LIVER TRANSPLANTATION IN THE TREATMENT OF PATIENTS WITH HEPATOCELLULAR CARCINOMA

MAREK KRAWCZYK, MICHAŁ GRĄT*, OSKAR KORNASIEWICZ, KRZYSZTOF ZIENIEWSICZ, PAWEŁ NYCKOWSKI, WALDEMAR PATKOWSKI, IRENEUSZ GRZELAK, KRZYSZTOF DUDEK, TADEUSZ WRÓBLEWSKI, RAFAŁ PALUSZKIEWICZ

Chair and Department of General, Transplant and Liver Surgery, Warsaw Medical University

Kierownik: prof. dr hab. M. Krawczyk

* student of the Warsaw Medical University

The aim of the study was to analyse liver transplantation results in patients with hepatocellular carcinoma, considering selected factors.

Material and methods. The study group comprised 82 patients subject to liver transplantation at the Department of General, Transplant and Liver Surgery, Warsaw Medical University, due to hepatocellular carcinoma. Retrospective analysis concerned the period between 2001 and 2010. Distant survival results were evaluated, depending on whether Milan criteria were fulfilled, and the preoperative level of alpha-fetoprotein estimated. The obtained results were subject to statistical analysis. p<0.05 was considered as statistically significant.

Results. Mean survival time considering patients subject to liver transplantation, due to hepatocellular carcinoma amounted to 66.7 months (95% PU 58.9-74.4), while survival without tumor recurrence – 62.3 months (95% PU 54-70.6). The one, three and five – year survival rate was 88.7%, 74.8% and 72.0%, respectively. Survival without tumor recurrence was 87.5%, 67.1% and 67.1%, respectively. The overall survival of patients fulfilling the Milan criteria (44 of 82 patients – 53.7%) was significantly longer, in comparison to patients not fulfilling the above-mentioned (74.4 and 48.3 months, respectively, p=0.025). A significant difference was also observed, considering the overall survival in the absence of cancer recurrence (72.5 and 42.4 months, respectively, p=0.007). Considering patients not fulfilling the Milan criteria who presented with preoperative alpha-fetoprotein levels > 100 ng/ml, overall survival was shorter, as compared to the mean survival rate: 32.5 and 64.4 months, respectively, p = 0.009. Similar values were obtained in case of patients without tumor recurrence (27 and 57.1 months, p=0.011).

Conclusions. The obtained results confirmed the significant value of Milan criteria, when qualifying patients with hepatocellular carcinoma for liver transplantation. The above-mentioned also showed the potential value of preoperative alpha-fetoprotein level measurements, not only in the diagnostics and early hepatocellular carcinoma diagnosis (patients with cirrhosis), but also in the prediction of survival and tumor recurrence after liver transplantation.

Key words: hepatocellular carcinoma, liver transplantation, tumor recurrence, survival

Hepatocellular carcinoma (HCC) is the most common primary malignant liver tumor, and the fifth worldwide, considering malignant carcinomas (1, 2, 3). In most cases the carcinoma develops in patients with liver cirrhosis (4, 5). Risk factors of hepatocellular carcinoma development include chronic hepatitis B, C and D infections, alcoholism, diabetes mellitus, obesity, smoking, and others (6, 7, 8). Prognosis is poor. The five-year survival in case of untreated patients is less than 5% (9).

Radical treatment of hepatocellular carcinoma consists in the excision of all lesions with a healthy tissue margin. The above-mentioned...
Liver transplantation in the treatment of patients with hepatocellular carcinoma

is only possible in case of two surgical methods—resection or liver transplantation (10). The possibility of resection is often limited, due to the coexistence of cirrhosis and risk of developing postoperative liver insufficiency (11). Distant results in case of resection are unsatisfactory, due to the significant risk of neoplastic development in the non-excised fragment of the liver (6, 12).

