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Liver Resection or Combined Chemoembolization and Radiofrequency Ablation Improve Survival in Patients with Hepatocellular Carcinoma

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Key Words
Vienna survival model for hepatocellular carcinoma · Long-term follow-up · Liver resection · Non-surgical minimally invasive treatment

Abstract
Background/Aims: To evaluate the long-term outcome of surgical and non-surgical local treatments of patients with hepatocellular carcinoma (HCC). ***Methods:*** We stratified a cohort of 278 HCC patients using six independent predictors of survival according to the Vienna survival model for HCC (VISUM-HCC). ***Results:*** Prior to therapy, 224 HCC patients presented with VISUM stage 1 (median survival 18 months) while 29 patients were classified as VISUM stage 2 (median survival 4 months) and 25 patients as VISUM stage 3 (median survival 3 months). A highly significant ($p < 0.001$) improved survival time was observed in VISUM stage 1 patients treated with liver resection (n = 52; median survival 37 months) or chemoembolization (TACE) and subsequent radiofrequency ablation (RFA) (n = 44; median survival 45 months) as compared to patients receiving chemoembolization alone (n = 107; median survival 13 months) or patients treated by tamoxifen only (n = 21; median survival 6 months). Chemoembolization alone significantly ($p \leq 0.004$) improved survival time in VISUM stage 1–2 patients but not ($p = 0.341$) in VISUM stage 3 patients in comparison to those treated by tamoxifen. ***Conclusion:*** Both liver resection or combined chemoembolization and RFA improve markedly the survival of patients with HCC.

T.H. and S.D. contributed equally to this study. Parts of this study have been included in S.D.'s MD thesis.

Hepatocellular carcinoma (HCC) is one of the most frequent malignancies and accounts for as many as 1 million deaths annually worldwide [1–4]. Most patients with HCC have two diseases – chronic liver disease and HCC – and complex interactions between the two have

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Table 1. Kind of treatment and median survival time in 278 patients with HCC according to VISUM stage

	VISUM stage		
	1	2	3
Liver resection	52	2	0
TACE + RFA	44	2	0
TACE	107	16	12
Tamoxifen	21	9	13
Total	224	29	25
Median survival time, months	18	4	3

major implications for diagnosis and prognosis as well as the management of HCC.

The clinical course of patients with HCC is determined by both liver function and the extent of HCC. Therefore, after surgical treatment, patients with HCC and liver cirrhosis have a less favorable prognosis than those without [5]. Until one decade ago it was generally accepted that surgical resection and liver transplantation are the only definitive treatments for patients with HCC [6, 7]. However, non-surgical HCC treatments such as ethanol injection, transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) have been successfully used as an alternative in patients with HCC without surgical options [8–30]. Only recently, the combination of TACE with subsequent RFA was proposed with a potential to eradicate HCCs up to 5 cm in diameter completely after one treatment session [31].

Up to now this kind of treatment has not been compared to liver resection (LR) or chemoembolization alone in HCC patients. This prompted us to study the long-term outcome of patients with HCC in respect to these different treatments in rather homogenous cohorts of HCC patients stratified by a newly constructed Cox proportional model (Vienna survival model for HCC = VISUM-HCC) [32].

Patients and Methods

Our retrospective study included 278 HCC patients (234 males and 44 females) who were diagnosed and staged in the Department of Medicine II, Klinikum Grosshadern, University of Munich, from 1995 to 2006. Patients with early HCC (single nodule <5 cm or three nodules <3 cm each) and impaired liver function who were considered for orthotopic liver transplantation were not evaluated in this investigation.

To address the problem of selection bias we stratified the cohort of 278 HCC patients using six independent predictors of survival. These included bilirubin (>2 mg/dl), portal vein thrombosis, prothrombin time (<70%), α-fetoprotein (AFP; >125 kU/l), tumor mass >50% and enlarged lymph nodes according to VISUM-HCC.

