Recurrence of Hepatocellular Carcinoma After Liver Transplantation: A Single-Center Experience

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Background: There is a worldwide increase in use of liver transplantation (LT) for treatment of hepatocellular carcinoma (HCC). We analyzed our experience with LT for HCC to determine long-term and recurrence-free survival, accuracy of imaging diagnosis of HCC compared to the explant pathology, recurrence rate of HCC, and predictors of recurrence.

Material/Methods: The whole explant was examined by the same pathologist and compared with the baseline diagnosis established according to clinical, laboratory, and radiological data. A group of patients with pathologically confirmed HCC was characterized, with special attention to etiology, survival, recurrence, and diagnostic accuracy of imaging techniques.

Results: Among 718 patients transplanted from 2000 to 2018 in our center, HCC was found in 166 explanted livers. In 42 cases the clinical diagnosis of HCC was not accurate, being either false positive or negative; however, the specificity and sensitivity of CT/MRI in HCC recognition was 97.87% and 88.24%, respectively. Five- and 10-year survival was 81.27% and 66.57%, respectively, and it was inferior to the overall survival. The recurrence rate was 9.6% with a median time to recurrence of 14 months and a median survival time of 9 months. Poor differentiation of HCC and HCV etiology of the baseline disease, but not previous DAA treatment, were the risk factors of HCC recurrence.

Conclusions: Adherence to strictly defined selection criteria for LT in HCC patients guarantees the success of LT in HCC treatment.

MeSH Keywords: Carcinoma, Hepatocellular • Liver Transplantation • Recurrence

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Background

The rise of liver transplantation (LT) for treatment of hepatocellular carcinoma (HCC) is being observed worldwide [1]. It is estimated that in the next decade the number of LTs due to HCC will exceed the number of transplants performed for cirrhosis type C in Europe and in the United States. In a longer perspective, the prevalence of HCC on top of HCV-positive cirrhosis should decline as a result of effective treatment of chronic HCV infection; however, a subset of patients with advanced cirrhosis may deteriorate and develop HCC despite successful treatment and clearance of the virus [2,3]. Moreover, the rise of LT for non-alcoholic fatty liver disease is being observed and because this disorder predisposes to HCC development, the number of NAFLD-related HCCs can be also expected to increase [4,5].

LT seems an ideal option for HCC treatment, because 2 goals are achieved at the same time – radical oncologic resection and a correction of the underlying liver dysfunction. However, initial results of LT for HCC showed poor survival and a high recurrence rate, which was related to inaccurate patient selection. Results significantly improved after introduction of stringent selection measures in 1996, widely known as the Milan criteria (single tumor <5 cm in diameter or up to 3 tumors ≤3 cm each) [6], allowing 5-year survival at 70% and decrease in recurrence rate up to 15% [7]. Cirrhotic livers contain very many regenerative nodules of a benign nature, and distinction of HCC tumors from other liver nodules can be difficult, especially when the lesion sizes are small. Biopsy of the focal lesion in the cirrhotic liver poses a risk of a false-negative result; therefore, according to the EASL panel experts, diagnosis of HCC nodules >2 cm in size may solely rely on noninvasive criteria [8]. In 2017, the Liver Imaging Reporting And Data System (LI-RADS) was up-dated and began to be applied for different imaging modalities, including CT/MRI for diagnosis and staging of HCC [9]. According to this system, patients at high risk for HCC tumors can be categorized as definitely benign (LR-1) through probably benign (LR-2) until definitely HCC (LR-5) taking into account tumor size, arterial phase hyperenhancement, and some major features such as washout, enhancing capsule, or threshold growth.

Prognosis of LT for HCC is a complex issue because it is not only related to the common complications of transplantation itself, but also to the risk factors responsible for post-LT recurrence [10]. Among the risk factors of recurrence, Milan criteria status, the AFP level at the time of LT, and the interval between diagnosis and surgery are most frequently elevated.

The aim of this study was to analyze our experience with LT for HCC to determine long-term survival, the accuracy of imaging diagnosis of HCC when compared to the explant pathology, the recurrence rate of HCC, and the predictors of recurrence.