Apart from tumor excision, liver transplantation also eliminates cirrhosis, where possible new lesions could develop. Early transplantation results, considering management of patients with HCC, were connected with a high recurrence level and low five-year survival values (13). Poor transplantation results were connected with the frequent qualification towards the above-mentioned methods, considering patients with numerous and extensive liver lesions. The turning point in the history of liver transplantation, considering patients with hepatocellular carcinoma was the publishing of an article, which demonstrated the overall, four-year survival rate, and survival without tumor recurrence (85% and 92%, respectively) in case of patients fulfilling strict criteria concerning tumor number and size. The above-mentioned comprised the presence of a single neoplastic lesion not exceeding 5 cm in size, or three lesions, each no greater than 3 cm (14). Mazzaferro et al. (14), as well as other authors obtained similar results. Thus, the above-mentioned criteria—the Milan criteria, have become a standard in qualifying patients with hepatocellular carcinoma for liver transplantation (15, 16).

Significantly high alpha-fetoprotein values in patients with hepatocellular carcinoma, qualified for transplantation is evidence of the increased risk of tumor recurrence, and shorter expected survival time (17,18). However, alpha-fetoprotein values above which the risk of recurrence is significant remain to be determined. The above-mentioned factor is currently not considered in the qualification of patients with hepatocellular carcinoma for liver transplantation (19).

Over the past two decades the number of therapeutic methods, considering patients with hepatocellular carcinoma has significantly increased. The following are recognized: transarterial chemoembolization, ethanol injections, cryoablation, and thermoablation (6). However, it should be underlined that only resection and transplantation render possible radical management with the curative intention (11).

According to the European Liver Transplantation Registry (ELTR) considering 69,981 adult patients, tumors constitute 14% of all indications for transplantation. Hepatocellular carcinoma represents 85% of the above-mentioned. According to data obtained from the ELT registry the one, three, and five-year survival rates after transplantation amounted to 82%, 68% and 60%, respectively.

MATERIAL AND METHODS

During the period between December, 1989 and May, 2010, 786 adult liver transplantations were performed at the Department of General, Transplantation, and Liver Surgery, Warsaw Medical University. The first transplantation, due to diagnosed hepatocellular carcinoma was performed in 2001.

Hepatocellular carcinoma was an indication for liver transplantation in 82 patients, which constituted 10.4% of all indications. The study group comprised 58 male and 24 female patients, with the male:female ratio of 2.4. Median patient age amounted to 54 years (ranging between 20-65 years).

In 80 (97.6%) cases the tumor developed in patients with liver cirrhosis. In 64 (80%) patients, cirrhosis developed as a consequence of viral hepatitis. Chronic hepatitis C was diagnosed in 36 (45%), type B in 20 (25%), and the combination of both in 8 (10%) patients. Alcohol was an etiological factor in 7 (8.8%) patients, while hemochromatosis in one (1.3%). Cryptogenic cirrhosis was confirmed in the remaining two (2.5%) patients.

In case of two female (2.5%) patients (24 and 29-years old) hepatocellular carcinoma developed in the previously healthy liver. The histopathological examination demonstrated the presence of the fibro-lamellar type of cancer.

Twenty-two (26.8%) patients underwent therapy by means of different methods, prior to transplantation. Cryoablation and thermoablation was performed in 8 patients, liver resection in six, and chemoembolization in five. Combined treatment (thermoablation and chemoembolization) was performed in two patients. One patient was subject to liver resection combined with thermoablation of unresectable lesions.
The study group comprised 33 group A, 28 group B, and 19 group C patients, according to Child’s classification. The median number of MELD (Model for End-stage Liver Disease) points at the time of transplantation was 11 (ranging between 6 and 39). The period from qualification to transplantation ranged from 10 days to 11 months (median of 3 months). The alpha-fetoprotein level before transplantation was elevated in 43 patients (52.4%) (upper limit of reference values –15 ng/ml). The median level was 24.1 ng/ml (ranging between 1.2 and 12317 ng/ml). Values exceeding 100 ng/ml were observed in 23 patients (28.1%).

