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Meta-analysis of Tumor Recurrence after Liver Transplantation for Hepatocellular Carcinoma Based on 1,198 Cases

G. C. Sotiropoulos[1], E. P. Molmenti[1], C. Lösch[2], S. Beckebaum[1], C. E. Broelsch[1], H. Lang[1]

[1]Department of General, Visceral, and Transplantation Surgery and
[2]Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, Essen, Germany

Abstract
Background: The purpose of this study was to systematically review tumor characteristics leading to recurrence of hepatocellular carcinoma (HCC) after liver transplantation (LT).
Material and Methods: A computer search of the Medline database was carried out. Tumor characteristics examined were: 1) no vascular versus vascular invasion, 2) solitary versus multifocal tumors, 3) well differentiated versus not well differentiated HCCs, 4) HCC meeting versus HCC exceeding the Milan criteria, 5) HCC ≤5cm versus HCC>5cm.
Results: Of 45 clinical studies screened, 9 fulfilled the study criteria. These studies included from 21 to 316 patients, for a total of 1198 patients. A fixed effects model was applied. A significant correlation between vascular invasion, not well differentiated HCC, tumor size >5cm, HCC exceeding the Milan criteria, and HCC recurrence post transplant was shown (common odds ratio of 8.727, 2.89, 13.32 and 4.205, respectively). Heterogeneity for the parameter solitary versus multifocal tumor was shown.
Conclusion: High risk pathology for HCC recurrence is characterized by not well differentiated tumors and by HCCs that exceed the Milan criteria. A clinical application of these data may be a scoring system which includes the tumor grading in the evaluation and listing of HCC patients to LT.

Key words: Liver transplantation; hepatocellular carcinoma; tumor recurrence; Milan criteria; tumor grading; vascular invasion; tumor staging

Abbreviations: CI = Confidence interval, HCC = hepatocellular carcinoma, LT = liver transplantation; OR = Odds Ratio

Introduction

Recurrence of hepatocellular carcinoma (HCC) after liver transplantation for HCC in the setting of liver cirrhosis is a frequent occurrence. Although some series report on prognostic factors resulting in higher rates of tumor recurrence [1-5], no systematic analysis exists until now in the published literature. The goal of our study was to systematically review tumor characteristics leading to HCC recurrence after liver transplantation (LT).

Material and Methods

Literature Search

A computer search of the Medline database for the years 1985 to 2005 was carried out using the MeSH headings: "hepatocellular carcinoma", "liver transplantation", "tumor recurrence", "tumor staging". The combined set was limited to English-language publications on human subjects. All titles and abstracts were scanned, and appropriate citations reviewed. Consultation with a content expert and a manual search of the bibliographies of relevant papers was also carried out to identify trials for possible inclusion.

Inclusion Criteria

Inclusion criteria for this analysis consisted of clinical studies of any size reporting on tumor recurrence after liver transplantation for HCC, under the prerequisite that adequate data about recurrence rate according to the examined tumor parameters listed bellow were available.

Data Collection

Critical appraisal and data extraction were conducted independently by the authors, and discrepancies resolved by consensus. In instances of multiple studies from a single institution, the most recent or more informative publication was chosen.

Analyses

Common analyses – if feasible – of results across studies were carried out for the presence of tumor recurrence. The following tumor characteristics were examined, according to pathological findings in the explanted liver: 1) no vascular versus vascular invasion, 2) solitary versus multifocal tumors, 3) well differentiated versus not well differentiated tumors, 4) tumors

meeting the Milan criteria (single tumor ≤5cm, or 2-3 tumors none of them >3cm, no vascular invasion) versus tumors exceeding them, 5) tumors ≤5cm versus tumors>5cm. Although the parameters of vascular invasion and tumor >5cm are somewhat included in the Milan criteria, we examined them independently since there were analyses in the literature that considered them as such prior to 1996, the year in which the Milan criteria were first proposed. Data analyses were conducted using Review Manager 3.0 (The Cochrane Collaboration, Software Update, Oxford). A fixed effects model was applied. Statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC) and StatXact (Cytel Software Corp., Cambridge, MA). The summary statistic used was the odds ratio, which represents the odds of an event (tumor recurrence) occurring in the group of patients with "unfavourable pathology" divided by odds of the control group. Odds ratios >1 display the higher risk in the group with "unfavourable pathology" (i.e. vascular invasion, multifocal HCC, not well differentiated HCC, beyond the Milan criteria, HCC >5cm, respectively), and the point estimate of the odds ratio is considered statistically significant at the alpha = 0.05 level only if the 95% confidence interval (95% CI) does not include 1. Any value lying within the 95% CI is considered to be consistent with the data, in the sense that it cannot be rejected at the 0.05 level. Because the sample size was relatively small in some studies, exact statistical methods were applied [6]. The exact confidence interval for the odds ratio of a single study was computed according to Cox [7]. Homogeneity of the odds ratios across the different studies was tested using the exact homogeneity test [8]. If this test was not significant, no evidence for heterogeneity was considered, i.e. for systematic differences between the studies. In that case a confidence interval for the common odds ratio was calculated [9].