Material and Methods

This was a retrospective analysis of 718 patients who underwent orthotopic LT between January 2003 and December 2018 at our institution. All patients received livers from deceased brain-dead donors. Listing was done accordingly to the commonly accepted clinical and biochemical criteria for LT, including Milan criteria for HCC. Allocation at our center is based on need rather than on the MELD score. Patients with a diagnosis of HCC have a local priority, especially when sizes and number of nodules are close to the limit values. A total of 166 transplants were performed for pathologically confirmed HCC. All cirrhotic explant livers were examined by the same pathologist (JM) who had a knowledge of the etiology of liver disease, but not about imaging data; suspicion of HCC was mentioned when appropriate. Explanted livers were fixed in formalin and then sectioned at 5–10 mm intervals. Lesions that were different from the surrounding tissue in terms of bulging, color, and texture were carefully removed, measured, and microscopically examined after a routine preparation of paraffin-embedded material. Grading of neoplastic nodules was performed according to the AJCC Cancer Staging Manual, 7th Edition, in which G1 means well-differentiated carcinoma and G4 is consistent with undifferentiated tumor [11].

Contrast-enhanced magnetic resonance and contrast-enhanced computed tomography examinations were performed in the pretransplant evaluation and interpreted according to internationally accepted criteria. Nodular lesions that were hyperenhanced in the arterial phase and showed "washout" in the venous phase were considered as consistent with HCC. Since 2017, CT/MRI LI-RADS criteria have been implemented in our institution. Computed tomography was performed on a Somatom Definition AS Plus device (Siemens) and in case of doubtful or inconclusive results, MR imaging was done on a Magnetom Vision 1,5 Tesla device (Siemens). Only examinations performed in our hospital using the same equipment and within a time interval of 6 months between examination and LT (preferably 3 months) were reviewed for further analysis. If there was more than 1 examination in this period, the most recent was used for comparisons. Taking the above into account, the detailed comparison of focal pretransplant lesions detected by imaging examinations and focal lesions discovered in the explanted livers during pathological examination was possible since 2013, when a new hospital database was installed with access to the full medical documentation, including radiological records. In this period of time, 273 liver transplantations were performed, and in 79 cases the baseline diagnosis of HCC was made according to CT/MRI results.

Information on demographics, medical history, laboratory results, tumor characteristics, and survival was collected from medical records and the Polish transplant registry

(*https://rejestry.gov.pl*). MELD score was calculated in every patient at the time of listing. Special attention was paid to patients with HCC recurrence after transplantation. These patients were compared to the patients free from recurrence in respect to the etiology of liver disease, time interval between listing and transplantation, tumor characteristics, baseline alfa-fetoprotein (AFP) level and AFP level at the time of recurrence, and immunosuppressive regimen.

Statistical analysis

The primary goal of our study was to assess patient and recurrent-free survival. Kaplan-Meier cumulative mortality in HCC patients *vs.* non-HCC recipients was calculated, and statistical significance of survival data were analyzed and compared using the log-rank test. Unadjusted Cox proportional hazards models were used to assess the effect of liver cancer on the risk of death and to calculate the hazard ratios (HR). Distribution of data was examined using Kolmogorov-Smirnov and Lilliefors tests, and if it was not normal, the non-parametric Mann-Whitney U test was used for comparisons between patients with and without HCC recurrence. Univariate and multivariate logistic regression analyses were used to assess risk factors for recurrence. We calculated sensitivity and specificity, as well as positive and negative predictive value of imaging examinations in HCC detection. Significance was assigned at the level of 0.05.

Results

The annual number of LTs for HCC in our institution rose from 3 in 2003 up to 30 in 2017. Since 2011 it has nearly tripled in comparison with the previous decade. During this 15 year period, 166 cases of HCC were diagnosed in the explant pathology, including 7 cases when grading of HCC was not possible due to previous locoregional procedures as radiofrequency ablation (RFA, 5) or trans-arterial chemoembolization (TACE, 2) resulting in massive necrosis within the examined nodules. In 16 cases, the pretransplant diagnosis of HCC was ruled out, as the focal lesions suspected of being HCC turned out to be dysplastic nodules. In 26 cases, the suspicion of HCC was not mentioned in the referral to the pathologist; therefore, an incidental tumor ("incidentaloma") was recognized. In older LTs (done before 2013), it was not always possible to verify whether it was a true incidentaloma due to incomplete or unreliable imaging reports.

