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Tumor recurrence after oLTX

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Abstract Although early survival following transplantation for primary hepatic cancer is excellent, previously reported high recurrence rates have generally discouraged liver replacement for this condition. The aim of this retrospective analysis was to examine the influence of risk factors on the development of early tumor recurrence. Between December 1982 and June 1995, 480 liver transplantations were performed at a single institution. Out of these, 103 patients had unresectable primary hepatic cancer (88 hepatocellular cancer; HCCA; 20 %) and 15 had cholangiocellular cancer (CHCA; 4 %). The influence of the following tumor-associated risk factors was assessed: tumor size, tumor distribution within the liver, grading, pseudocapsular formation, vascular invasion, lymph node metastasis, and cirrhotic alteration. The diagnosis of tumor recurrence was made using various radiological imaging techniques, reelavation of serum alphafetoprotein, or autopsy. For patient survival and disease-free period, data analysis was performed by the method of Kaplan-Meier. The Cox model was used for multivariate analysis; a P-value of less than 0.05 was considered to be significant. The mean age of the 103 patients was 54 years (range 15–63 a). There were 22 female and 81 male patients. The follow-up period ranged between 4 and 108 months. Twenty-nine patients (50 %) died during the follow-up period due to recurrence of disease. The survival rates of the 88 patients with HCCA were 57 %, 34 %, and 26 % at 1, 3, and 5 years, respectively, after orthotopic liver transplantation (oLTX; follow-up 36 month). Of the 15 pts with CHCA the rates were 53 %, 33 %, and 33 %, respectively, with a median follow-up of 60 months. The influence of the risk factors studied showed a significantly longer disease-free period for the following tumor characteristics: grading below or equal 2 ($P = 0.009$) and absence of vascular invasion ($P = 0.04$). Regarding a median survival rate of 2–4 months for patients with unresectable malignant liver tumors, these results confirmed the indication for oLTX, especially if the patient does not compete with someone on the waiting list for benign liver disease.

Key words Liver transplantation · Primary hepatic cancer · Outcome

Introduction

Worldwide, primary hepatic carcinoma is a common malignant tumor with variable incidence. Compared to the natural course of the disease, it has been clearly demonstrated that surgical tumor removal offers the only chance for long-term cure [1]. Without surgical resection the tumor biology leads to survival times of a maximum of 6 months. Only 20–40 % of primary liver malignancies are resectable conventionally because of bilobular tumor spread at the time of diagnosis or underlying advanced liver cirrhosis. Orthotopic liver transplantation has been considered as the only therapeutic possibility to achieve acceptable survival times, but high recurrence rates have been reported and therefore have impaired the good early survival rates [2, 3]. Therefore, some centers have recommended that patients with unresectable primary cancers and advanced-stage tumors should not be candidates for liver transplantation [3]. Other studies have shown that the rate of tumor recurrence is influenced by tumor size, the number of tumors, histological type and differentiation, and the presence of vascular or lymph node involvement [1, 4–6]. A review of the recently puplished data suggests that there is again a trend in favour of liver transplantation at an early stage of the hepatic cancer, where resection has been the method of choice for a long time because of survival rates that are comparable to those for benign conditions requiring liver transplantation [7]. Another option for better long-term disease-free survival in advanced hepatocellular malignancies is multimodal treatment with neoadjuvant chemotherapy and subsequent liver transplantation, which has been reported with 3-year survival rates of over 60 % [8–10]. This therapeutic option seems to be the method of choice for the majority of the cancer patients transferred to transplant centers because the proportion of patients treatable by other surgical methods is infinitely small.

We report on a series of 103 orthotopic liver transplants of otherwise unresectable primary hepatic cancers that were transplanted at our unit throughout the last 14 years and a subgroup of patients who received neoadjuvant chemotherapy, consisting of doxorubicin, throughout the last year. The aim of this study was to evaluate tumor characteristics and determine their potential risk in regard to recurrence rates after complete removal of the tumor. Is the neoadjuvant chemotherapeutic treatment a possible way to destroy undetected micrometastases, allowing these patients to lead a long life without recurrence of their tumor?

