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Monitoring Liver Function of Patients Undergoing Transarterial Chemoembolization (TACE) by a 13C Breath Test (LiMAx)

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Abstract

Purpose Transarterial chemoembolization (TACE) is associated with the risk of deteriorating liver function, especially in patients with preexisting liver damage. Current liver function tests may fail to accurately predict the functional liver reserve. Aim of this study was to investigate whether changes of liver function caused by TACE are associated with detectable changes of LiMAx values.

Methods and Materials Forty patients with primary or secondary liver cancer underwent TACE and LiMAx test on the day before, the day after, and 4 weeks after TACE. LiMAx results were evaluated, referenced to liver volume (CT/MR volumetry), correlated with the respective TACE volume (subsegmental vs. segmental vs. lobar), established liver function tests, and Child–Pugh and ALBI scores.

Results The individual LiMAx values were significantly reduced by 10% ($p = 0.01$) on the day after TACE and fully recovered to baseline 1 month after treatment. Similar changes were observed regarding levels of bilirubin, transaminases, albumin, INR, and creatinine. LiMAx did not correlate significantly with the treated liver volume, but did correlate with the baseline liver volume (< 1200 ml vs. > 1200 ml; $p < 0.01$). No significant changes were observed in the Child–Pugh score or ALBI score.

Conclusion LiMAx is capable of detecting changes in liver function, even modulations caused by superselective TACE procedures. Accordingly, it could be used as a tool for patient selection and monitoring of transarterial therapy. In comparison, Child–Pugh and ALBI scores did not reflect any of these changes. Some biochemical parameters also changed significantly after TACE, but they tend to be less specific in providing sufficient information on actual cellular dysfunction.

Keywords TACE · Transarterial chemoembolization · Liver function · LiMAx

Introduction

Transarterial chemoembolization (TACE) is an established treatment for patients with primary and secondary liver tumors to help control local tumor growth, prolong survival, palliate symptoms, or bridge the time to liver transplantation. However, TACE can deteriorate liver function. Since TACE is commonly offered to patients with primary liver cancer secondary to liver cirrhosis, or as an individual therapy option in patients with liver dominant metastatic disease of different primary tumors who did not respond to state-of-the-art systemic chemotherapy, the functional reserve of patients who are TACE candidates can be substantially impaired. Acute hepatic failure is one of the most serious complications after TACE with

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incidence of 5–20% [1–4] and mortality rate up to 60–80% [5]. Accordingly, there is a substantial clinical demand for accurate measures of liver functional reserve to improve selection of patients who can tolerate TACE. Currently, the most commonly used metric to describe the liver function and decide on patient treatment is the Child–Pugh score [6–9], with patients with Child C often considered unsuitable for TACE [10]. Another score, based on serological parameters, ALBI, has shown to be a better predictor of post-therapeutic outcome and overall survival than the Child–Pugh score in patients with HCC [11–13].

To assess synthetic and excretory liver function, serological tests are used. However, it has been shown that typical "liver parameters" such as bilirubin, transaminases, and serum albumin, are relatively non-specific and insensitive [14]. Furthermore, changes of these serological parameters are sometimes lagging behind by several days [15, 16].

In contrast, dynamic liver function tests that determine hepatic clearance and specific enzyme activities, in particular, the 13C-methacetin breath test, have been shown to correlate well with clinical and histological parameters of patients with liver disorders [17–21]. However, their role as a tool to guide patient selection in interventional oncology has so far not been established.

LiMAx (liver maximum capacity test, Humedics, Berlin, Germany) is a dynamic liver function test based on metabolism of intravenously injected 13C-methacetin by a liver-specific cytochrome P450 1A2-system. It has been shown to be a reliable tool for the evaluation of liver function and patient selection in patients who are candidates for major liver surgery [17, 22, 23] and liver transplantation [24–26] and has demonstrated its potential to predict postoperative outcome and the outcome in patients with acute liver failure [27] and liver transplant candidates [28].