The median follow-up in our study was 808.5 days (range, 31–5309 days). The median age of HCC patients was 58 years (IQR: 52–61 years). There was a male predominance in the group (124 males *vs.* 42 females). Clinical characteristics of the HCC group are shown in Table 1. The most frequent etiologies

Table 1. Clinicopathological characteristics of the patients (n=166).

Age (years), median & IQR, mean ±SD	58 (52–61), 56.45±7.71
Sex (n)	
Male	124
Female	42
MELD score (points), median & IQR	10 (8–24)
Underlying liver disease	
HCV	94
HBV	16
ALC	26
HBV+HCV or HCV+ALD	15
NASH	2
Others	13
Locoregional therapy (n)	7
Median follow-up (days)	808.5 (31–5309)
Death, n (%)	37 (22.8)
Early post-LT	12
Due to recurrence of HCC	14
Another reasons	11
Time to recurrence (days), median and range	440 (79–2451)
Survival after recurrence (days), median and range	276 (23–1894)

of liver cirrhosis were chronic HCV infection (94 cases) and ALD (26 cases). In 16 cases, HCC developed on top of chronic HBV infection, and in 15 cases the etiology was mixed (HBV+HCV, or ALD+HCV) (Table 1). There were 37 (22.28%) deaths in HCC patients – 12 in the early post-LT period (≤30 days), 14 due to HCC recurrence, and 11 deaths not related to the recurrent HCC (7 cardiovascular and 4 cancer other than HCC). The 5- and 10-year survival rates in HCC patients were 81.27% and 66.57%, respectively, which are inferior to the overall post-LT survival at 5 years (81.27% *vs.* 87.91%, p=0.032) and at 10 years (66.57% *vs.* 83.18%, p=0.008). The Kaplan-Meyer curves representing survival estimates at 10 years are shown in Figure 1. According to the Cox proportional hazard model, the risk of death in HCC recipients was 1.85 times higher than in non-HCC patients at 5 years after LT (HR 1.85; CI95% 0.04–0.57, p=0.022) and 2.08 times higher at 10 years (HR 2.08, CI95%: 0.12–0.61, p=0.0036). Recurrence-free survival at 5 years was 78.8% and at 10 years it was almost the same as in the whole HCC group – 66.55% (Figure 2).

To date, HCC recurrence has been noted in 16 (9.6%) patients, and most of them (14 patients, 87.5%) died. Median time to recurrence was 440 days (range, 79–2451 days). In 15 cases, HCC recurred within 5 years after LT, and late recurrence was noted in 1 case (>6 years). Recurrence was noted in 2 patients who had TACE as a locoregional bridging therapy prior to LT, but not in any of the 5 patients who underwent RFA. The median time of survival after recurrence was 276 days
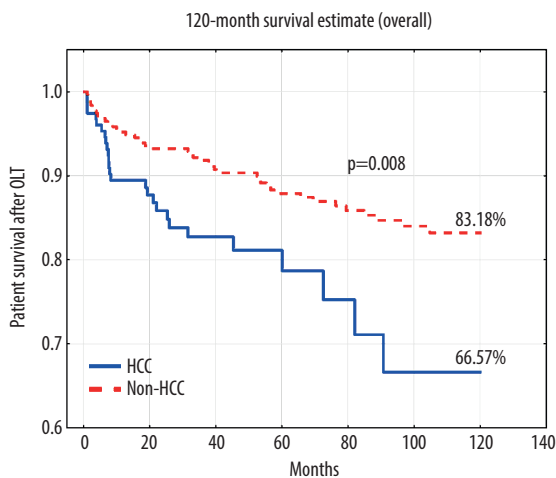
Figure 1. Kaplan-Meier curves for 120-month survival rates after liver transplantation: HCC *vs.* non-HCC patients.
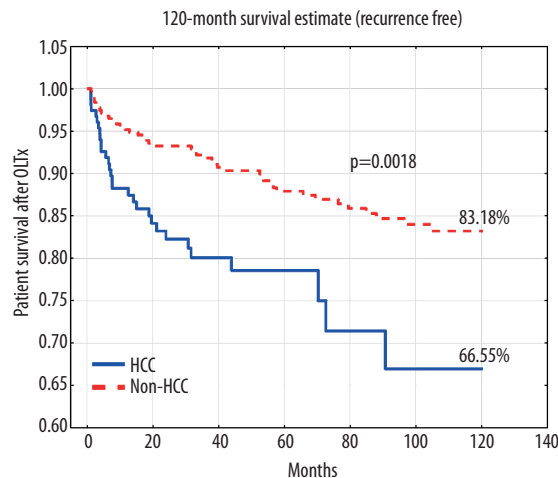

