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Liver Transplantation for Liver-Originated Malignancy: A Single Center Experience

Karaciğer Kaynaklı Malignitelerde Karaciğer Nakli: Tek Merkez Deneyimi

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ABSTRACT

Objective: We aimed to evaluate liver transplantation (LT) effectiveness for liver-originated malignancies, focusing on hepatocellular carcinoma (HCC), at a single center.

Methods: Retrospective data review of LT cases between 2006 and 2023. Inclusion criteria: no extrahepatic involvement and liver-originated malignancy. Demographic characteristics, etiology, alpha-fetoprotein (AFP) levels, Milan Criteria compliance, pre-transplant treatments, complications, recurrence, and mortality were analyzed.

Results: Fourteen liver-originated tumors underwent LT, half of which were from deceased donors. Hepatitis B virus was the common etiology (71%). The median AFP level was 4 ng/mL. Fifty percent received pre-transplant therapy. Patient survival rates at 1, 3, and 5 years: 72%, 72%, 68% respectively. The recurrence-free survival rates for the same years were 93%.

Conclusion: LT, including living donor LT, is effective for liver-originated tumors, especially HCC. Encouraging survival rates align with the Milan and University of California, San Francisco Criteria. Despite limitations, ongoing research is vital for LT's role in liver cancer management, considering tumor size, positron emission tomography/computed tomography, grade, and AFP levels for candidate selection beyond the current criteria.

Keywords: Hepatocellular carcinoma, liver, liver transplantation, neuroendocrine tumor, primary liver tumor, transplant oncology

ÖZ

Amaç: Karaciğer kökenli tümörlerde tek bir merkezde yapılan, özellikle hepatosellüler karsinom (HCC) odaklı karaciğer nakli (LT) etkinliğini değerlendirmektir.

Yöntemler: 2006 ile 2023 yılları arasında gerçekleştirilen LT olgularına ait veriler retrospektif olarak incelendi. Dahil etme kriterleri; ekstrahepatik tutulumun olmaması ve karaciğer kökenli maligniteye bağlı nakillerdi. Demografik özellikler, etiyoloji, alfa-fetoprotein (AFP) seviyeleri, Milan Kriterleri uyum, pre-nakil tedavileri, komplikasyonlar, nüks ve mortalite analiz edildi.

Bulgular: On dört karaciğer kökenli tümör hastasına, yarısı kadaverik donörlerden olmak üzere LT yapıldı. Hepatit B virüs en yaygın etiyoloji (%71) olarak belirlendi. Medyan AFP düzeyi 4 ng/mL idi. Hastaların %50'si transplantasyon öncesi tedavi almıştı. Çalışmada 1, 3 ve 5 yıllık sağkalım oranları sırasıyla %72, %72 ve %68 olarak tespit edildi. Aynı yıllar için nükssüz sağkalım oranları %93'tü.

Sonuç: LT, özellikle HCC için etkili bir tedavi seçeneği olarak ortaya çıkmıştır. Umut verici sağkalım oranları, Milan ve University of California, San Francisco Kriterleri'yle uyumluluğu vurgular niteliktedir. Sınırlılıklara rağmen, karaciğer kanseri yönetiminde naklin rolünü doğrulamak ve mevcut kriterlerin ötesinde aday seçiminde tümör boyutu, pozitron emisyon tomografisi/bilgisayarlı tomografi sonuçları, tümör derecesi ve AFP düzeylerini dikkate almak için daha fazla araştırma gereklidir.

Anahtar Sözcükler: Hepatoselüler karsinom, karaciğer, karaciğer nakli, nöroendokrin tümör, primer karaciğer tümörü, transplant onkolojisi

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INTRODUCTION

Liver-originated malignancies represent a significant global burden and contribute substantially to cancer-related mortality. Liver transplantation (LT) has emerged as a pivotal therapeutic avenue for carefully selected patients with such tumors. Hepatocellular carcinoma (HCC), in particular, is a formidable health challenge, ranking as the sixth most prevalent cancer globally and the third leading cause of cancer-related deaths (1,2). Although liver resection serves as the primary curative modality for resectable HCC, its efficacy is hampered by a notable recurrence rate attributed to underlying hepatitis and cirrhosis. LT stands out as the gold standard radical intervention for HCC cases fulfilling established criteria, notably the Milan and University of California, San Francisco (UCSF) Criteria. Initially, many transplant centers favor liver resection for cases of resectable HCC with compensated liver function, reserving LT as a salvage option in scenarios involving disease recurrence or liver decompensation (3). However, owing to organ scarcity, the adoption of living donor liver transplantation (LDLT) for HCC has surged over the past decade, even extending to salvage settings with acceptable safety profiles. Against this backdrop, our study endeavors to scrutinize the efficacy of LT procedures for liver-originated malignancies and to appraise the insights gleaned from our institution's experience.

