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Use of the liver maximum function capacity test (LiMAX) for the management of liver resection in cirrhosis – A case of hypopharyngeal cancer liver metastasis



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ABSTRACT

INTRODUCTION: The presence of liver cirrhosis goes along with a higher chance for the need of liver resection. As established laboratory parameters often underestimate the degree of cirrhosis this is associated with an increased risk for postoperative liver failure due to the preoperatively impaired liver function. Known liver function tests are unlikely to be performed in daily use because of high cost or expenditure of time. Liver maximum function capacity test (LiMAX) provides a novel tool for measurement of liver function and references for the safety of liver resection.

PRESENTATION OF CASE: A 63-year old patient presented at our hospital with a large, solitary liver metastasis from hypopharyngeal cancer in segments VII/VIII with infiltration of the diaphragm. Liver resection was unsuccessful in a peripheral hospital 10 months before due to considerable macroscopic liver cirrhosis (CHILD B). Upon presentation conventional laboratory parameters revealed sufficient liver function. LiMAX was performed and showed regular liver function (354 $\mu\text{g}/\text{kg}/\text{h}$; at norm $>315 \mu\text{g}/\text{kg}/\text{h}$). Consequently, atypical liver resection (R0) was performed resulting in a postoperative LiMAX value of 281 $\mu\text{g}/\text{h}/\text{kg}$ ($>150 \mu\text{g}/\text{kg}/\text{h}$). The patient was discharged from hospital 37 days after surgery without any signs of postoperative liver failure.

CONCLUSION: The LiMAX-test enables determination of liver function at a so far unavailable level (metabolism via cytochrome P450 1A2) and hence might provide crucial additional diagnostic information to allow for safe liver resection even in cirrhotic patients.

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1. Introduction

Liver cirrhosis is associated with a higher risk for several malignant tumors of the liver. For these tumors, surgical resection usually represents the only curative option [1]. Secondary tumors represent the most frequent liver tumors. Many of them are also associated with liver cirrhosis like in our case [2]. If liver metastasis represents the only systemic tumor spread, surgery is a feasible therapeutic option in these patients [3]. An improved survival for patients with nasopharyngeal carcinoma who received partial hepatectomy over patients treated interventionaly was already shown [4].

Cirrhosis further is associated with higher mortality in abdominal surgery [5] and results in a higher rate of patients suffering from small-for-size syndrome after surgery which eventually increases

mortality [6]. This is due to a disproportion of liver size and function in diseased livers.

Volumetry of the liver consequently fails as a prediction value [7]. Conventional liver function parameters are also not reliable in every case and can be affected by medication.

Recently developed liver maximum function capacity test (LiMAX) offers the possibility to measure the activity of the liver-specific cytochrome P450 1A2 system by metabolizing methacetin as a surrogate parameter of the liver function capacity [8] (expressed as μg methacetin/kg body weight/hour; reference $>315 \mu\text{g}/\text{kg}/\text{h}$).

In this article, we report our experience with the LiMAX-test in a patient with a large, solitary metastasis of hypopharyngeal cancer in a severe cirrhotic liver. The report was written according to the SCARE guidelines [9].

2. Presentation of case

We here present the case of a 63-year old male with hypopharyngeal carcinoma (T3, N2), which was diagnosed 7 years ago. The patient had already undergone R2-neck dissection and stan-

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Fig. 1. Pre-operative portalvenous phase CT in the axial (A) and coronal (B) plane, demonstrating a large solitary liver metastasis (arrow) subdiaphragmatic in segment 7, abutting the diaphragm. In addition, irregularity of the liver capsule can be appreciated, confirmative with known cirrhosis.

standardized radio-chemotherapy. Several pulmonary metastases were resected successfully and a Barrett-carcinoma of the esophagus was cured by mucosectomy 8 years ago. Other diagnoses in this patient included hypertension, non-insulin-dependent diabetes and cryptogenic liver cirrhosis.

The patient now suffered from a newly diagnosed suspicious lesion in segments VII/VIII of the liver (see Fig. 1). The lesion showed progress under chemotherapy with three cycles of Cetuximab/Cisplatin and two cycles of 5-Fluorouracil (5-FU). The doses of the last chemotherapy with Gemcitabine had to be lowered after one cycle because of pancytopenia. Hence, tumor resection was approached, which failed in a peripheral hospital due to severe macroscopic liver cirrhosis (see Fig. 2).

The patient was then admitted to our hospital, which is a tertiary referral center for hepatobiliary surgery. Further diagnostics revealed a 6.4 × 7.8 cm tumor in segments VII/VIII of the liver and additional infiltration of the diaphragm. The tumor touched the right hepatic vein, while portal vein and liver artery showed safe distance from the tumor. Liver volume was measured to be 2026 ml with an estimated tumor volume of 285 ml in contrast CT-scan. Aiming at an atypical resection with minimal loss of healthy liver parenchyma this would result in a future liver remnant (FLR) of 2000 ml (total resection volume 311 ml). While the tumor reached the right hepatic vein, there was a distant risk that right hepatectomy would become necessary which would result in an even smaller FLR. The organ showed distinct nodular cirrhosis with signs of portal hypertension, e.g. splenomegaly, varicosis of the esophagus and ascites. Blood analysis provided normal liver enzymes, elevated γ -glutamyltransferase (320U/l) and alkaline phosphatase (164U/l), cholinesterase (CHE) of 4.96kU/l and INR of 1.15. Total protein levels were reduced with 70 g/l and albumin 26 g/l. These data added up to a Child-B cirrhosis.