Figure 2. Kaplan-Meier curves for 120-month recurrence-free survival rates after liver transplantation: HCC *vs.* non-HCC patients.

Table 2. Comparison of patients with and without HCC recurrence after LT.

	No HCC recurrence n=150	HCC recurrence n=16	P value
Age, mean ±SD	57.17±7.14	53.6±4.79	0.012
Male sex, n(%)	102　(73.9)	12　(75)	0.946
AFP before LT, (ng/mL)	89.57	148.5	0.246
Tumor grading, median and range	2　(1–4)	3　(1–4)	0.048
Microinvasion, n	1	2	NS
Locoregional therapy before LT	5	2	NS
HCV etiology of the disease (n,%)	95　(63.3)	14　(87.5)	0.052
Waiting time (days), median and range	41　(0–971)	69　(9–322)	0.576

(range, 23–1894 days). Survival longer than 1 year after diagnosis of recurrence was only achieved in 2 patients and both received surgical therapy for recurrence. The other patients received nonsurgical therapy or supportive care. Using the Mann-Whitney U test for comparisons between groups with and without recurrence, we found that patients with recurrence were significantly younger at the time of LT (53.6±4.79 *vs.* 57.17±7.14, p=0.012, Table 2); therefore, the same parameters (sex, age at LT, waiting time, and tumor grade) were analyzed using univariate and multivariate logistic regression analysis (Table 3). Age at transplant was not a risk factor of recurrence in univariate and multivariate hazard regression analysis. Another risk factor of recurrence that has been studied is tumor grading. Using the Mann-Whitney U test, the median grading in the group with recurrence was G3 and it was

significantly higher than the median grading in the other patients, which was G2 (p=0.048, Table 2). In uni- and multivariate logistic regression analysis, grade 3 HCC increased the risk of recurrence by more than 4 times (OR 4.4 and 4.606, respectively), but it did not reach statistical significance (p=0.0742 and 0.076, respectively, Table 3). Extrahepatic metastases occurred in 10 cases (3 in lungs, 3 in suprarenal glands, 2 in bones, and 2 in hilar lymph nodes), and 1 patient is was diagnosed after a sudden rise of AFP to above 1000 ng/mL, and in 5 patients there was HCC recurrence in the grafted liver. History of HCV infection was noted in 14 cases of recurrence, and it significantly increased its risk (HR 4.05, CI95%: 0.88–18.49, p=0.052). Surprisingly, microinvasion was found by the pathologist in only 3 cases – 1 with recurrence and 2 without recurrence. The mean pretransplant AFP level differed between groups

Table 3. Univariate and multivariate logistic regression analysis of the chosen parameters between patients with and with no HCC recurrence.

