 months compared to 9 months in those with palliative treatment only) [5].

In the current study, it was noted that rHCC presentation is of the very late pattern, where there are limited options for therapeutic options and only palliation is possible. This might indicate vulnerability in screening protocol for rHCC and immunosuppression in the current study. It calls for more tailored approach for patients with high risk for HCC recurrence.

The use of rapamycin in patient transplanted for HCC was suggested and practiced in many transplant center [13-15]. It was hypothesized that rapamycin will improve recurrence free survival in these vulnerable patients. Nevertheless; (SiLVER trial) failed to show such effect [16].

Risk factors for HCC recurrence were traditionally reported to include male gender, those beyond Milan criteria, or those with partial response to LRT, AFP >400 ng/dL, those microvascular invasion, poor differentiation, TTV>115 cm^3, and LDLT [6-9].

Only vascular invasion and poor tumor differentiation were shown to significantly related to HCC recurrence in the current study. Conversely, transplant criteria, TTV and type of transplant did not show significant relation.

As regards HCC outcome, much emphasis was always credited to the classical volume related tumor criteria e.g., number of HCC lesions, size of the HCC lesions, TTV, etc. the results of current study confirm that volume related criteria are at least insufficient to predict high risk patients for HCC recurrence [17-21]. More factors should be included in this regards namely, the biology-related tumor criteria e.g., poor differentiation, and vascular invasion. It is thus feasible to apply risk stratification scores for HCC recurrence which encompass various radiological, pathological and laboratory variables like RETREAT score [12, 22, 23].

In the current study, HCC recurrence was entirely reported in patients with 3 or more points on the RETREAT score, the incidence of rHCC incidence increased from nil in those of ≤2 points to around one third of those with 3-5 points and up to 70 % of those with more than 5 points. RETREAT score predicted the occurrence of rHCC in our patients and correlated significantly with its occurrence, P=0.00.

Conclusion

HCC recurrence is still a significant medical concern for transplanted HCC patients. Early detection is imperative for the use of more curative options for the management of rHCC.

Volume related criteria are insufficient to predict high risk patients for HCC recurrence. More factors should be included in this regard, namely poor differentiation, and vascular invasion. Risk stratification models for HCC recurrence should be employed to identify high risk patients for HCC recurrence. RETRAET score is a valid and feasible option in this regards.

Screening protocols should be tailored to the risk of HCC recurrence. Closer follow up, and more liberal use of dynamic imaging should be employed in those with high risk for HCC recurrence.

Conflict of interest

This research received no external funding. The authors declare no conflict of interest.

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Рецидивы гепатоцеллюлярной карциномы после трансплантации печени: клинические особенности, лечение и исходы

Мохамед Рабей Абдельфаттах [1], Хуссейн Эльсиеси [2]

[1] Департамент хирургии, Факультет медицины, Университет Александрии, Египет
[2] Центр органной трансплантации, Госпиталь короля Фейсала и научный центр, Эр-Рияд, Королевство Саудовской Аравии

Резюме

Риск рецидивов гепатоцеллюлярной карциномы (рГЦК) значителен, и их общий прогноз все еще неблагоприятен. Целью исследования является обобщение данных о частоте рецидивов ГЦК после трансплантации печени (ТП), рассмотрение их клинических особенностей и существующих вариантов терапии в нашем центре. Мы также рассматриваем потенциальные факторы риска рецидивирования ГЦК.

Материалы и методы

Трансплантация печени была выполнена 148 пациентам в сроки с августа 2006 по декабрь 2020 г. в нашем центре. Выявлены случаи рецидивов ГЦК и систематизированы их клинические характеристики.

Результаты

Средние сроки наблюдения после ТП составляли 53±34,8 мес. Рецидивы ГЦК были обнаружены у 16 пациентов (8,9%). Большинство этих больных (68,8%) наблюдали в течение первых двух лет после ТП. Инвазия в лимфатические сосуды, низкая степень дифференцировки опухоли и оценки по шкале RETREAT были достоверно связаны с рецидивами ГЦК.

Выводы

Раннее выявление рецидивов необходимо для применения более эффективных способов контроля рГЦК. Критерии, основанные на оценке объема опухоли, не достаточны для прогнозирования случаев рецидивов ГЦК высокого риска. Следует использовать модели стратификации риска для выявления пациентов с плохим прогнозом при рГЦК. Протоколы их обследования должны быть адаптированы с риском рецидивирования ГЦК.

Ключевые слова

Гепатоцеллюлярная карцинома, трансплантация печени, рецидив опухоли.