Prior to therapy, 224 HCC patients presented with VISUM stage 1 (0–2 points) while 29 patients were classified as VISUM stage 2 (3 points) and 25 patients as VISUM stage 3 (4–6 points). The kind of treatment and survival time in relation to VISUM stage is illustrated in table 1.

We selected for LR mainly those patients who had solitary HCC and normal liver function as documented by a Child-Turcotte-Pugh (CTP) score between 5 and 6. Patients who did not fit into the surgical criteria either for resection or liver transplantation were considered for combined treatment with chemoembolization and RFA, chemoembolization alone, or systemic therapy. Disease extension was assessed using ultrasound, computed tomography (CT) and magnetic resonance tomography (MRI).

Diagnosis of HCC was confirmed via needle biopsy or via radiological criteria (two coincident imaging techniques) or combined criteria (one imaging technique associated with elevated AFP levels) according to Barcelona EASL Conference 2000 [33]. Informed consent in writing was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutional review committee.

Treatment Procedures

Liver Resection

LR was performed according to international surgical standards for hepatic surgery. Pringles maneuver to reduce blood loss was used in most patients. Extension of resection included wedge resections, segmental resections, bisegmental resections, as well as right and left hepatectomy, respectively.

Radiofrequency Ablation

Patient selection for both RFA and chemoembolization followed a consensus decision of an interdisciplinary tumor board considering tumor size, number of tumor nodules, localization, vascularization, and patients' general condition. Thus, tumors with a size of up to 5 cm in diameter and not more than 5 nodules were considered suitable for combined treatment with TACE and RFA.

Since 1999, RFA has usually been performed within 1 week after chemoembolization as a minimally invasive, percutaneous procedure under conscious analgo-sedation followed by a periinterventional, single-shot, broad-spectrum antibiotic.

All RFA procedures were performed under CT-fluoroscopic guidance on a four-slice multidetector scanner (Somatom Sensation 4, Siemens, Erlangen, Germany) with/without a virtual guiding system (Ultraguide®). After defining the needle-entry site on the skin and giving local anesthesia at the puncture site, the RFA electrode (RITA, Starburst XL 5 cm, RITA Medical, Mountain View, Calif., USA; LeVeen 4 and 5 cm, Boston Scientific, Munich, Germany; Cool-tip cluster, Tyco Healthcare, Neustadt, Germany) was inserted and the progress of the electrode to the target lesion controlled by CT-fluoroscopy. The electrode size and placement was chosen in a way that the target lesion was covered completely by the expected ablation volume including a safety margin of 5–10

mm to destroy also potential microscopic satellite tumor nests in the surrounding lesion [28, 34].

Due to the tumor sizes of up to 5 cm, we applied ablation protocols resulting in delivered energy of at least 100 kJ per tumor. At the end of the procedure, a contrast-enhanced scan was performed with the electrode still in place to document that the tumor was fully covered by the ablation volume and to check for potential complications. If an incomplete ablation was suspected an immediate subsequent ablation cycle was added. In cases of 'critical' tumor localization, specific precautions were taken such as air dissection of adjacent bowel loops or of the gallbladder to avoid secondary thermal damage.

The electrodes were removed under track ablation to avoid bleeding from the needle track and potential tumor cell seeding.

Follow-up studies after TACE and RFA were performed by CT or MRI after 6 weeks, then every 3 months in the first year, every 6 months in the second year, and then every year. Dependent on localization and extent of a tumor recurrence, the initial kind of treatment was repeated or a chemoembolization alone was performed. A mean number of 1.5 for RFA and 4.2 for TACE was applied in all of these patients.

Transarterial Chemoembolization

Patients not suitable for surgery or combined treatment with TACE and RFA were considered for chemoembolization alone. They constitute our study's largest group which contains patients with more than 5 tumor nodules up to 8 cm in diameter. Patients with multifocal large (>8 cm tumor nodules) and diffuse growing tumors were not included for TACE.