MATERIALS AND METHODS

Between 2006 and 2023, data of patients who underwent LT at the Gazi University Transplantation Center were retrospectively reviewed. The inclusion criteria comprised absence of extrahepatic involvement and transplantation due to liver-originated malignancy, while the exclusion criteria included inability to access patient archive and follow-up data. All data were retrospectively collected from patient charts and surgical files. Demographic characteristics (age and gender), donor type (living or deceased), tumor etiology and histopathology, alpha-fetoprotein (AFP) levels, compliance with the Milan Criteria, pre-transplant treatments [trans-arterial chemoembolization (TACE) or radiofrequency ablation (RF)], complications, recurrence, and mortality data were analyzed.

All procedures performed in this study were in compliance with the ethical standards of the institutional and/or national research committee, as well as with the principles outlined in the 1964 Helsinki and 2008 İstanbul Declarations; subsequent revisions or equivalent ethical standards. This study was approved by the Local Ethical Committee of Gazi University (approval number: 2024-194, date: 15.02.2024).

Statistical Analysis

All the statistical analysis was performed using SPSS software, version 20, (SPSS Inc., Chicago, IL, USA). Data are expressed as median and range. Relevant variables were analyzed using descriptive statistics. Survey analysis was conducted using the Kaplan-Meier estimator test.

RESULTS

LT has been performed on 14 liver-originated tumors at the Gazi University Transplantation Center in Ankara, Türkiye, since 2006. There were 9 (64%) male and 5 (36%) female recipients with a median age of 45 years (range, 19-61 years). Seven (50%) out of 14 LTs were performed from deceased donors (Table 1).

The etiology of the tumors was hepatitis B virus (n=10), cryptogenic (n=2), hepatitis C virus (n=1), and neuroendocrine tumor (n=1), respectively. The tumor origin included neuroendocrine (n=1) and HCC (n=13). Six (43%) out of 14 recipients were outside the Milan Criteria. One (7%) patient had been downgraded to the Milan Criteria. The median AFP level was 4 ng/mL (range, 1.4-399 ng/mL) (Table 1).

All patients in this group underwent positron emission tomography/computed tomography (PET/CT) to confirm the absence of extrahepatic involvement. The tumor was invisible on CT/magnetic resonance (MR) and was found in the liver explant in 1 (7%) patient. Seven (50%) patients received pre-transplant adjuvant therapy as TACE (n=6) and RF (n=1) (Table 1). None of the patients underwent liver surgery for tumors before LT. Only 1 patient was downgraded while outside the Milan Criteria and was added to the national waiting list.

The tumor sizes of patients outside the Milan Criteria were 25, 15, 8, and 8 cm (four lesions: total 11.5 cm), respectively. Two (14%) patients died after transplantation because of sepsis, hepatic artery

Table 1. Demographic and transplantation characteristics

Characteristics	Results
Age (year)	Median 45 (range; 19-61)
Gender	
Male	9 (64%)
Female	5 (36%)
Donor type	
Deceased	7 (50%)
Live	7 (50%)
Tumor histopathology	
Neuroendocrine	1 (7%)
Hepatocellular carcinoma	13 (93%)
Tumor etiology	
Hepatit B virus	10 (72%)
Cryptogenic	2 (14%)
Hepatit C virüs	1 (7%)
Neuroendocrine	1 (7%)
Pre-transplant therapy	7 (50%)
Tran-sarterial chemoembolization	6
Radiofrequency ablation	1
Milan criteria	
Inside	8 (57%)
Outside	6 (43%)
Alpha-fetoprotein level (ng/mL)	Median 4 (range; 1.4-399)
Follow-up (months)	Median 171 (range; 96-225)
Mortality	2 (14%)
Hepatic artery thrombosis	1
Tumor recurrence	1

thrombosis (n=1), and tumor recurrence (n=1). One recurrence was observed 6 months after transplantation in this patient group. All remaining patients are doing well with a median follow-up of 171 months (range, 96-225) (Table 1).