In conclusion, our seriously ill patient was in urgent need for liver resection which had failed once because of his cirrhosis and the risk of postoperative liver failure (PLF). As the previously performed investigations allowed us no distinct suggestion about another surgical approach we finally decided to perform the LiMAX-test, which was performed as previously reported [10]. This revealed a LiMAX-value of 354 $\mu\text{g}/\text{kg}/\text{h}$, which indicates a normal liver function capacity (see Fig. 3). The calculated LiMAX-value after resection was 341 $\mu\text{g}/\text{kg}/\text{h}$. Consequently, the indication for liver resection was set and informed consent was obtained from the patient. Intraoperatively we were able to separate the right hepatic vein from the tumor resulting in atypical liver resection with partial resection

of the diaphragm. Resection volume eventually was 300 ml in the postoperative volumetry. Histology later confirmed a metastasis of the known hypopharyngeal cancer.

The INR was 1.30 after surgery and remained stable at values of 1.10–1.15 during the hospital stay. Liver enzymes rose to a maximum of 336U/l (GPT; see Fig. 4). Postoperative LiMAX-test showed a decrease to 281 $\mu\text{g}/\text{kg}/\text{h}$ (see Fig. 3). This was far below the calculated LiMAX-value and indicated a relevant loss of liver function but the value was above the cut-off for a safe liver resection (>150 $\mu\text{g}/\text{kg}/\text{h}$) [8]. The patient was discharged from intensive care unit on postoperative day (POD) 4.

During the further hospital stay our patient developed posthepatectomy liver failure (PHLF) grade B according to the International study group of Liver Surgery [11] with prolonged production of ascites. This could be treated by diuretics, venous pooling with propranolol and substitution of albumin.

After an episode of erosive esophagitis, the patient eventually was discharged at POD 37 from hospital with liver function at baseline. The patient died of pulmonary metastasis 12 months later with no signs of hepatic or abdominal tumor growth until then.

3. Discussion

Postoperative liver failure is a much-feared complication which is associated with high mortality. Two groups of risk factors have been identified: Directly perioperative factors like the extent of liver resection, need for re-operation or ASA grading are general risk factors for perioperative mortality [12]. The second group of risk factors is related to the liver's condition like ongoing hepatitis or cirrhosis [13].

As more and more multimorbid patients require liver surgery, several scores and tests have been developed to estimate the risk for an insufficient liver remnant [12]. Child-Pugh- or MELD-score are based on laboratory data and can be calculated in every patient. Other methods are unlikely performed in every patient due to high cost and complexity [12].

The presented patient's liver laboratory data resulted in a Child-B classification of cirrhosis. In selected patients with this classification surgery can usually be performed safely [14].

In contrast, the macroscopic aspect (see Fig. 2) of cirrhosis in our patient did not correlate with the relatively good laboratory findings. Additionally, the patient suffered from several other severe chronic diseases and underwent multiple chemotherapies in the recent past, which is an independent risk factor for PLF [15]. Known