Sixty (73.2%) transplantations were performed by means of the method maintaining the continuity of the inferior vena cava (piggy-back method). The remaining 22 (26.8%) transplantations were performed by means of the classical method with the excision of the retrohepatic segment of the inferior vena cava. Temporary veno-venous extracorporeal circulation was used in all classical transplantation cases and in none considering the piggy-back method.

The size and number of lesions was determined on the basis of the histopathological examination of the excised liver. Milan criteria at the time of transplantation were fulfilled in 44 (53.7%) patients.

Postoperative mortality, the incidence and type of complications were determined. We compared the general survival rate and survival without tumor recurrence, depending on whether the Milan criteria were fulfilled, and on the basis of preoperative alpha-fetoprotein levels. Survival without cancer recurrence was considered from the time of transplantation to death not connected with the procedure, presence of recurrence in the transplanted liver, and metastatic lesions.

Analysis was performed by means of Kaplan-Meier’s method and the logistic rank test. Mean survival was presented in months with the use of 95% confidence intervals, being considered as the basic method of estimation. The confidence intervals indirectly estimate the accuracy of the obtained survival results. In contrast to particular values of survival calculated for the study group they show the extent of the confidence interval which is sought. The 95% confidence intervals were presented in brackets and marked with the abbreviation 95%U. p< 0.05 was considered as statistically significant.

RESULTS

The incidence of postoperative complications in the described material was 32.9%. Three patients required liver re-transplantation. Indications for the above-mentioned procedure were as follows: early hepatic artery thrombosis, primary hepatic insufficiency, and liver rupture after reperfusion without known cause. One relaparotomy was performed, due to bleeding to the peritoneal cavity.

The mortality rate during the postoperative period amounted to 3.7%. Two patients died because of sepsis. In case of one patient we observed primary failure of the transplanted liver. After emergency re-transplantation the patient developed multiorgan failure and died.

Mean survival for all patients was 66.7 months (95% PU 58.9-74.4). One, three, and five-year overall survival was 88.7%, 74.8% and 72%, respectively (fig. 1a). One, three, and five-year survival without tumor recurrence was 87.5%, 67.1% and 67.1%, with the mean overall survival without cancer recurrence amounting to 62.3 months (95% PU 54.0-70.6) (fig. 1b).

Tumor recurrence after transplantation was observed in 13 (15.9%) patients after an average of 70.3 months (95% PU 62.6-77.9). The recurrence rate in case of patients outside the Milan criteria was 26.3%, as compared to 6.8% of patients according to these criteria. The mean time of cancer recurrence was 48.8 (95% PU 37.9-59.6) and 79.8 (95% PU 73-86.5) months. The difference was statistically significant (p = 0.004).

Considering patients fulfilling the Milan criteria the one, three, and five-year survival rate was 95.4%, 86% and 81.5%, respectively, as compared to 80.8%, 60.7% and 60.7% in case of patients outside the Milan criteria. The mean survival rate amounted to 74.4 (95% PU 65.8-82.9) and 48.3 (95% PU 37-58.6) months, p = 0.025 (fig. 2a). The survival rate without tumor recurrence was 95.4, 81.1% and 81.1%, as well as 78.3%, 49.7% and 49.7%, respectively, considering Milan criteria and patients outside these criteria. The estimated mean survival time without tumor recurrence amounted to 72.5 (95% PU 63.4-81.6) and 42.4
Liver transplantation in the treatment of patients with hepatocellular carcinoma

(95% PU 31.6-53.1) months, p = 0.007 (fig. 2b).

In case of patients outside the Milan criteria, values of alpha-fetoprotein levels exceeding 100 ng/ml before transplantation were connected with shorter mean survival rates (fig. 3a), and survival without cancer recurrence (fig. 3b) amounting to 32.5 (95% PU 14.3-50.7) and 27 (95% PU 10.4-43.7) months. In case of patients with alpha-fetoprotein levels <100 ng/ml, these values amounted to 64.4 (95% PU 55.8-73.1) and 57.1 (95% PU 45.2-69.1) months. Differences were statistically significant (p=0.009 and p=0.011, respectively).