Results

Of 45 retrospective clinical studies screened [1-5, 10-49], 9 providing special information about tumor recurrence post LT according to the examined tumor parameters described in Patients and Methods were identified [1, 5, 10-16]. The studies dated from 1989 to 2004 and ranged from 21 to 316 patients, yielding a total of 1198 patients. Information on HCC recurrence after LT was available for 1065 recipients. On review of the data extraction, there was 100% agreement among the authors who performed the literature review. Of the two studies from the Mount Sinai Medical Center in New York [1, 13], information on vascular invasion and tumor grading was obtained from the larger/most recent series (Roayaie et al, 2004), while data for recurrences according to number of tumor lesions, tumor size, and Milan criteria, was procured from the smaller/initial one (Gondolesi et al, 2002) since such information was not available in the former series. Although hospital mortality was for the most part not considered in the recurrence analysis [5, 10, 14-16], in some instances it was not considered at all [1, 12], or was included in the recurrence analysis [11, 13].

1. HCC-Recurrence according to the Presence of Vascular Invasion in the Explanted Liver (No Vascular versus Vascular Invasion)

Six studies were identified [1, 5, 11-13, 16], resulting in a total of 483 patients (Table 1). There were 19 recurrences among 290 patients with no vascular invasion (6.5%). On the other hand, 65 recurrences were identified among 193 patients presenting vascular invasion in the liver explants (33.7%). The study of Mazzaferro et al., having no control group, was not included in the meta-analysis. The test of heterogeneity revealed no significant differences between the studies (exact p = 0.2937), permitting for a common analysis of the data using a fixed effects model. The study-specific as well as the common odds ratios for the outcomes are displayed in Figure 1. The width of the horizontal bars reflects the 95% CI expressed on a logarithmic scale. The estimate of size effect (odds ratio of vascular infiltration vs. the control group) on recurrence was 8.727 (exact estimation of common odds ratio, 95% CI 4.557 to 17.72), showing a significant correlation between vascular invasion and recurrence of HCC.

2. HCC-Recurrence according to Number of HCC Lesions in the Explanted Liver (Solitary versus Multifocal Tumors)

Five studies were identified [5, 11-14], resulting in a total of 226 patients (Table 2). There were 10 recurrences among 107 patients with solitary HCCs (9.3%). On the other hand, 17 recurrences were identified among 119 patients with multifocal HCCs in their liver explants (14.3%). The study-specific odds ratios for the outcomes are displayed in Figure 2. The point estimates of odds ratio for recurrence ranged from 0.0769 to infinity, so that no common trend could be seen. Moreover the test of heterogeneity revealed significant differences among the studies (exact p = 0.0428), impeding the conduction of a common analysis of the data by means of a fixed effects model.

3. HCC-Recurrence according to Tumor Grading in the Explanted Liver (Well Differentiated versus not Well Differentiated Tumors)

Three studies were identified [1, 12, 15], resulting in a total of 630 patients (Table 3). There were overall 24 recurrences among 256 patients with well differentiated HCCs (9.4%). On the other hand, 76 recurrences were identified among 374 patients with not well differentiated HCCs in the liver explants (20.3%). The test of heterogeneity revealed no significant differences among the studies (exact p = 1.00), permitting a common analysis of the data using a fixed effects model. The study-specific as well as the common odds ratios for the outcomes are displayed in Figure 3. Meta-analysis resulted in a common odds ratio of 2.89 (exact estimation of common odds ratio, 95% CI 1.708 to 5.036), showing a significant correlation between not well differentiated tumors and recurrence of HCC.