The patient survival rates for 1, 3, and 5 years are 72%, 72%, and 68%, respectively. The recurrence-free survival rates at 1, 3, and 5 years are 93%, 93%, and 93%, respectively.

DISCUSSION

The ethical dilemma of expanding transplantation criteria for cancer patients is complicated by the potential for cancer recurrence, a risk absent in non-malignant transplant candidates. While no models suggest a percentage of recurrence-free survival necessary to justify expansion criteria, this study demonstrated a 72% recurrence-free survival at 5 years, comparable to the 74% and 54% observed in the Milan Criteria group (3,4). Allograft survival is a potential concern for liver transplant recipients with a history of HCC requiring both chemotherapy and immunosuppression, with a lack of literature standardization on advantageous modalities (1-4).

The principal challenge is identifying preoperative criteria to select tumors with favorable biology and patients achieving a 5-year survival meeting or exceeding 75%, as advocated by the Barcelona group (3). Currently, preoperative tumor staging relies on an up-to-date CT or MR scan within 6 months of LT. However, the crucial role of tumor biology, especially histological grade and lymphovascular invasion, suggests biopsy and histological examination before LT in all cases. Despite concerns about patient acceptance, sampling error, and technical complications in cirrhotic and coagulopathic patients, the purported risk of tumor dissemination is minimal with proper patient selection and meticulous attention to the biopsy technique. The development of a reliable, noninvasive method to identify aggressive tumor biology without biopsy remains a fertile area for technological research (4-6).

The results of our study highlight the efficacy of LT as a viable treatment option for liver-originated tumors, particularly HCC. The favorable patient survival rates at 1, 3, and 5 years underscore the potential curative impact of transplantation in carefully selected cases, aligning with established criteria such as Milan and UCSF (4). The use of PET/CT for thorough pre-transplant assessment demonstrated its significance in confirming the absence of extrahepatic involvement, aiding in more precise patient selection.

Notably, the inclusion of LDLT in our study reflects the pragmatic response to organ shortages, extending the application of transplantation to salvage scenarios.

Study Limitations

It is crucial to acknowledge the limitations of our study. The relatively small sample size and single-center retrospective design may influence the generalizability of our findings. In addition, the presence of tumor recurrence, albeit infrequent, emphasizes the ongoing challenges in achieving long-term success.

CONCLUSION

Our study supports LT, including LDLT, as a valuable and life-extending treatment for liver-originated tumors. The encouraging survival rates warrant further exploration and consideration in the evolving landscape of liver cancer management. Despite the promising outcomes, ongoing research and multicenter studies are essential to validate our findings and address the inherent limitations, thereby ensuring a comprehensive understanding of the role of transplantation in this complex patient population.

We have a small patient group in this study, but we believe that, regardless of the tumor size, PET/CT scans, tumor grade, and AFP levels are possible parameters of the biological behavior of tumors, which will help in decision-making about the inclusion or exclusion of LT candidates with HCC beyond the current selection criteria.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethical Committee of Gazi University (approval number: 2024-194, date: 15.02.2024).

Informed Consent: Retrospective study.

Author Contributions

Concept: R.K., M.H.S., A.D., Design: R.K., M.H.S., A.D., Supervision: R.K., M.H.S., A.D., Data Collection or Processing: R.K., M.H.S., Analysis or Interpretation: R.K., M.H.S., Literature Search: M.H.S., A.D., Writing: R.K., M.H.S., Critical Review: R.K., M.H.S.

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REFERENCES

1. Rumgay H, Arnold M, Ferlay J, Lesi O, Cabasag CJ, Vignat J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. J Hepatol. 2022; 77: 1598-606.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71: 209-49.
3. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022; 76: 681-93.
4. Dageforde LA, Fowler KJ, Chapman WC. Liver transplantation for hepatocellular carcinoma: current update on treatment and allocation. Curr Opin Organ Transplant. 2017; 22: 128-34.
5. Karakayali H, Moray G, Sozen H, Dalgic A, Emiroglu R, Haberal M. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma. Transplant Proc. 2006; 38: 575-8.
6. Tabrizian P, Zeitlhoefler M, Hassan AT, Marino R. Immunotherapy for transplantation of hepatocellular carcinoma: the next frontier in adjunctive therapy. Curr Opin Organ Transplant. 2024; 29: 144-54.