Analyzed parameter	Univariate analysis				Multivariate analysis			
	P value	OR	CI −95%	CI +95%	P value	OR	CI −95%	CI +95%
Male sex	0.9252	1.059	0.321	3.493	0.422	1.925	0.389	9.537
Grading 2	0.7409	1.331	0.245	7.236	0.903	0.891	0.139	5.718
Grading 3	0.0742	4.400	0.865	22.378	0.076	4.606	0.852	24.904
Grading 4	0.50074	2.537	0.187	29.747	0.491	2.507	0.184	34.179
Age at LT	0.2112	0.963	0.908	1.022	0.185	0.954	0.889	1.023
Waiting time for LT	0.9165	1.000	0.996	1.004	0.894	1.000	0.996	1.005

Table 4. Radiological – pathological correlation of HCC among 273 liver transplant recipient (true positive=75, false positive=4, false negative=10).

	Value	95% CI
Sensitivity (75 out of 85)	88.24%	79.43–94.21
Specificity (184 out of 188)	97.87%	94.64–99.42
PPV	94.94%	87.64–98.02
NPV	94.85%	91.13–97.05

Table 5. Characteristics of HCC identified and not identified by CT/MRI.

	False negative, n=10	True positive, n=75
Size		
<20 mm	8	22
>20 mm	2	51
Number of nodules		
1	6	39
2	2	26
3	1	7
>3	1	3
Grading		
G1	3	17
G2	3	39
G3	3	15
G4	1	4

with and without recurrence, but the difference was not statistically significant (148.5 ng/mL *vs.* 89.57 ng/mL, p=0.246). These data are shown in Table 2.

In the detailed analysis of radiological-pathological correlation (within 273 LTs performed 2015–2017), in 75 cases the radiological diagnosis or suspicion of HCC was consistent with the pathological report, whereas in 4 cases HCC was not confirmed in the explanted liver. In 10 cases malignant nodules were recognized neither by CT nor by MR, and true incidentaloma was diagnosed. In our series, the sensitivity of CT/MR in HCC recognition was 88.24% (95% CI: 79.43–94.21), and specificity was 97.87% (95% CI: 94.64–99.42). PPV was almost equal to NPV (94.94% and 94.85%, respectively). These data are shown in Table 4. Among incidental tumors, in 8 cases nodules were smaller than 20 mm and they were more frequently single (6 out of 10). These lesions were described as probably benign (Li-RADS 2) or were not mentioned in the radiological report if smaller than 10 mm. Grading of incidental HCCs did not differ from grading of the other HCCs, and there were well-differentiated tumors (G1 – 3 cases) as well as poorly or undifferentiated HCCs (G3 – 3 cases, G4 – 1 case) in the group. This is shown in Table 5. Analyzing the radiological-pathological correlation of HCC for 73 patients (in 2 cases sizes were not precisely mentioned in radiological reports) showed that there is a higher accuracy in respect to the number of lesions than to

the diameter of nodules. In 42 cases, the number of lesions was identical in radiological report and in pathological report, and in 31 cases there was a difference in numbers (in 16 cases the number of lesions was higher in the explanted liver, and in 15 cases it was lower). As far as diameters are concerned, there more incompatibility than compatibility (31 *vs.* 42). In most cases (30) the size of nodules given by the pathologist was larger than that described in the imaging examination.

Discussion

The incidence of HCC is increasing, and LT is the best option of treatment in a subset of patients. The expected survival significantly improved after implementation of tumor size criteria; after 5 years it almost equals transplantation survival for non-HCC indications. Our study confirms very good 5-year survival and acceptable 10-year survival in patients who were listed for LT according to Milan criteria [12,13]. Expansion of

