Outcomes of Patients With Poorly Differentiated Hepatocellular Carcinoma After Liver Transplantation

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ABSTRACT

Background. Liver transplantation (LT) outcomes for patients with poorly differentiated (G3) hepatocellular carcinoma (HCC) are unsatisfactory. The aim of this study was to evaluate outcomes in patients with poorly differentiated HCC undergoing LT.

Patients and Methods. There were 192 HCC patients after LT in the Department of General, Transplant and Liver Surgery, Medical University of Warsaw, between January 2001 and April 2014. The study group comprised 24 patients with poorly differentiated tumors.

Results. Disease-free survival (DFS) for all patients was 49.5% at 5 years. The 5-year DFS for patients who met the Milan criteria (n = 9, 88.9%) was significantly better compared to those who did not (n = 15, 28.0%, $P = .025$). Multivariable analysis revealed that only the largest tumor diameter ($P = .014$) and α-fetoprotein (AFP) concentration ($P = .001$) were independent risk factors for DFS. The optimal cut-off AFP and tumor size that could distinguish patients with the highest risk were ≥500 ng/mL and ≥3.5 cm, respectively. DFS for patients with AFP <500 ng/mL and tumor size <3.5 cm was 100% after 2.8 years, and for those with ≥500 ng/mL or tumor size ≥3.5 cm was 46.9% after 5 years. However, the DFS for patients with AFP ≥500 ng/mL and tumor size ≥3.5 cm was only 12.5% after 4.7 years ($P = .002$).

Conclusions. Outcomes of patients with poorly differentiated HCC treated with LT can be characterized with acceptable survival when applying criteria based on tumor size <3.5 cm and AFP <500 ng/mL.

HEPATOCELLULAR carcinoma (HCC) is the most common primary malignant tumor of the liver and is responsible for up to 80% of all liver tumors [1]. The main risk factors that increase the probability of HCC differ globally. Overall, the main cause is chronic liver disease, resulting mainly from hepatitis viruses and/or alcohol consumption. The high prevalence of HCC in Asia and Africa resembles the high incidence of hepatitis B infection. On the other hand, in western countries, hepatitis C infection is responsible for the majority of HCC cases [2]. At the Department of General, Transplant and Liver Surgery, Medical University of Warsaw, HCC patients treated with liver transplantation (LT) account for approximately 15.3% of all primary transplant recipients [3].

The fact that the majority of HCC develops in cirrhotic livers dramatically limits treatment modalities. The potential curable option for early HCC is resection and LT. Only 5%–10% of patients can safely undergo radical liver resection when liver failure is present [4]. Patients who cannot be treated by resection are potential candidates for LT. The first outcomes for HCC patients treated with LT were unsatisfactory and not ethically acceptable, as the liver graft could be transplanted to other patients on waiting lists without cancer. Fortunately, the Milan criteria proposed in 1996, based on tumor number and size, provided a means to select those patients with HCC for whom the outcomes after

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LT were most favorable [5]. Since then, many other qualification protocols have been proposed expending or modifying the Milan criteria. Yet, the search for optimal candidates with HCC who could benefit the most from LT is ongoing.

Poorly differentiated HCC tumors (G3), according to modified Edmondson-Steiner classification [6], are associated with a significantly higher recurrence rate after LT [7]. In fact, the recurrence rate of HCC G3 tumors is an independent risk factor regardless of tumor number and size [7,8]. Moreover, some authors support a strategy for selecting HCC patients suitable for LT based on pretransplantation tumor grading [9]. Therefore, the aim of this study was to evaluate outcomes in patients with poorly differentiated HCC treated with LT.

PATIENTS AND METHODS

A total of 192 patients with HCC were treated with LT at the Department of General, Transplant and Liver Surgery, Medical University of Warsaw, between January 2001 and April 2014. This retrospective cohort study was performed by using data for 24 patients with HCC Grade 3 according to the Edmondson-Steiner classification. The study was performed in accordance with the Declaration of Helsinki of 1975.

The risk factors for worse disease-free survival (DFS) were studied. Three survival groups with low, moderate, and high survival risk were distinguished on the basis of those risk factors. The tumor with the poorest Edmondson-Steiner grade served as representative in the case of more than 1 tumor being present.