All TACE procedures were performed under angiographic control (Polystar and Axiom Artis, Siemens, Germany) and under local anesthesia. After inserting a 4-Fr pigtail catheter into the femoral artery via a microincision in the groin, a pan-viscerography was performed to detect potential aberrant or additional hepatic and potentially tumor-feeding arteries. After identifying the tumor-feeding arteries, a 4-Fr catheter (e.g. cobra configuration) for selective use or a superselective microcatheter, which could be placed through the primary 4-Fr catheter, were directed as close as possible to the tumor(s)-feeding vessels. The embolizing moiety was prepared by extensive mixing between two syringes (typically 3–5 ml Lipiodol, microparticles of 150–500 μm (e.g. Contour SE®, Boston Scientific, Ratingen, Germany) and farmorubicin (1 mg/kg b.w.). The embolizing agents were then injected slowly under fluoroscopic control until stasis within the tumor vessels occurred.

One day after the procedure a baseline CT was performed to document the storage of the embolizing agents within the tumor. Follow-up studies by triphasic (native and arterial and portal venous) contrast-enhanced CT were performed 6–12 weeks after the initial procedure and then every 3 months. A new TACE was performed if there were signs of 'de-storage' with revascularization of the treated tumor or if new tumors were detected. A mean number of 5.0 chemoembolizations was applied in all of these patients .

Systemic Therapy

Forty-three HCC patients without options of the above treatments received 20–40 mg tamoxifen as a single dose daily up to 24 months. Tamoxifen treatment of HCC patients was used until 2002 in our clinic. Since multiple randomized trials have shown that tamoxifen does not prolong survival of patients with HCC [28], this treatment appeared no longer justified. However, we used these patients as a control group reflecting most likely the natural course of the disease.

Follow-Up and Statistical Analysis

Survival was set as the primary endpoint of the study. Follow-up every 3–6 months was computed as starting from the beginning of treatment and was maintained until death or the last visit before March 2006. Patients received clinical examination, blood analysis including AFP and imaging techniques (ultrasound, spiral CT or MRI, alternatively). Upon detection of failure or recurrence, patients were considered for new treatment sessions.

Probability curves obtained via the Kaplan-Meier method were compared using the log-rank test, and for group comparisons the χ^2 and Kruskal-Wallis rank sum test for non-parametric values were performed.

Calculations were done with SPSS package (SPSS Inc., Chicago, Ill., USA) and the level of significance was set at $p < 0.05$.

Results

Table 2 depicts the characteristics of the four subgroups of the 224 VISUM stage 1 HCC patients. No significant difference between the four groups was obtained concerning VISUM score, AFP, presence of portal vein thrombosis or enlarged lymph nodes. However, prior to therapy, bilirubin levels were significantly lower ($p < 0.001$) and prothrombin times (%) were significantly higher ($p < 0.001$) in surgical patients compared to patients treated with TACE and RFA. In contrast, patients selected for combined treatment with chemoembolization and RFA had a significantly lower tumor size than surgical patients ($p < 0.001$) or patients treated with chemoembolization ($p < 0.001$) or tamoxifen alone ($p < 0.001$). Furthermore, table 2 illustrates survival time (median and range) in the 224 patients with HCC (VISUM stage 1) and local treatment or systemic therapy. Statistical analysis showed a longer survival time in the subgroup of patients treated with LR or chemoembolization and RFA compared to patients treated with chemoembolization alone ($p < 0.001$) or of all groups compared to systemic therapy ($p < 0.003$). Interestingly, median survival was similar (37 vs. 45 months) in HCC patients treated by LR or the combination of chemoembolization and RFA.