There were no significant differences considering overall survival and survival without cancer recurrence in case of patients fulfilling Milan criteria, depending on Milan criteria. Continuous line – patients fulfilling Milan criteria, interrupted line – patients outside Milan criteria.

Elevated alpha-fetoprotein values (<100 ng/ml) had no influence on overall survival and
survival without cancer recurrent, regardless whether patients fulfilled Milan criteria.

**DISCUSSION**

The presented distant liver transplantation results in cases of patients with hepatocellular carcinoma correspond to results obtained by leading European and world centers (5, 10, 20, 21). In comparison to data obtained from the European Liver Transplantation Registry the one, three, and five-year survival rates in our study are higher.

The previous report from the Department of General, Transplant and Liver Surgery described liver transplantation results obtained from 26 patients with hepatocellular carcinoma in the period up to April, 2005 (22). The results considering the overall survival rate, and survival without tumor recurrence were much worse, in comparison to current data. This is obvious since these patients were diagnosed with advanced lesions, outside the Milan criteria, and recurrence was observed shortly after the transplantation. One should not forget that the observation period during the current analysis was significantly prolonged, as compared to the previous analysis. Irrespective of the high values of one, three, and five-year survival rates, and survival without tumor recurrence, tumor recurrence was observed in 15.9% of patients. This justifies the need for eligibility of patients for transplantation according to strict criteria, in order to minimize the risk of cancer recurrence (11). Metastatic lesions or cancer relapse was also observed in cases of patients fulfilling the Milan criteria at the time of transplantation. This is evidence that proper patient qualification does not eliminate the risk of tumor recurrence after transplantation.

During the past years one can observe the insufficient number of donors in relationship to the number of recipients awaiting transplantation. Thus, the expected waiting time for the organ is prolonged, and one can observe disease progression outside the Milan criteria (23). The median waiting time was three months with the longest amounting to 11 months. The non-fulfillment of Milan criteria at the time of transplantation can result from disease progression during the waiting period.

However, disease progression does not explain all transplantation cases outside the Milan criteria. Patients not fulfilling the above-mentioned criteria comprised nearly 50% of the study group. Such a percentage of patients not meeting the criteria might result from the underestimation of the number or size of lesions observed during imaging examinations.
performed during the qualification procedure. The above-mentioned phenomenon was observed even in 30 to 45% of cases (14, 21).

Long-term transplantation results were better in case of patients fulfilling the Milan criteria. Differences concerned both the overall survival, and survival without tumor recurrence. This is evidence of the legitimacy of the Milan criteria when qualifying patients with hepatocellular carcinoma for transplantation.

The role of alpha-fetoprotein levels in the qualification of patients with hepatocellular carcinoma for transplantation is ambiguous (19). The presented study showed worse results in case of alpha-fetoprotein levels exceeding 100 ng/ml, although only in case of patients outside the Milan criteria. This is evidence of the possibility to combine radiological criteria with alpha-fetoprotein values when qualifying patients for transplantation. However, further prospective investigations are required.

Liver transplantation is a recognized method of treatment considering patients with small hepatocellular carcinoma lesions (10). A significant limitation is connected with the insufficient number of donors. In the face of shortage of organs it is necessary to select patients with best prognosis. The available qualification system which is based on Milan criteria is characterized by good distant results. However, attempts to clearly distinguish patients who are candidates for transplantation seem reasonable.

A retrospective analysis published in 2009, considered 1556 patients with hepatocellular carcinoma subject to liver transplantation (including patients who underwent transplantation in our center). Based on the obtained results patients with a diagnosed single lesion, 7 cm in diameter, or smaller lesions, less than seven, are candidates for liver transplantation. The above-mentioned are termed the „up to seven” criteria. The publication begins the discussion on the extension of Milan criteria (24). Our future investigation will evaluate initial results considering the „up to seven” criteria classification.

REFERENCES