Table 1. Characteristics of clinical studies evaluating tumor recurrence after LT for HCC according to vascular invasion.

	Gondolesi	Herrero	Mazzaferro	Moreno	Roayaie	Ojogho	Total
Year	2002	2001	1996	1995	2004	1996	
Total number of subjects	27	47	48	31	311	22	483
Study group (no vascular invasion)	11	38	48	19	162	15	290
Reference group (vascular invasion)	16	9	0	12	149	7	193
Recurrences in study group	0	2	4	3	7	3	19
Recurrences in reference group	2	4	0	7	50	2	65
p-value in chi-square test	0.512	0.027	1.000	0.144	<0.001	1.000	<0.001

Table 2. Characteristics of clinical studies evaluating tumor recurrence after LT for HCC according to number of HCC lesions.

	Gondolesi	Herrero	Mazzaferro	Ojogho	Vivarelli	Total
Year	2002	2001	1996	1996	2002	
Total number of subjects	27	47	48	22	82	226
Study group (solitary HCC)	11	21	25	8	42	107
Reference group (multifocal HCC)	16	26	23	14	40	119
Recurrences in study group	0	1	1	4	4	10
Recurrences in reference group	2	5	3	1	6	17
p-value in chi-square test	0.512	0.382	0.610	0.139	0.739	0.417

Table 3. Characteristics of clinical studies evaluating tumor recurrence after LT for HCC according to tumor grading.

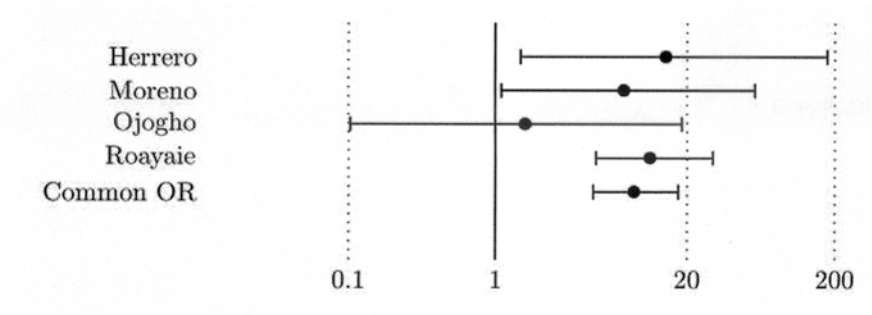
	Herrero	Roayaie	Todo	Total
Year	2001	2004	2004	
Total number of subjects	40	311	279	630
Study group (well differentiated tumor)	6	165	85	256
Reference group (not well differentiated tumor)	34	146	194	374
Recurrences in study group	0	19	5	24
Recurrences in reference group	6	38	32	76
p-value in chi-square test	0.579	0.010	0.051	0.002

Table 4. Characteristics of clinical studies evaluating tumor recurrence after LT for HCC according to the Milan criteria.

	Gondolesi	Mazzaferro	Vivarelli	Total
Year	2002	1996	2002	
Total number of subjects	27	48	82	154
Study group (within Milan criteria)	6	35	63	104
Reference group (exceeding Milan criteria)	21	13	19	50
Recurrences in study group	0	1	6	7
Recurrences in reference group	2	3	4	9
p-value in chi-square test	1.000	0.081	0.261	0.104

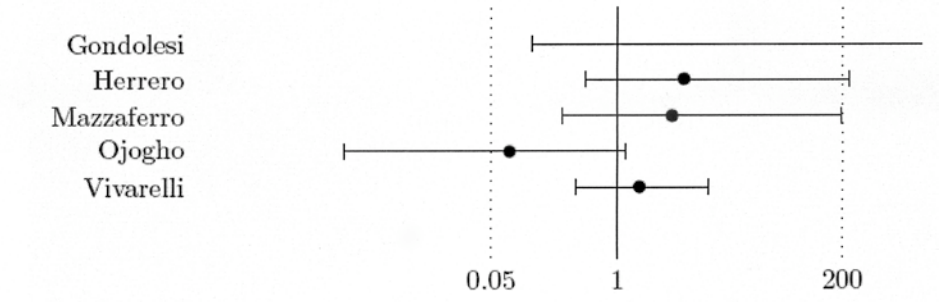
Table 5. Characteristics of clinical studies evaluating tumor recurrence after LT for HCC according to tumor size.