Kaplan-Meier plots of the four groups of HCC patients (VISUM stage 1) are illustrated in figure 1 and again show a marked survival benefit of HCC patients treated by LR or chemoembolization combined with RFA as compared to patients treated with chemoembolization or

Table 2. Characteristics of 224 patients with HCC (VISUM stage 1) prior to local treatment or systemic therapy

Variables	Liver resection (n = 52)	TACE + RFA (n = 44)	TACE (n = 107)	Tamoxifen (n = 21)
Age	61.9 ± 8.9	65.3 ± 8.3	64.6 ± 10.0	65.2 ± 11.4
Males/females	42/10	37/7	89/18	18/3
Etiology				
HCV	14	11	22	7
HBV	6	5	8	5
Alcohol	11	11	28	5
Other	21	16	41	4
Mixed	0	1	8	0
VISUM score				
0	18	18	21	4
1	18	16	39	6
2	16	10	47	11
Bilirubin, mg/dl	1.0 ± 0.6	1.7 ± 1.1	1.5 ± 1.1	1.8 ± 2.3
Bilirubin, mg/dl				
≤2	49	34	88	18
>2	3	10	19	3
Prothrombin time, %	81.4 ± 13.5	74.5 ± 10.0	76.6 ± 13.9	76.9 ± 12.8
Prothrombin time, %				
>70	46	29	78	16
≤70	6	15	29	5
AFP, kU/l				
≤125	36	37	78	14
>125	16	7	29	7
Portal vein thrombosis				
Yes	2	1	6	2
No	50	43	101	19
Enlarged lymph nodes				
Yes	9	4	16	1
No	43	40	91	20
Tumor size, %				
≤50	37	44	73	11
>50	15	0	34	10
Survival time				
Months	37	45	13	6
Median/range	<1–96	2–77	2–63	<1–31

tamoxifen alone. Table 3 illustrates characteristics and survival time of 50 VISUM stage 2–3 HCC patients.

Comparing 28 patients after chemoembolization to 22 patients treated by tamoxifen alone, no significant difference between the two treatment groups was obtained in regard to bilirubin, prothrombin time and AFP. However, patients treated with tamoxifen showed a higher presence of portal vein thrombosis and tumor size appeared to be larger compared to those who received chemoembolization. Similar as found in VISUM stage 1 patients, chemoembolization improved the survival (p = 0.022) in VISUM stage 2–3 patients in comparison to those treated with tamoxifen alone. However, this overall difference mainly reflected the efficiency of therapy on survival after chemoembolization in VISUM stage 2 patients (fig. 2a) while chemoembolization did not significantly improve survival in VISUM stage 3 patients when compared to treatment with tamoxifen (fig. 2b).

Discussion

The management of HCC has improved in recent years. However, all kinds of HCC treatment have only a limited impact on outcome since most patients with HCC suffer from two diseases – chronic liver disease, usually at the stage of cirrhosis, and HCC [35]. Thus, besides the extent of the HCC, the grade of liver dysfunction affects

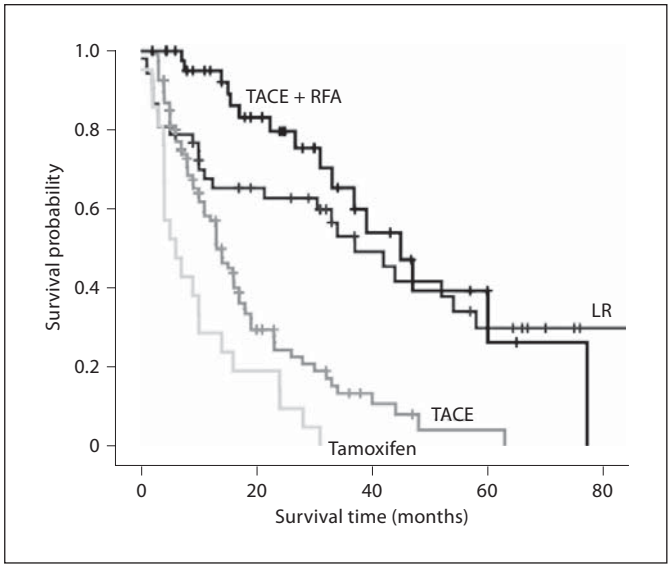

Fig. 1. Survival rates determined by Kaplan-Meier of HCC patients (VISUM stage 1) treated by liver resection (LR) (n = 52), combined TACE and RFA (n = 44), TACE alone (n = 107) or tamoxifen (n = 21). Statistical evaluation by log-rank test showed an improved survival of patients treated by LR compared to TACE ($p < 0.001$) and tamoxifen ($p < 0.001$); of patients treated by TACE and RFA compared to TACE alone ($p < 0.001$) or tamoxifen ($p < 0.001$), and of patients treated by TACE alone to tamoxifen ($p < 0.003$).