Therefore, the aim of this study was to investigate whether changes of liver function caused by TACE procedures are associated with detectable changes of the patient's LiMAx values and to compare those effects to the common biochemical parameters and clinical scores. Long-term goal is to establish LiMAx as a tool for patient management in hepatic interventional oncology.

Methods and Materials

Study Design and Inclusion Criteria

A retrospective study was conducted on consecutive patients who underwent TACE between April 2014 and December 2016 at a tertiary care academic comprehensive cancer center, and who underwent assessment of liver function based on the LiMAx test as well as based on established serological liver function tests specified below, all obtained on the day before and on the day after the procedure, as well as at 4 weeks after TACE. Unit of observation were the individual TACE procedures. All patients provided written informed consent to the study provisions.

The following data were collected: patient demographics, type of cancer, Child–Pugh score, ALBI score, comorbidities, type and date of previous treatments, liver volume, TACE approach (subsegmental, segmental, lobar), chemotherapeutic drugs and embolization agents, and results of LiMAx and serological liver tests.

The demographic data are summarized in Table 1.

LiMAx

This breath test is based on the metabolic function capacity of the cytochrome P450 isoenzyme 1A2 (CYP450 1A2), which is hepatocyte specific, active throughout the liver, and not affected by medications or genetic polymorphisms. The activity of the enzyme is measured by i.v. bolus

Table 1 Demographic data and patients characteristics before treatment

	$N = 40$
Age (years)	65.5 (± 12.5)
Gender	
Male	30
Female	10
Tumor type	
Hepatocellular cancer	15
Cholangiocarcinoma	16
Colorectal metastases	2
Metastases of melanoma	3
Metastases of ovarian cancer	3
Metastases of breast cancer	1
Liver cirrhosis	
None	27
Child A	7
Child B	6
Number of TACE sessions	
$n = 1$	19
$n = 2$	8
$n = 3$	5
$n > 3$	8
Previous surgical/interventional procedures	
Right hemihepatectomy	4
Left hemihepatectomy	7
Atypical resection	4
Radioembolization	4

injection of non-radioactive ^{13}C-methacetin, which is metabolized exclusively by CYP450 1A2 into acetaminophen (Paracetamol) and $^{13}CO_2$ which is exhaled. The exhaled air is collected using a facial mask. Methacetin itself has no known adverse effects. First, the baseline ratio of $^{13}CO_2/^{12}CO_2$ concentrations in the exhaled air was determined. After intravenous administration of 2 mg/kg body weight ^{13}C-methacetin, followed by a bolus of 20 ml saline solution, the dynamics of $^{13}CO_2$ production were measured in the exhaled breath over a period of 20–60 min. The result is given in μg/kg/h (μg methacetin/kg body weight/h). Patients should be fasting for at least 3 h before the test.

Transarterial Chemoembolization (TACE)

All chemoembolizations were performed via femoral access. Angiographic workup included celiac, common hepatic, and mesenteric angiograms using standard 5F catheters. The actual treatment was delivered via a microcatheter, positioned depending on the tumor load distribution. Contrast-enhanced cone-beam CTs were performed to verify the localization and the tumor-feeding vessels. Depending on type, number, size, localization, and arterial supply of the tumor, a superselective (subsegmental), selective (segmental), or non-selective (lobar) approach was chosen. An emulsion of cytotoxic agents and iodized oil (lipiodol, Guerbert GmbH, Villepinte, France) or degradable starch microspheres (DSM, Embocept, PharmaCept GmbH, Berlin, Germany) was injected under fluoroscopic guidance until stasis was reached. Patients were discharged on the day after the procedure.

Measurement of Liver Volume and Volume Treated by TACE

Liver volume was assessed on the basis of contrast-enhanced CT or MR images obtained within 4 weeks prior to TACE using Philips IntelliSpace software package (Koninklijke Philips N.V., Amsterdam, Netherlands). Main blood vessels (the three hepatic veins, the main right and left portal vein, and the segmental portal branches) as well as the tumor and necrotic areas were manually excluded to determine the functional liver volume as accurately as possible. Also, the volume of liver treated by TACE was segmented in correlation to the angiographic approach (subsegmental, segmental, or lobar).