	Gondolesi	Michel	Ojogho	Total
Year	2002	1995	1996	
Total number of subjects	27	13	22	62
Study group (tumor ≤5cm)	15	7	11	33
Reference group (tumor >5cm)	12	6	11	29
Recurrences in study group	0	0	1	1
Recurrences in reference group	2	3	4	9
p-value in chi-square test	0.224	0.212	0.342	0.015



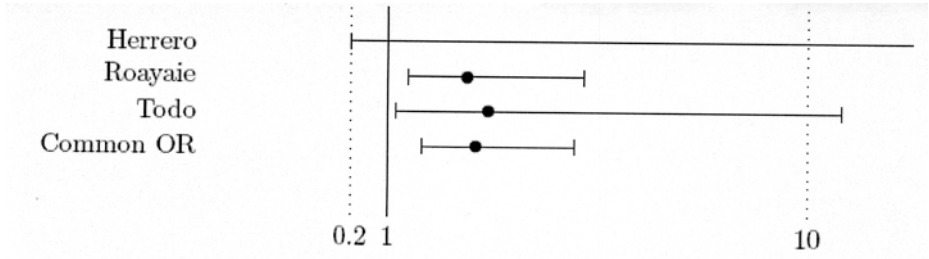
Study	OR	lower bound of 95% CI	upper bound of 95% CI
Common OR	8.727	4.557	17.72
Herrero	14.4	1.468	180.8
Moreno	7.467	1.085	58.47
Ojogho	1.6	0.1012	18.77
Roayaie	11.18	4.758	30.2

Fig. 1. Odds ratios (OR) and confidence interval (CI) of clinical studies evaluating tumor recurrence after LT for HCC according to vascular invasion. Meta-analysis resulted in a common odds ratio of 8.727.



Study	OR	lower bound of 95% CI	upper bound of 95% CI
Gondolesi	infinity	0.1288	infinity
Herrero	4.762	0.4589	236.3
Mazzaferro	3.6	0.2586	196.7
Ojogho	0.0769	0.0015	1.216
Vivarelli	1.676	0.3598	8.736

Fig. 2. Odds ratios and confidence interval (CI) of clinical studies evaluating tumor recurrence after LT for HCC according to number of tumors. Due to heterogeneity of the studies, no common odds ratio could be calculated.

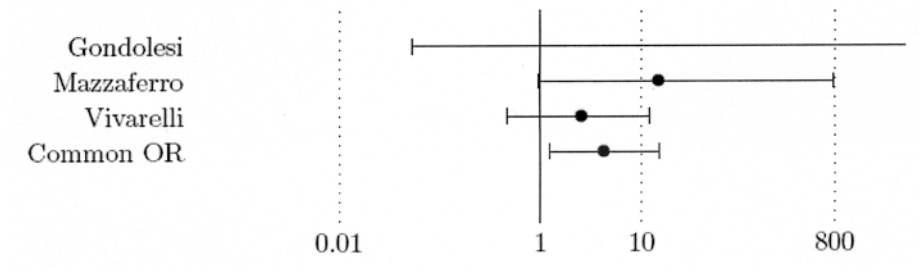


Study	OR	lower bound of 95% CI	upper bound of 95% CI
Common OR	2.89	1.708	5.036
Herrero	infinity	0.1905	infinity
Roayaie	2.704	1.425	5.241
Todo	3.16	1.157	10.75

Fig. 3. Odds ratios and confidence interval (CI) of clinical studies evaluating tumor recurrence after LT for HCC according to tumor grading. Meta-analysis resulted in a common odds ratio of 2.89.

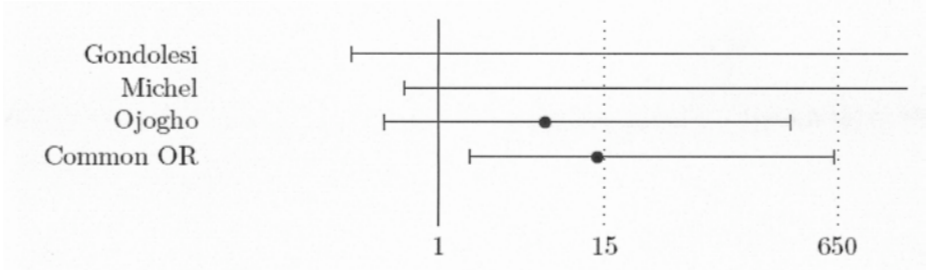
4. HCC-Recurrence according to Pathological Milan Criteria (Tumors Meeting versus Tumors Exceeding the Milan Criteria)

