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SURGICAL TREATMENT OF HEPATOCELLULAR CARCINOMA: LIVER TRANSPLANTATION

Summary. The article presents the surgical treatment of 126 patients with hepatocellular carcinoma. Univariate Kaplan-Meier and multivariate Cox proportional hazards models were used to analyze overall and disease-free survivals. The level of alpha-fetoprotein was the only indicator of overall survival. The authors concluded that living donor liver transplantation is the only treatment option for patients in countries with limited sources of cadaveric organs .

Key words: *liver transplantation, hepatocellular carcinoma, alpha-fetoprotein, survival.*

Hepatocellular carcinoma (HCC) one of the most common malignancies, causes about 1 million deaths annually. Orthotopic liver transplantation (OLT) is a generally accepted treatment modality for HCC. In recent years, the indications of living donor liver transplantation (LDLT) in adults include hepatitis B virus (HBV) hepatitis C virus (HCV) related cirrhosis with carcinoma. LDLT plays an important role to treat early malignant hepatic tumors [1]. In our center, we perform OLT for patients with HCC within the Milan criteria. Additionally, we reserve the LDLT option for subjects without macrovascular invasion whose tumor cannot be treated or downstaged by other treatments. In this study, we sought to describe patient characteristics and outcomes at a single institution and to analyze the effect of our criteria on survival of HCC patients.

METHODS

We reviewed medical records of all HCC (n=126) patients who underwent liver transplantation at the Organ Transplantation Unit of Inonu University Turgut Ozal Medical Center of the Turkish Republic between 2009 and August 2013 mostly including 91 % LDLT. Early postoperative death and deceased donor liver transplantation (DDLT) patients were excluded we retrospectively reviewed the remaining 96 patients. In our center, patients with HCC limited to the liver without macrovascular invasion were accepted as LDLT candidates. Preoperative workup included computed tomography (CT) scans, alpha-fetoprotein (AFP) levels, liver function tests, complete blood counts, and coagulation parameters. AFP tests were repeated monthly in the follow-up period. Tri-phasic liver CT scans were obtained for patients with high AFP levels. We evaluated demographic data, tumor characteristics, liver functions, and survival parameters. Univariate Kaplan-Meier and multivariate Cox proportional hazards model were used to analyze overall and disease-free survivals. The level of statistical significance was set at P <0,05.

RESULTS

Demographic and clinical parameters of the patients: 84 (87,5 %) patients were males and 12 (12,5 %) were females. Median age was 53 years (range, 19–69). The most common etiologic factor for HCC was HBV (n=79; 82,3 %). There was hepatitis delta virus (HDV) co-infection in 20 % of HBV patients. The other etiologic factors were cryptogenic (6,7 %; n=7), HCV (6,4 %; n=6), fibrolamellar HCC (2,1 %; n=2), alcohol (1,04 %; n=1), and Wilson disease (1,04 %; n=1). HCC was diagnosed incidentally in 4 (5 %) patients. The median follow-up duration was 12 months (range, 3–52). Preoperative AFP level was <200 IU/mL in 74 % of patients. Preoperative AFP level was unknown in 3 patients. Fourty two (43,7 %) patients were within the Milan criteria, whereas 54 (56,3 %) exceeded them. Recurrence was diagnosed in 17 patients; it was hepatic (n=4; 23,5 %), extrahepatic (n=2; 11,8 %), or both hepatic and extrahepatic (n=11; 64,5 %).

One-, 2-, and 3-year overall and disease-free survival rates were 66 %, 62 %, and 56 % and 65 %, 60 %, and 54 %, respectively. One- and 2-year overall survival rates for the patients within versus exceeding the Milan criteria were 72 % versus 68 %, and 61 % versus 58 %, respectively. One and 2-year disease-free survival rates for the patients within versus exceeding the Milan criteria were 72 % versus 68 %, and 60 % versus 55 %, respectively (P>0,05). Tumor recurrence for patients within versus exceeding the Milan criteria were 0 % versus 36 %, respectively (P=0,0002).

On univariate analysis AFP level was the only predictor of overall survival, AFP level and tumor differentiation were predictors of disease-free survival. On multivariate analysis, AFP level was the only independent predictor of both overall and disease-free survival (P=0,01). Mortality was due to nononcologic reasons in 52 % of patients who died in the follow-up period. **61** patients are still alive; 31 (50,8 %) of them exceeded the Milan criteria. Tumor recurrence occurred in only 3 of these 31 patients.

DISCUSSION

The increased incidence of HCC reflects the increasing prevalence of chronic viral hepatitis [1]. OLT is considered the treatment of choice for early HCC patients with end- stage liver failure, but its availability is limited by the donor organs. In recent years, LDLT has been an alternative to DDLT for patients with HCC [2–4].

Organ donation rate in our country is 3–4 per million population. Cadaveric grafts are a poor source of donor organs. According to the legislation, transplant candidates are determined by The National Coordination Center.

In our country, the Milan criteria are used for DDLT for patients with HCC. We believe that these criteria are not suitable for LDLT. A living donor graft should be considered as an individual gift, not as a public domain like deceased donor grafts. Our transplantation program is mainly based on LDLT. Patients with HCC limited to the liver without macrovascular invasion are accepted as candidates for LDLT. In our study we observed that neither being within nor exceeding the Milan criteria had a significant effect on overall or disease-free survival rates, similar to the results in the literature [5].