Laboratory Parameters

Blood tests were taken on the day before and after TACE, as well as on the routine follow-up 4 weeks after the procedure. The following parameters were assessed: direct and total bilirubin, glutamate-pyruvate transaminase (GPT), aspartate aminotransferase (GOT), alkaline phosphatase (AP), gamma-glutamyl transferase (GGT), free albumin, INR, creatinine, and glomerular filtration rate (GFR).

Statistical Analysis

SPSS 22.0 software (SPSS, Chicago, IL, USA) was used for statistical analysis. Changes in LiMAx were compared with changes in blood tests, ALBI and Child–Pugh scores, and to liver volume and volume of the treated liver parenchyma using Wilcoxon signed-rank tests. A p value ≤ 0.05 was considered significant. Values are presented with mean and standard deviation (SD) or median and interquartile range (IQR) if not otherwise specified.

Results

In 68 cases, the patient underwent LiMax before TACE. However, 28 were lost to follow-up. Thus, a total of 40 TACE procedures in 29 patients were included in the study, as shown in Fig. 1.

In 14 patients, all with HCC, a conventional doxorubicin/lipiodol TACE was performed. Twenty-two patients with secondary liver cancer were treated with DSM-TACE (cisplatin/mitomycin C/doxorubicin and embocept), two patients underwent TACE using irinotecan-eluting beads, and two patients underwent bland embolization.

Detailed information on the TACE protocols is summarized in Table 2.

Thirteen patients had liver cirrhosis, either Child–Pugh A ($n = 6$) or B ($n = 7$). The median Child–Pugh score was 6 (IQR = 2). The mean baseline LiMAx value in patients with liver cirrhosis was 250.42 μg/kg/h (± 110.87 μg/kg/h), which was significantly lower than that in patients without cirrhosis (361.00 ± 107.92 μg/kg/h, $p = 0.01$); moreover, the LiMAx values were significantly higher in patients with mild cirrhosis (Child–Pugh A) versus advanced cirrhosis (Child–Pugh B) (298.29 ± 105.27 vs. 183.40 ± 86.93 μg/kg/h). There were no patients in Child–Pugh stage C.

The ALBI grade in all the patients was either 1 ($n = 27$) or 2 ($n = 13$).

Volumetry yielded a median liver volume of 1449.35 ml (IQR = 455.4 ml). The median volume of treated liver parenchyma was 871.15 ml (IQR = 796.2 ml): 1104.80 ml (IQR = 596 ml) in cases of lobar TACE, 549.50 ml (IQR = 275.3 ml) in cases of segmental TACE, and 214.20 ml (IQR = 888.7 ml) in cases of subsegmental TACE. The median number of treated segments was 4 (IQR = 2).