Table 3. Characteristics of 50 patients with HCC (VISUM stage 2–3) prior to chemoembolization or systemic therapy

Variables	TACE (n = 28)	Tamoxifen (n = 22)
Age	58.9 ± 9.4	62.5 ± 9.3
Males/females	25/3	19/3
Etiology		
HCV	5	5
HBV	3	3
Alcohol	8	10
Other	10	4
Mixed	2	0
VISUM score		
3	16	9
4	10	9
5	2	3
6	0	1
Bilirubin, mg/dl	3.0 ± 1.9	7.1 ± 8.5
Bilirubin, mg/dl		
≤2	7	5
>2	21	17
Prothrombin time, %	65.0 ± 12.6	67.3 ± 9.1
Prothrombin time, %		
>70	7	7
≤70	21	15
AFP, kU/l		
≤125	7	4
>125	21	18
Portal vein thrombosis		
Yes	4	11
No	24	11
Enlarged lymph nodes		
Yes	12	3
No	16	19
Tumor size, %		
≤50	9	2
>50	19	20
Survival time		
Months	5.9	2.0
Median/range	<1–26	<1–55

the prognosis of HCC patients. Therefore, most prognostic scores include parameters of liver function.

An independent evaluation of prognostic scores in a Central European cohort of 120 patients with HCC has been presented recently by Rabe et al. [36]. CTP score, Okuda score, VISUM-HCC score, Chevret score, Barcelona clinic liver cancer classification (BCLC), and cancer of the liver Italian programme score (CLIP) were calculated. Receiver-operating characteristics analysis was performed using 6 months of survival as outcome measure. When the ability to detect a survival of more than 6 months was tested, all scores performed similarly to the Okuda score. Kaplan-Meier analysis of patient survival according to VISUM-HCC revealed for stage 1 a cumulative survival between CTP A and B patients, Okuda I–II patients, Chevret A–B patients, CLIP 1–2 patients and BCLC A–C patients. For VISUM-HCC stage 2–3 patients, a cumulative survival comparable to CTP C patients, Okuda III patients, BCLC D patients, Chevret C patients and CLIP 5–>5 patients had been determined. In the study of Rabe et al. [36] the VISUM-HCC appeared most suitable in differentiating a group of HCC patients (VISUM stage 1) with at least moderate survival time (median 12 months) from HCC patients with an unfavorable prognosis (VISUM stage 2–3) and a short median survival of 2–3 months [36].

Therefore, in our retrospective study we used the new VISUM-HCC survival model [32] to select rather homogenous cohorts of patients with at least moderate prognosis (VISUM stage 1) or dismal prognosis (VISUM stage 2-3), who had received local treatment of their HCCs by LR, combined treatment with chemoembolization and RFA, chemoembolization alone or a systemic therapy with tamoxifen.