DFS at 5 years, defined as the time between LT and tumor recurrence or patient death was set as the primary outcome measure. Data were censored at the date of the last available follow-up visit. Continuous data were expressed as medians and ranges, and categorical variables were expressed as numbers and percentages. The Kaplan-Meier estimator was applied for calculation of DFS. Survival curves were compared with the log-rank test. Cox proportional hazards regression models were used for conducting both univariate and multivariable analyses. Outcome cut-offs for continuous variables in predicting worse DFS were based on analysis of the receiver operating characteristic curves. The level of significance was set at 0.05. Statistica version 10 software (StatSoft Inc, Tulsa, OK, USA) was used for computing statistical analyses.

RESULTS

Table 1 summarizes the characteristics of patients. Table 2 presents the data for both univariable and multivariable analyses of risk factors for worse DFS.

The DFS for whole group was 60.5% after 1 year and 49.5% after 5 years. The DFS for patients fulfilling the Milan criteria (n = 9, 88.9%) was significantly better compared to those who did not fulfill these criteria (n = 15, 28.0%, $P = .025$).

Univariable analyses revealed that α-fetoprotein (AFP) concentration was a significant risk factor for worse DFS ($P = .006$). The negative effect of size of the largest lesion was close to, but did not reach, statistical significance ($P = .064$). In fact, multivariable analyses revealed that both the size of the largest lesion ($P = .014$) and AFP concentration ($P = .001$) were independent risk factors for DFS.

Table 1. Baseline Characteristics of Study Group

Number of patients	24
Recipient sex (male)	21 (87.5%)
Recipient age (y)	58 (53–61)
Number of lesions	2 (1–3)
Size of largest lesion (mm)	35 (25–50)
Total tumor volume (cm^3)	33.5 (20.3–77.4)
α-Fetoprotein (ng/mL)	65.4 (10.2–566.7)
MELD score	11 (8–13)
HBV infection	9 (37.5%)
HCV infection	15 (62.5%)
Neoadjuvant treatment	9 (37.5%)
Microvascular invasion	11 (45.8%)
Fulfillment of Milan criteria	9 (37.5%)

Abbreviations: MELD, Model for End-Stage Liver Disease; HBV, hepatitis B virus; HCV, hepatitis C virus.

The optimal cut points for AFP concentration and tumor size that could distinguish patients with the highest risk were ≥500 ng/mL and ≥3.5 cm, respectively. The DFS for patients with AFP <500 ng/mL and tumor size <3.5 cm was 100% after 2.8 years, and for patients with either an AFP ≥500 ng/mL or a tumor size ≥3.5 cm was 46.9% after 5 years. However, for patients with both an AFP level ≥500 ng/mL and tumor size ≥3.5 cm, the DFS was only 12.5% after 4.7 years ($P = .002$).

DISCUSSION

Historically, the outcomes of HCC patients treated with LT have been unsatisfactory. There were no optimal criteria to adequately allocate HCC patients with different stages of disease to LT. This situation led to the decisive study by Mazzaferro et al, published in 1996, in which the Milan criteria were presented [5]. The Milan criteria have set a standard for allocation of HCC patients to LT and have created a "benchmark" for other criteria proposed with the aim to modify or expand the Milan criteria. The qualification protocol was based on tumor number and size. Since then, there have been numerous studies, and new qualification protocols have been proposed.

The search for the new criteria was imposed by the restrictiveness of the Milan criteria on one hand and the increasing number of confirmed risk factor for worse survival on the other [10]. The percentage of HCC recurrence after LT can be as high as 65%, and is always a result of a combination of various risk factors [8]. The Milan criteria were based solely on radiologic characteristics of the HCC tumors, and such criteria as the University of California, San Francisco (UCSF) [11] or Up-to-7 [12] were intended to expand them. However, the qualification protocols based on radiologic features of HCC tumors, despite their simple clinical applicability, had, and still have, major disadvantages in predicting tumor biology and behavior. Apart from the size and number of tumors, there are studied risk factors that are more related to tumor biology, such as AFP