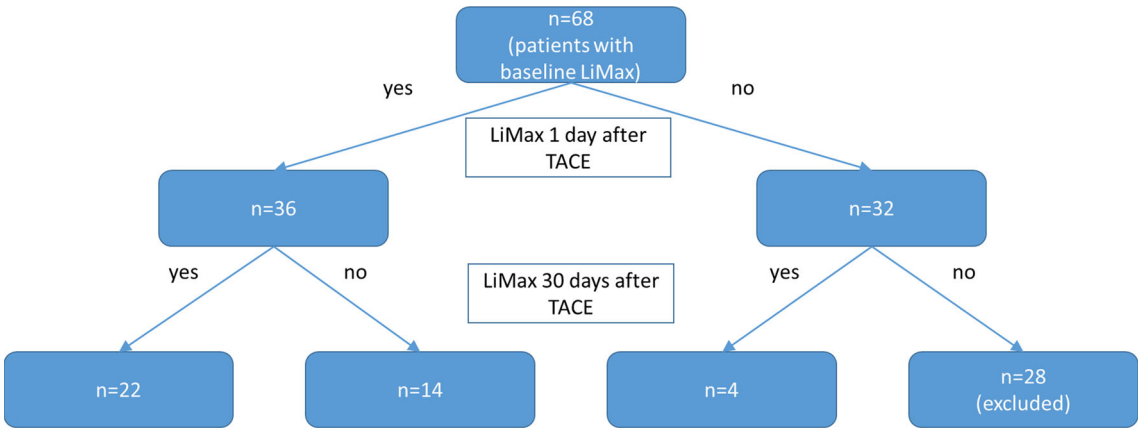

Fig. 1 Patients follow-up after TACE

Table 2 TACE protocols

	N = 40
Approach	
Superselective	7
Selective	10
Unilobar/bilobar	23
Number of treated lesions	
1	2
2–3	14
4 ore more	24
Cytotoxic and embolic agents	
Doxorubicin/lipiodol	14
Cisplatin/mitomycin C/doxorubicin	22
Irinotecan or bland embolization	4
Area of treated liver parenchyma (%)	
< 25%	7
25–50%	9
50–75%	8
> 75%	16

Regarding the changes of LiMAx and of blood parameters between the baseline and the day after TACE, there was a significant decrease in LiMAx by 10% (327 ± 119.2 µg/kg/h vs. 294.3 ± 128.27 µg/kg/h; $p < 0.01$) as well as an increase in bilirubin (0.075 ± 0.81 mg/dl vs. 1.14 ± 1.3 mg/dl; $p < 0.01$), GOT (38.3 ± 16.92 U/l vs. 224.31 ± 638.72 U/l; $p < 0.01$), and GPT (26.78 ± 18.2 vs. 198.44 ± 502.93 U/l; $p < 0.01$). The levels of albumin, creatinine, and INR also changed significantly after therapy. Detailed information is summarized in Table 3. There were no significant changes in AP and GGT.

At the 1-month follow-up, all LiMAx values and blood parameters returned to baseline, except for GGT (D0: 178.7 ± 225, D1: 260.11 ± 195, D30: 196.14 ± 163.14; $p < 0.01$). All changes are summarized in Table 3 and Fig. 2.

None of the patients showed deterioration of the Child–Pugh stage after TACE. Five patients changed from ALBI grade 1 to grade 2 and one from grade 2 to grade 3 ($p = 0.01$). All of these patients had HCC and were treated with conventional TACE.

Comparing unselective to (sub-) segmental TACE approaches, there was no significant difference in the decrease in LiMAx ($p = 0.58$). There were also no significant differences in the decrease in LiMAx comparing conventional and DSM-TACE ($p = 0.41$). There was no correlation between the impairment of liver function, measured by the decrease in LiMAx, and the treated liver volume assessed by volumetry ($p = 0.16$) (Fig. 3).

To assess whether reduced liver volume is a risk factor for TACE, a subgroup analysis of patients in the lowest quartile was performed ($n = 10$, liver volume < 1200 ml). Although the mean baseline LiMAx in these patients did not differ significantly to the cohort with liver volumes beyond 1200 ml (326.50 ± 121.17 µg/kg/h vs. 327.14 ± 120.63 µg/kg/h), these patients had a more pronounced decrease in LiMAx on the day after treatment Δ(LiMAx1–LiMAx2): 95 µg/kg/h vs. 44.1 µg/kg/h; $p = 0.04$).

Regarding the changes in blood parameters between the day before and the day after TACE, there were no significant differences comparing unselective to selective TACE (for GOT $p = 0.93$, for GGT $p = 0.07$, for AP $p = 0.94$) and no correlation between these changes and the treated liver volume (for GOT $p = 0.89$, for GGT $p = 0.09$, for AP $p = 0.51$).

One patient with HCC developed acute liver failure on the day after TACE with an increase in bilirubin (0.59–2.17 mg/dl), GOT (25–3521 U/l) and GPT (18–2077 U/l) as well as a decrease in LiMAx (350–70 µg/kg/h). The patient was immediately admitted to an