Material and methods

From December 1982 to June 1995, 480 patients were treated by total hepatectomy and subsequent transplantation at the transplantation department of the University of Vienna. Of these 480 transplants, the indication for liver replacement in 103 patients was a primary malignant tumor of the liver that was not treatable by resection because of underlying cirrhosis or tumor spread. In 88 patients, the indication was primary hepatocellular carcinoma (HCCA) and in 15 patients, primary cholangiocellular carcinoma (CHCA).

The HCCA group consisted of 72 male and 16 female patients with a mean age of 54 years (14–67 a). The CHCA group included 9 male and 6 female patients with a mean age of 50 years (31–62 a). All patients had a preoperative diagnosis of solitary liver tumor without metastatic disease. Preoperative investigations included chest radiography, hepatic doppler ultrasonography, computerized tomography, bone scintigraphy, and echocardiography. Orthotopic liver transplantation was done in the standardized way without using veno-venous bypass. Immunosuppression consisted of induction therapy with antithymocyte globulin (ATG-Fresenius) followed by cyclosporin and prednisolone, using azathioprine as a third therapeutic agent only in case of histologically proven rejection. In the recent transplants starting in January 1995, we introduced a neoadjuvant chemotherapeutic approach consisting of up to five cycles of doxorubicin 15 mg/m^2 i. v. preoperatively, one intraoperative cycle of doxorubicin 15 mg/m^2 i. v. after induction of general anaesthesia and before manipulation of the liver and, again, doxorubicin therapy 15 mg/m^2 i. v. in the postoperative period when the recipient's condition had stabilized, normally starting 2 weeks after transplantation and thereafter every second week up to a total dosage of 300 mg/m^2.

We collected the following pathological variables to get information about their possible prognostic relevance: histological diagnosis of the primary tumor and the associated liver disease, grade of tumor differentiation, intrahepatic tumor size (maximum diameter in centimeters), number and location of the nodules, presence or absence of vascular invasion, tumor thrombosis of the portal vein, and lymph node involvement. Patients were routinely seen at our outpatient department monthly for the first 6 months after transplantation, thereafter every 3 months until the second year of follow-up, and then semi-annually. Blood samples were routinely controlled at every visit, liver ultrasonography and chest radiography were done half yearly, and computerized tomography and bone scintigraphy in case of suspected recurrence of the primary carcinoma.

Statistical analysis was calculated using the univariate model in the first step (chi-square test), entering variables found to be significant in the multivariate Cox regression model. Overall survival was summerized using the Kaplan-Meier method.

Results

Considering the 30-day mortality rate, we had 1 death (7 %) in the CHCA group and 13 deaths (14.8 %) in the HCCA group. Reasons for that were cardiac complications, sepsis, and nonfunction of the hepatic graft complicated by no available organ for retransplantation. The overall survival rates 1, 3, and 5 years after transplantation were 53 %, 33 %, and 33 %, respectively, in the CHCA group after a median follow-up of 60 months and 57 %, 34 %, and 26 %, respectively, in the HCCA

group after a median follow-up of 36 months. The disease-free survival rates at the same times were 72%, 52%, and 39%, respectively, in the CHCA group and 85%, 56%, and 43%, respectively, in the HCCA group. Median survival times after transplantation were 18 months in the HCCA group and 14 months in the CHCA group. Death due to recurrence of disease was observed in 48% of the patients in the HCCA group and in 55% of the patients in the CHCA group.