Three studies were identified [11, 13-14] resulting in a total of 154 patients (Table 4). There were overall 7 recurrences among 104 patients meeting the Milan criteria (7.2%). On the other hand, 9 recurrences were identified among 50 patients exceeding these criteria in the liver explants (18%). The test of heterogeneity revealed no significant differences among the studies (exact p = 0.5761), permitting a common analysis of the data using a fixed effects model. The study-specific as well as the common odds ratios for the outcomes are displayed in Figure 4. The estimate of size effect (odds ratio for patients beyond the Milan criteria vs. the control group) on recurrence was 4.205 (exact estimation of common odds ratio, 95% CI 1.188 to 15.33), showing a significant correlation between HCC beyond the Milan criteria and tumor recurrence.



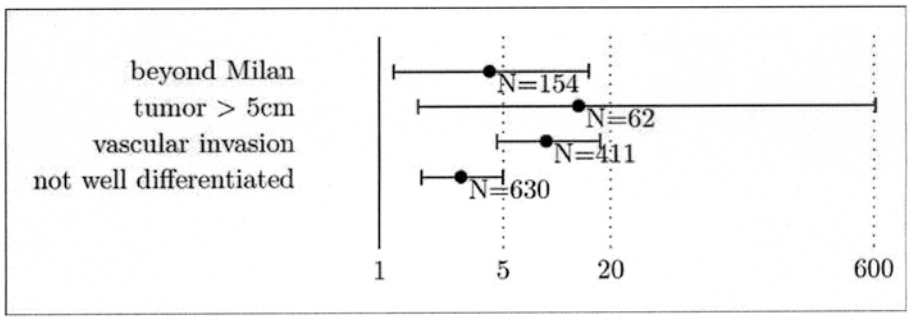
Study	OR	lower bound of 95% CI	upper bound of 95% CI
Common OR	4.205	1.188	15.33
Gondolesi	infinity	0.0512	infinity
Mazzaferro	14.57	0.9255	786.3
Vivarelli	2.533	0.4586	12.2

Fig. 4. Odds ratios and confidence interval (CI) of clinical studies evaluating tumor recurrence after LT for HCC according to the Milan criteria. Meta-analysis resulted in a common odds ratio of 4.205.



Study	OR	lower bound of 95% CI	upper bound of 95% CI
Common OR	13.32	1.634	622.1
Gondolesi	infinity	0.2399	infinity
Michel	infinity	0.5631	infinity
Ojogho	5.714	0.4057	308.9

Fig. 5. Odds ratios and confidence interval (CI) of clinical studies evaluating tumor recurrence after LT for HCC according to tumor size. Meta-analysis resulted in a common odds ratio of 13.32. Due to the small sample size of the corresponding studies (overall n = 62) there is a greater uncertainty of the common OR. Two of the ORs are infinity, resulting in a very high common OR.



Parameter	COR	lower bound of 95% CI	upper bound of 95% CI	p-value	N
Beyond Milan	4.205	1.188	15.33	0.024	154
Tumor>5cm	13.32	1.634	622.1	0.0045	62
Vascular invasion	8.727	4.557	17.72	<0.0001	411
Not well differentiated HCC	2.89	1.708	5.036	<0.0001	630

Fig. 6. *Common OR and confidence interval (CI) of clinical* studies evaluating tumor recurrence after LT for HCC according to the parameters "Milan criteria", "tumor size", "vascular invasion" and "grading". For the parameter "solitary/multifocal lesions" no Common OR was calculated because the corresponding studies lacked homogeneity. Exact p-value was calculated for Common OR = 1. In the cases of bigger sample size meta-analysis (for example "vascular invasion" n = 411, "tumor differentiation" n = 630), the statistical effect was more significant.

5. HCC-Recurrence according to Tumor Size in the Explanted Liver (Tumors ≤5cm versus Tumors >5cm in Diameter)

Three studies were identified [5, 10, 13], resulting in a total of 62 patients (Table 5). There was 1 recurrence among 33 patients with HCCs ≤5cm (3%). On the other hand, 9 recurrences were identified among 29 patients exceeding these criteria in the liver explants (31%). The test of heterogeneity revealed no significant differences among the studies (exact p = 1.00), permitting a common analysis of the data using a fixed effects model. The study-specific as well as the common odds ratios for the outcomes are displayed in Figure 5. Meta analysis resulted in a common odds ratio of 13.32 (exact estimation of common odds ratio, 95% CI 1.634 to 622.1), showing a significant correlation between HCC >5 cm and tumor recurrence.