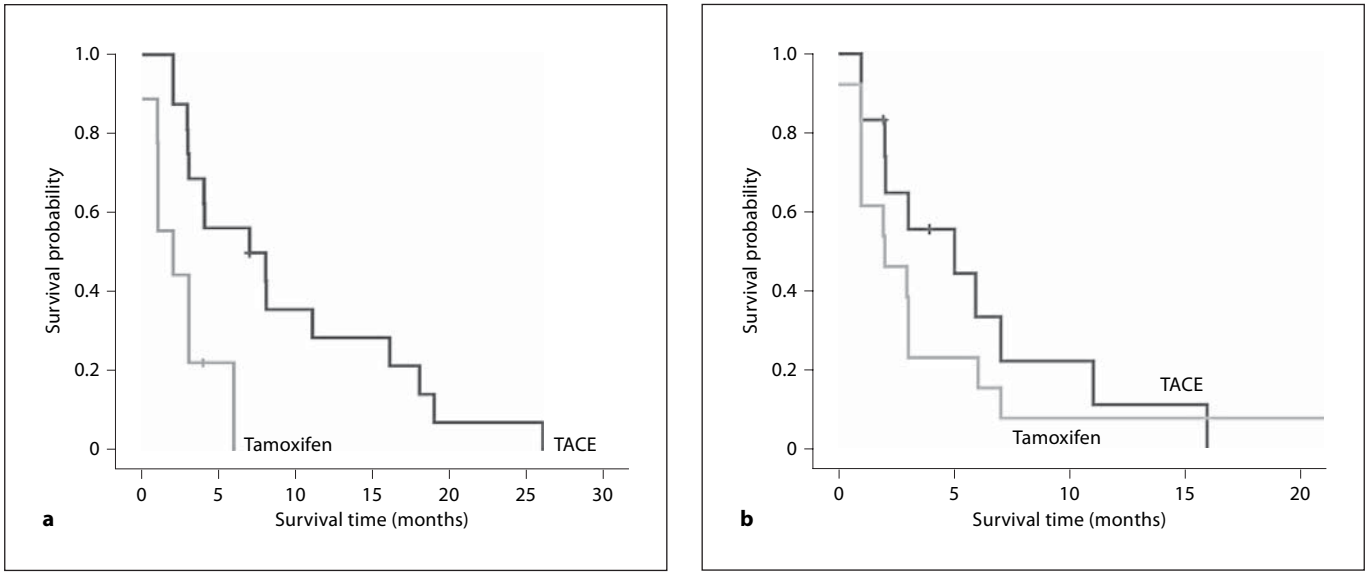

Fig. 2. Survival rates determined by Kaplan-Meier of HCC patients (VISUM stage 2–3) treated by TACE alone (n = 28) or tamoxifen (n = 22). Statistical evaluation by log-rank test showed an improved survival of patients treated by TACE compared to those treated by tamoxifen in VISUM stage 2 patients (p = 0.004) (**a**) but not in VISUM stage 3 patients (p = 0.341) (**b**).

Surgical therapeutic options for patients with HCC are largely determined by the underlying severity of liver disease and the extent of the HCC. Liver transplantation is the only treatment with the potential to cure both liver cirrhosis and HCC. However, due to a worldwide shortage of donor organs, this undoubtedly most favorable treatment is not available for all suitable candidates with HCC [2, 37]. Therefore, local surgical or non-surgical treatments of patients with HCC are of increasing importance. Furthermore, due to improvements of surveillance programs of patients with liver cirrhosis and thus at risk for HCC, the number of patients available for local treatment of their HCCs will increase in the future [38]. However, as in our study, >90% of patients with HCC in Europe and other Western countries have underlying liver cirrhosis and are therefore prone to postoperative complications after LR. Even in patients with favorable CTP scores (5–6), peri- and postoperative mortality cannot be neglected and has led to the recommendation to select for resection only those subjects who had solitary HCC, CTP scores from 5 to 6 and absence of significant portal hypertension [39].

In our study, LR was performed mainly in patients with CTP scores from 5 to 6 (CTP class A) and only exceptionally also in patients with more impaired liver function (CTP class B). In recent years a more strict selection was applied which excluded patients with significant portal hypertension for LR of their HCCs. The outcome of our HCC patients treated by LR is comparable to other studies [7, 40–42]. However, when LR is limited to patients with CTP class A and without significant portal hypertension, actuarial survival rates increase up to 74% at 5 years [43].

Interestingly, non-surgical patients with HCCs (VISUM stage 1) treated by the combined application of chemoembolization and RFA demonstrated significantly better results with regard to survival compared to the groups of patients treated with chemoembolization alone or systemic therapy with tamoxifen. The combined treatment leads to a definitive necrosis of tumors up to 5 cm in diameter in many cases after one single treatment [31]. In comparison to LR, we and others have observed fewer side effects and no procedure-related mortality [44].