Table 3 Changes in LiMAx and laboratory parameters

	D0: Baseline (n = 40)		D2: Day after TACE (n = 36)			D30: Follow-up (n = 26)		
	Mean	SD	Mean	SD	p value	Mean	SD	p value
LiMAx (µg/kg/h)	327	119.2	294.3	128.27	**0.01**	330.6	149	0.42
Total bilirubin (mg/dl)	0.75	0.81	1.14	1.3	**0.01**	0.81	1.35	0.36
GOT (U/l)	38.3	16.92	224.31	638.72	**0.01**	36.8	15.11	0.47
GPT (U/l)	26.78	18.2	198.44	502.93	**0.01**	25.38	13.95	0.34
AP(U/l)	126.6	80.20	167.52	131.2	0.98	135.46	90.93	0.06
GGT(U/l)	178.7	225	260.11	219.45	0.11	196.14	163.14	**0.01**
Albumin (g/dl)	4.13	0.44	3.78	0.52	**0.01**	4.01	0.53	0.38
INR	1.03	0.12	1.08	0.14	**0.01**	1.18	0.85	0.44
Creatinine (mg/dl)	0.95	0.27	1.08	0.31	**0.02**	0.94	0.25	0.84

Bold values indicate (p value $\leq$ 0.05) are significant changes

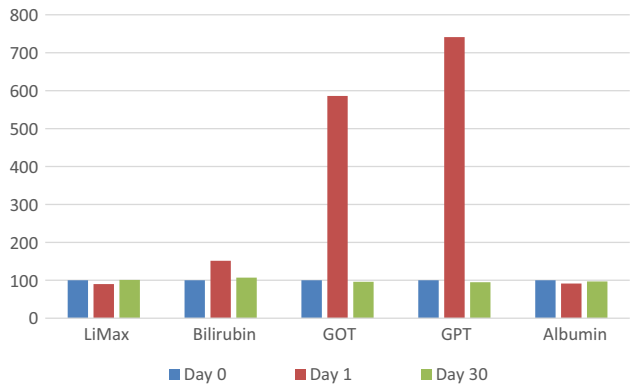

Fig. 2 Changes in LiMAx and laboratory parameters

intensive care unit, received conservative treatment, and was discharged 7 days later. At the follow-up 4 weeks later, all values had fully recovered to baseline.

Discussion

In our study, we investigated whether the changes of liver function caused by TACE procedures were associated with detectable changes of the patient's LiMAx values and compared those with established laboratory parameters and clinical scores. Our analysis showed that TACE induced an immediate deterioration of hepatic function which was reflected in a significant decrease in LiMAx by 10% and an increase in bilirubin, GOT and GPT, as well as changes in albumin and creatinine blood levels. Other biochemical parameters revealed no significant changes.

Even though the changes in blood parameters by means of bilirubin and transaminases were significant, they mostly reflect liver cell damage and are considered inadequate in the assessment of liver function or impairment of metabolic activity of the liver [14]. Reduced concentration of albumin is not only a sign of reduced synthesis capacity of the liver, but may also occur due to inflammatory changes after TACE, as albumin is a negative acute phase protein. Increase in creatinine 1 day after TACE might be due to the application of contrast agent during TACE or due to a shift of intracellular fluid levels. INR might be influenced by anticoagulation therapy. Clinical parameters such as ascites (as a measure of Child–Pugh score) might also be caused by the patient's tumor burden, while the metabolic liver function might still be preserved. Therefore, serum liver biochemistry might not accurately identify impaired liver function.

The most commonly used functional criteria to choose candidates for TACE is the Child–Pugh classification. However, studies show that the Child–Pugh score alone is not an effective measure to predict post-TACE acute hepatic failure [29]. So far, only one study focused on the assessment of liver function after TACE by means of a dynamic breath test, and it showed disconcordance between the Child–Pugh score and the breath test score [30].

Our study shows that short-term changes in liver function were successfully detected by LiMAx, while there were no significant changes regarding the Child–Pugh score. There was a significant change in the ALBI grade, but as being composed of bilirubin and albumin, it might not reflect the actual liver damage, as mentioned above.