Discussion

The largest series report a recurrence of HCC after LT of 11% - 18% (1, 31). Although the role of post transplant immunosuppression is still unclear [2, 50], the vast majority of recurrences seems to be related to metastatic disease that either was present but not iden-

tifiable prior to transplantation or was released during the transplant procedure. Recurrence of HCC after transplantation results in significantly diminished survival [1]. Patients whose explant tumor characteristics are within the currently accepted criteria for transplantation have a recurrence rate of about 8% [51]. Patients whose tumors lie outside of such criteria have a 50% incidence of recurrence, suggesting that characteristics of the pathological evaluation of the resected specimen should be used to stratify screening [51]. A multivariate analysis of survival at the time of recurrence showed that the absence of bone metastasis, a time lapse of more than 12 months from transplantation to recurrence, and surgical treatment of the recurrence were independently associated with significantly longer survival [1]. Median time to recurrence was 12.3 months in this study, with approximately 75% of cases occurring within 2 years [1]. Patients who underwent surgical treatment of their recurrence had significantly longer survival than those who did not, with 47% alive 5 years after transplantation [1]. These results (high rates of recurrence in patients with high risk pathology, relatively early HCC recurrence post transplant, significantly longer survival for patients undergoing surgical therapy for recurrences) introduced a discussion about screening strategies for recurrence of HCC after LT [51]. Roberts in his editorial in the periodical "Liver Transplantation" proposed that screening for recurrence should be limited only to patients with tumors whose explant pathology is outside the Milan criteria in order to be cost effective [51].

With the increasing number of hepatitis C induced HCC [52] and the corresponding increase in LT for HCC on one side, and the efforts to "expand" the Milan criteria in several centers performing live donor LT on the other side [13, 17, 53], an increased number of patients with post-transplant HCC recurrence is expected. Since no systematic review of the literature about post transplant HCC recurrence existed until now, we tried to systematically determine "high risk" tumor characteristics that could lead to an early HCC recurrence in order to better identify patients at risk and optimize tumor surveillance. Surprisingly, after decades of studies reporting on liver transplantation for HCC, little information is available on HCC recurrence after LT. Furthermore, there are only a few reports providing this specific information in regard to the application of Milan criteria, an issue with important "political" interest. This conclusion reflects on the facts that most reports have short median post transplant follow ups and that when information about HCC recurrence is available, it is presented briefly and not in a way that could be used in a meta-analysis.

Our systematic review of the literature and meta-analysis of 45 clinical studies on HCC recurrence after LT for HCC showed that the parameters vascular invasion, not well differentiated HCC, tumor size >5cm, and HCC exceeding the Milan criteria constitute significant negative prognostic factors for post-transplant recurrences (common odds ratio by 8.727, 2.89, 13.32 and 4.205 for the above mentioned parameters, respectively, Fig. 6). As demonstrated in Figure 6, the effect was statistically more significant for the parameters "vascular invasion" and "not well differentiated HCC", which represent the higher-volume meta-analyses of the present study (411 and 630 patients reviewed, respectively). For the parameter solitary versus multifocal HCC, no homogeneity of the studies was provided, preventing us from calculating a common odds ratio. Given that the parameters tumor size>5cm and presence of vascular invasion are now nearly automatically considered as "exceeding" the Milan criteria, we could summarize the results of our meta-analysis by reporting that high risk pathology for HCC recurrence is characterized by tumors beyond the Milan criteria and by HCCs not well differentiated. Potential clinical applications of these data could serve to optimize patient selection, including tumor grading in the evaluation/listing criteria, as well as to better survey for early, eventually surgically treatable recurrence.

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Address for correspondence:
Dr. Georgios C. Sotiropoulos, MD
Department of General, Visceral and Transplantation Surgery
University Hospital Essen,
Hufelandstr. 55
45122 Essen
Germany
Tel.: +49-201-723-1102
Fax: +49-201-723-1142
e-mail: Georgios.sotiropoulos@uni-essen.de