As has been shown recently, the initial response to percutaneous ablation predicts survival in patients with HCC [45]. Using RFA alone, the initial complete response to percutaneous ablation is associated with an improved survival in both CTP class A and B patients with non-surgical HCC. It was concluded that initial tumor necrosis should be considered a relevant therapeutic target irrespective of tumor size and liver function [45].

The success of chemoembolization relies on the fact that HCC derives its blood supply predominantly from the hepatic artery, whereas the surrounding liver receives both portal and arterial blood [16, 17, 46]. However, chemoembolization is generally considered as palliative treatment because it does not achieve a complete necrosis of the tumor. This drawback is overcome by combining chemoembolization and RFA. The reduced blood flow to the tumor by chemoembolization is advantageous since it counteracts the rapid transmission of heat supplied by the RFA. This is the major reason why the combination of chemoembolization and RFA might be superior to treatment with RFA alone in HCC patients, although a comparative study has not yet been performed. Still, RFA is somewhat limited by tumor size and proximity of the lesions to larger vascular structures leading to unwanted regional cooling effects at the tumor.

Our patients treated with chemoembolization alone showed a less favorable prognosis in the long term. As illustrated in figure 1, within the first year their survival is not different from patients after LR. However, after an extended follow-up period, only a few patients survived 3 years. Although all patients belong to a group of patients with an at least moderate prognosis (VISUM stage 1), it is evident from table 2 that HCC patients treated with chemoembolization alone had more extended HCCs than patients treated with chemoembolization and RFA, and a more impaired liver function than patients treated by LR. The different liver function might contribute to the median survival difference (24 months) between VISUM stage 1 HCC patients treated by LR compared to VISUM stage 1 HCC patients treated by chemoembolization alone. Furthermore, it cannot be neglected that the median survival difference (32 months) between patients treated with TACE and RFA vs. TACE alone might partially reflect the more extended and/or multifocal presentation of HCCs in the latter group. Indeed, due to our selection criteria for the different treatments, TACE and RFA were restricted to HCC patients with a tumor size of up to 5 cm in diameter and not more than 5 nodules, while HCC patients with >5 nodules up to 8 cm in diameter were accepted for treatment with TACE alone. However, it is very unlikely that a median survival difference of 32 months (45 vs. 13 months) between both groups of patients is solely due to a different extension of the HCC. In the analysis of Rabe et al. [36], tumor extension as determined by the number of nodules, largest nodule, lymph node metastases, involvement of both liver lobes and involvement of >50% of the liver was not different between HCC patients surviving <6 and >6 months.

Finally, our group of patients with VISUM stage 1 treated by tamoxifen alone shows the least favorable prognosis in the long term and no surviving patients after 3 years. The statistical evaluation of survival times revealed that besides LR and the combined treatment with TACE and RFA, TACE alone improved the survival of our HCC patients in VISUM stage 1 compared to patients treated by tamoxifen only. The extent of the median survival benefit of 7 months is in accordance with a recent systematic review of randomized trials for unresectable HCC, which showed a significant benefit of chemoembolization in comparison to tamoxifen alone [28]. Similarly, chemoembolization in HCC patients of VISUM stage 2 is superior to tamoxifen alone and seems therefore justified, while chemoembolization in HCC patients of VISUM stage 3 did not significantly improve survival time in comparison to systemic therapy by tamoxifen and thus should be avoided.

In conclusion, our data show that patients with HCC and an at least moderate prognosis according to the VISUM-HCC have a more favorable long-term survival if LR or a combined treatment with chemoembolization plus RFA is possible. These results underscore the importance of surveillance programs for the early detection of HCCs in patients with chronic liver disease. Interestingly, the outcome of the non-surgical patients treated by combined TACE and RFA was comparable to the group of HCC patients treated with LR.

If these results hold true in a larger cohort of patients, combined treatment with TACE and RFA may also be an alternative to surgery in some patients with small HCCs and preserved liver function.

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