Histological evaluation revealed multicentricity in 74% of the patients in the HCCA group and in 71% of the patients in the CHCA group. Overall survival was not statistically significantly better in either unifocal group. The median tumor diameter was 5 cm (0.5–27 cm) in the HCCA group and 11.5 cm (2–23 cm) in the CHCA group. As we had only a small number of patients in both treatment groups with a median tumor diameter below 5 cm, disease-free survival was not found to be statistically significantly better in these patients. An associated cirrhotic alteration of the liver was present in 78% of the HCCA group and in 7% in the CHCA group. No statistical benefit was observed in nonchirrhotic patients. A significantly better overall survival was observed in patients without vascular invasion. On histological examination, 66% of the tumors did not show vascular invasion and 34% of the tumors did show vascular invasion. After a median follow-up of 36 months, 81% of the patients without vascular invasion had no signs of recurrence compared to only 63% of the patients with vascular invasion of the tumor at histological examination ($P = 0.04$, Mantel-Cox).

The second histopathological variable that was found to be significant in the multivariate model was the grading of the tumor. Twenty-three percent of the patients in the HCCA group had a good differentiation (grade I) of the tumor, 55% had a moderate (grade II), and 22% had poor tumor differentiation (grade III). Comparing grades I and II tumors with grade III tumors revealed a significantly better disease-free survival in the more differentiated tumor group ($P = 0.009$). A 3-year disease-free survival of 82% in the grade I tumor patients compared to 68% in the grade II and 50% in the grade III tumor patients was observed.

An improved disease-free survival in the so-far very small group of patients entered into the neoadjuvant chemotherapeutic program was not observed because the follow-up was too short; nevertheless, we have not seen any recurrent tumor, and one of the explanted livers showed complete remission after preoperative doxorubicin therapy.

Discussion

Primary hepatic cancer remains difficult to treat. Early disease is diagnosed infrequently and survival after the onset of symptoms is extremly poor. Many treatment modalities have been applied, but without surgical ablation, chemoembolization, chemotherapy, and radiation remain palliative at best. The present study was a retrospective analysis of patient's outcome after liver transplantation for primary hepatic cancer at our unit throughout the last 14 years. The results demonstrated better overall survival compared to other treatment options for advanced liver malignancy. Nevertheless, we have to confess that recurrence is the crucial point for this disease. Median overall survival times of 18 months for our large number of stage III and IVa patients could be considered excellent results in comparison to those of other groups [11]. The data presented here showed that postoperative tumor recurrence rates correlate significantly with the differentiation of the hepatoma and the presence of vascular invasion. Known risk factor such as the tumor size and the tumor distribution within the liver were not found to be significant in our study because there was an unimportant incidence of positive tumor characteristics (tumor < 3 cm, unilobular) in our patients. This could be underlined by the fact that none of our patients was a candidate for liver resection either because of advanced underlying liver disease (child B or C) or because of bilobular or central tumor spread.

Despite these results, many series report occasional long-term survival even of patients with advanced-stage disease. Therefore, it seems that cure is possible, and patients with advanced tumors should not be excluded from transplantation. Instead, attempts at improving therapy should be undertaken. Three recent studies emphasize the use of neoadjuvant treatment besides the surgical option to extend the long-term cure of patients with advanced tumor [8–10]. Three rationales are used to explain its usefulness: control of tumor growth during the waiting period, elimination of tumor cells that are disseminated during the operation, and control of remaining micrometastases postoperatively. In Stone's report 59% of the patients were alive at 3 years with 54% disease-free when concomitant neoadjuvant chemotherapy was used [9]. In over a half of the patients the tumor size was greater than 5 cm. We believe that multimodal treatment is the treatment of the future, and we have therefore started a program of pre-, intra- and postoperative adjuvant chemotherapy at the beginning of this year. So far we have one complete remission, no major side effects, and no recurrence of disease in the first patients treated with this regime. It is reasonable to advocate that tumor patients should continue to receive transplants as long as there is no competition with other patients on the waiting list for benign disease, in the expectation of a cure for some and good long-term pallia-

tion in the remainder. Recurrence rates in advanced-stage tumor patients with an actuarial survival figure of under 30% at 3 years should lead to the decision to give these patients a low priority for transplantation. These recurrence rates illustrate the importance of early diagnosis of tumors in the cirrhotic liver by ultrasound screening of these patients in order to prolong survival after transplantation.

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