these criteria in our series in terms of tumor size and multifocality was found in the explanted livers in a few patients only. Recurrence rate in our series was low (< 10%). It seems to be slightly better than the recurrence of around 15%, reported elsewhere [14–16]. However, some authors consider Milan criteria too restrictive and conclude that there are patients outside Milan measurements who might benefit from transplantation as well. Therefore, there is a tendency to expand Milan criteria and to introduce new systems like the one proposed by the University of California, San Francisco group (UCSF criteria) or the Metroticket Study group (known as the up-to-seven criteria) [17,18]. One of the arguments is that in addition to size, total tumor diameter, number of HCC nodules, and microvascular invasion, there are other important prognostic factors, such as alfa-fetoprotein level, tumor differentiation, or portal vein thrombosis. Recently, 2 new scoring systems to identify patients with a low risk of post-LT HCC recurrence, who are otherwise beyond Milan criteria, were proposed. Both systems use variables that are easy to obtain before LT. The scoring system named MoRAL combines AFP >200, neutrophil-to-lymphocyte ratio, and tumor size > 3 cm, and patients with a low MoRAL score (<10) show excellent outcomes after LT, despite being outside Milan criteria [19]. Another system, named TRAIN, predicts recurrence-free survival based on the combination of radiological response to locoregional therapy, AFP, inflammatory markers, and time waiting for LT [20]. Sapisochin et al. suggested moving away from the simplistic size and number approach by proposing the Extended Toronto Criteria for advanced HCC (beyond Milan and UCSF criteria), which are based on tumor differentiation, alpha-fetoprotein level, and tumor progression while on the waiting list. In the selected group of patients (highly differentiated HCC, AFP <400 ng/mL, significant reduction in tumor burden and progression after bridging therapy) the Toronto group achieved an overall actuarial survival rate of 47% after 5 years, and it was significantly better than survival in patients who received palliative treatment [21,22].

In our study, prognostic factors strongly related to the HCC recurrence were not identified. Usually, multivariate predictors of recurrence include tumor differentiation, microvascular invasion, tumor size outside Milan criteria, longer waiting time, and AFP level. Poorer differentiation of HCC was a risk of recurrence in our study (OR 4.6), although the statistical significance of this finding was rather weak. Another risk factor of recurrence was HCV etiology of liver cirrhosis. Three patients were treated with DAAs and cleared the virus (2 before transplantation and 1 due to reinfection after surgery), but at this stage it is not possible to relate antiviral treatment to HCC development, especially because recurrence was not observed in most treated patients (another 55 subjects: 14 pretransplant, 41 post-transplant). Neither sex, age at LT, nor waiting time for LT were predictors of recurrence in our study.

Our study confirms that recurrence of HCC almost inevitably leads to the patient's death, mostly because of the metastatic nature of the recurred HCC, which limits therapeutic options. The median time of survival after recurrence is reported to be 8–18 months [13,23]. In our study it was approximately 9 months, the longest in patients in which the recurrence was treated surgically. According to Bodzin et al. [24], surgical treatment should be highly recommended for all suitable patients because it significantly improves survival in comparison with nonsurgical treatment or supportive care.

The diagnostic accuracy of imaging techniques in HCC recognition is satisfactory and has improved in recent years. In our study a total of 42 patients were either over- or underdiagnosed, but the number of inaccurate baseline diagnoses has decreased by 2-fold since 2013. Similar to the other studies, the vast majority of the misdiagnosed nodules in our series were <2 cm in size [25]. It is worth noting that after implementation of LI-RADS criteria, only 1 suspicion of HCC was not confirmed by the pathologist in the explanted liver. Of course, detection by CT and/or MRI has some limitations such as lower sensitivity in diagnosis of small lesions (<20 mm) and reflection of anatomic, but not functional, information on HCC such as location, size, and number. Additionally, the quality of MRI can be affected by breathing, cardiopulmonary disorders, and disabilities related to age; nevertheless, the combination of these methods provides excellent specificity and, in tumors greater than 20 mm in size, also a very good sensitivity, but caution is required in smaller focal lesions that cannot be easily distinguished from benign cirrhotic nodules. In such cases, biopsy of the lesion can be considered. Another option is vigilant surveillance imaging, as interval growth is the best indicator of malignancy [26].

Conclusions

In our experience with LT for HCC, an excellent long-term survival was achieved and a low recurrence rate confirms good patient selection. Correlation of the whole explant with diagnostic imaging modalities shows increasing experience and a high accuracy of CT/MRI in HCC recognition; however, results are still suboptimal for nodules smaller than 20 mm. In such cases, CT/MRI examinations should be repeated at shorter time intervals and/or liver biopsy can be considered. The risk of recurrence increases in HCV etiology of liver cirrhosis and also in higher grading of HCC. To date, we have not noticed any influence of DAAs treatment on HCC recurrence.

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