In previous studies, LiMAx has shown to provide reliable information about quantitative liver function [31] and prognostic accuracy in patients undergoing liver resection: The combination of LiMAx and CT volumetry allowed estimation of the future remnant liver function [17, 23]. In regard to TACE, we could detect a more pronounced decrease in LiMAx after therapy in patients with reduced liver volume (< 1200 ml), which might be an indicator that these patients might have an increased risk of post-interventional complications. Nevertheless, at the monthly follow-up, these patients had fully recovered to baseline

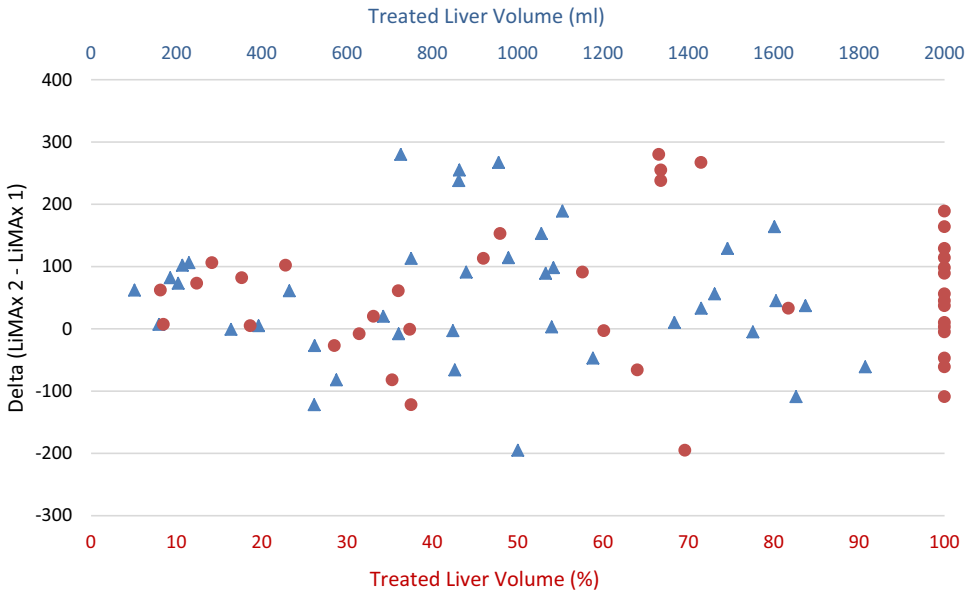

Fig. 3 Correlation between treated liver volume and decrease in the LiMAx value

LiMAx levels. We could not detect a correlation between changes in the LiMAx or blood parameters and the treated liver parenchyma (assessed by volumetry) or the respective TACE approach; however, this is most likely related to the relatively small patient number and should be investigated further.

Although being clinically asymptomatic, one patient developed a transient liver failure on the day after TACE, which was treated successfully at an intensive care unit. It was recognized by an imminent decrease in hepatic function measured by the LiMAx and increase in hepatic enzymes. None of the patients, even those with small liver volume (< 1200 ml) or liver cirrhosis or extensive tumor burden, had a permanent decrease in hepatic function at the follow-up 1 month after treatment, and thus, TACE seems to cause only a reversible liver dysfunction.

Limitations of this study were the relatively small size of the patient cohort and the diversity of liver tumors and of TACE protocols. Additionally, a relatively large number of patients were lost to follow-up, which might bias the results. Another limitation is the LiMAx dependency on patients' compliance, as the test results can be distorted by prior food intake.

The cutoff value of 1200 ml as the definition of strongly reduced liver volume was chosen based on the distribution in our patient cohort and might therefore not be of significance in other patient groups.

Altogether our results show that LiMAx is capable of detecting changes of liver function caused by TACE procedures. Biochemical parameters might not provide sufficient information on actual cellular dysfunction due to methodological restrictions. The Child–Pugh score did not reflect any of the mentioned changes.

In conclusion, patients with advanced liver cirrhosis or extended tumor burden could benefit from LiMAx, as it may help to identify patients who might be valid candidates for TACE even though they are clinically considered unsuitable. On the other hand, patients with poor hepatic function, which might not be reflected by laboratory or clinical parameters, might have an increased risk of post-interventional liver failure and should therefore undergo LiMAx as a monitoring tool before and after TACE.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent For this type of study, formal consent is not required. Consent for publication was obtained for every individual person's data included in the study.

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