In the literature, MELD score and preoperative serum AFP levels have been reported to be independent risk factors for survival. AFP level, tumor size, vascular invasion, and bilobar distribution have been reported to be independent risk factors for HCC recurrence [6]. But in our study, we observed only AFP level as an independent risk factor for overall survival; AFP level and degree of differentiation were independent risk factors for disease free survival.

The reported 1- and 3-year overall survival rates in the literature range between 70 % and 77 % and 66 % and 69 %; the 1- and 3-year disease-free survival rates range between 72 % and 82 % and 64 %, respectively [7-10]. But in our study, 1- and 3-year overall survival rates were 66 % and 56 %; 1- and 3-year disease-free survival rates were 65 % and 54 %, respectively. Our survival results are lower than those reported in the literature because the numbers of patients who died due to non-oncologic reasons were much greater than the tumor-related cases.

In conclusion, AFP level was the only predictor of overall survival. AFP level and tumor differentiation were the predictors of disease-free survival. In terms of recurrence the results are worse among patients exceeding the Milan criteria as expected, but we believe that LDLT is the only treatment chance for these patients who live in countries with poor sources of cadaveric organs. As a general principle, we believe that the use of cadaveric liver grafts is not suitable for patients exceeding the Milan criteria.

REFERENCES

1. Qin J.M. Present status and recent advances in living donor liver transplantation for malignant hepatic tumors. / J. M. Qin, Y. Takada, S. Uemoto // Hepatobiliary Pancreat Dis Int. — 2008. — 7:126. — P. 205 – 215

2. Kew M.C.: Epidemiology of hepatocellular carcinoma. / M.C. Kew // Toxicology. — 2002. — Vol. 35. — P. 181– 182

3. Sarasin F.P. Living donor liver transplantation for early hepatocellular carcinoma: a life-expectancy and costeffectiveness perspective. / F. P. Sarasin, P. E. Majno, J. M. Llovet // Hepatology. — 2001. — Vol. 33. — P. 1073 - 1080

4. Malago M. Ethical considerations and rationale of adult-to-adult living donor liver transplantation. / M. Malago, G. Testa, A.Marcos // Liver Transpl. — 2001. — Vol. 7. — P. 921 – 927

5. Yokoi H. The role of living-donor liver transplantation in surgical treatment for hepatocellular carcinoma. / H. Yokoi, S. Isaji, K. Yamagiwa. // J. Hepatobiliary Pancreat Surg. — 2006. — Vol. 13. — P. 123 – 130

6. Todo S. Japanese Study Group on Organ Transplantation. / S. Todo, H.Furukawa // Ann Surg. — 2004. — Vol. 23. — P. 240 – 245,

7. Todo S. Living donor liver transplantation for adult patients with hepatocellular carcinoma / S. Todo, H. Furukawa // Ann Surg. — 2004. — Vol. 24. — P. 451 – 460

8. Gondolesi G. Hepatocellular carcinoma: a prime indication for living donor liver transplantation / G. Gondolesi, L. Munoz, C. Matsumoto // J. Gastrointest Surg. — 2002. — N 6. — P. 102 – 106

9. Lo C.M. The role and limitation of living donor liver transplantation for hepatocellular carcinoma / C. M. Lo, S. T. Fan, C. L. Liu // Liver Transpl. — 2004. — Vol. 10. — P. 440 – 448

10. Karabulut K. Resection and radiofrequency ablation in the treatment of hepatocellular carcinoma: a single-center experience / K. Karabulut, F. Aucejo, H. Akyildiz // Surg Endosc. — 2011. Vol. 22. — P. 1150 – 1155

ХИРУРГИЧЕСКОЕ ЛЕЧЕНИЕ ГЕПАТОЦЕЛЛЮЛЯРНОЙ КАРЦИНОМЫ: ТРАНСПЛАНТАЦИЯ ПЕЧЕНИ.

П. А. Аббасов

Резюме. В статье представлены данные хирургического лечения 126 больных с гепатоцеллюлярной карциномой. Модели опасности одномерного Каплана-Мейера и многомерного пропорционального Кокса были использованы для анализа общего и безрецидивного выживания. Уровень альфа-фетопротеина был единственным показателем общей выживаемости. Авторы пришли к выводу, что трансплантация печени от живых доноров является единственным вариантом лечения для пациентов в странах с ограниченными источниками трупных органов.

Ключевые слова: *трансплантация печени, гепатоцеллюлярная карцинома, альфа-фетопротеин, выживаемость.*

ХІРУРГІЧНЕ ЛІКУВАННЯ ГЕПАТОЦЕЛЮЛЯРНОЇ КАРЦИНОМИ: ТРАНСПЛАНТАЦІЯ ПЕЧІНКИ.

П. А. Аббасов

Резюме. У статті представлені дані хірургічного лікування 126 хворих з гепатоцелюлярною карциномою. Моделі небезпеки одновимірного Каплана-Мейєра і багатовимірного пропорційного Коксу були використані для аналізу загального і безрецидивного виживання. Рівень альфа-фетопротеїну був єдиним показником загальної виживаності. Автори дійшли висновку, що трансплантація печінки від живих донорів є єдиним варіантом лікування для пацієнтів в країнах з обмеженими джерелами трупних органів.

Ключові слова: *трансплантація печінки, гепатоцелюлярна карцинома, альфа-фетопротеїн, виживаність.*