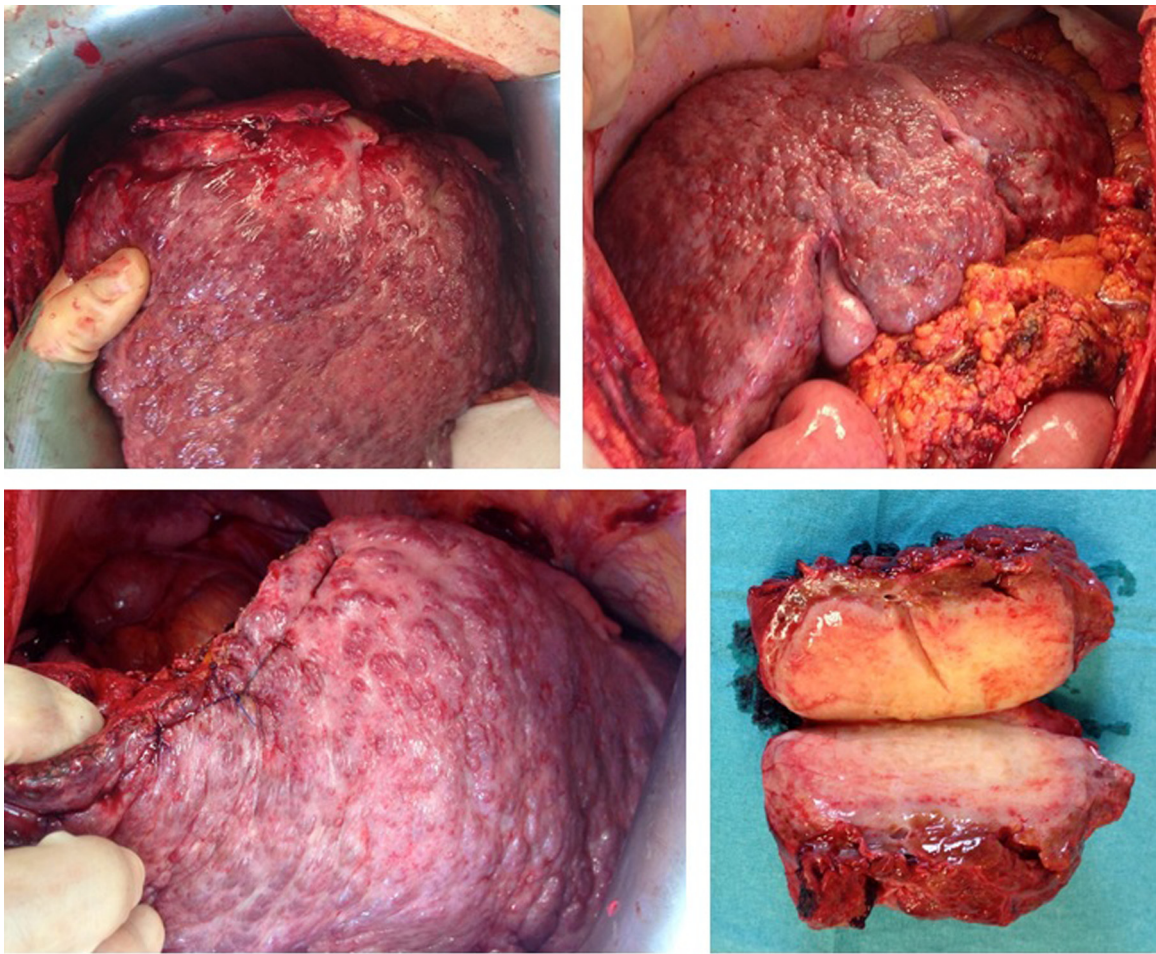


Fig. 2. Intraoperative aspect of severe liver cirrhosis (top row: before resection; bottom row: after resection).

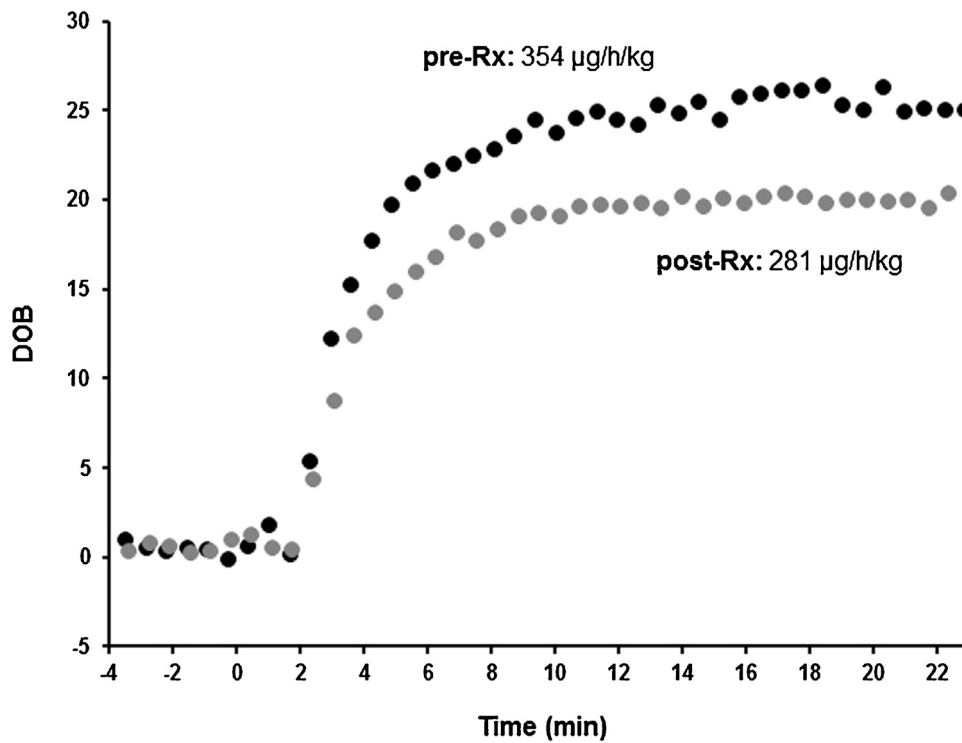


Fig. 3. Pre- and postoperative LiMAX measurement (black: preoperative day; grey: after resection; DOB: Delta over baseline of CO₂ exhalation as a surrogate for methacetin metabolism in the liver).

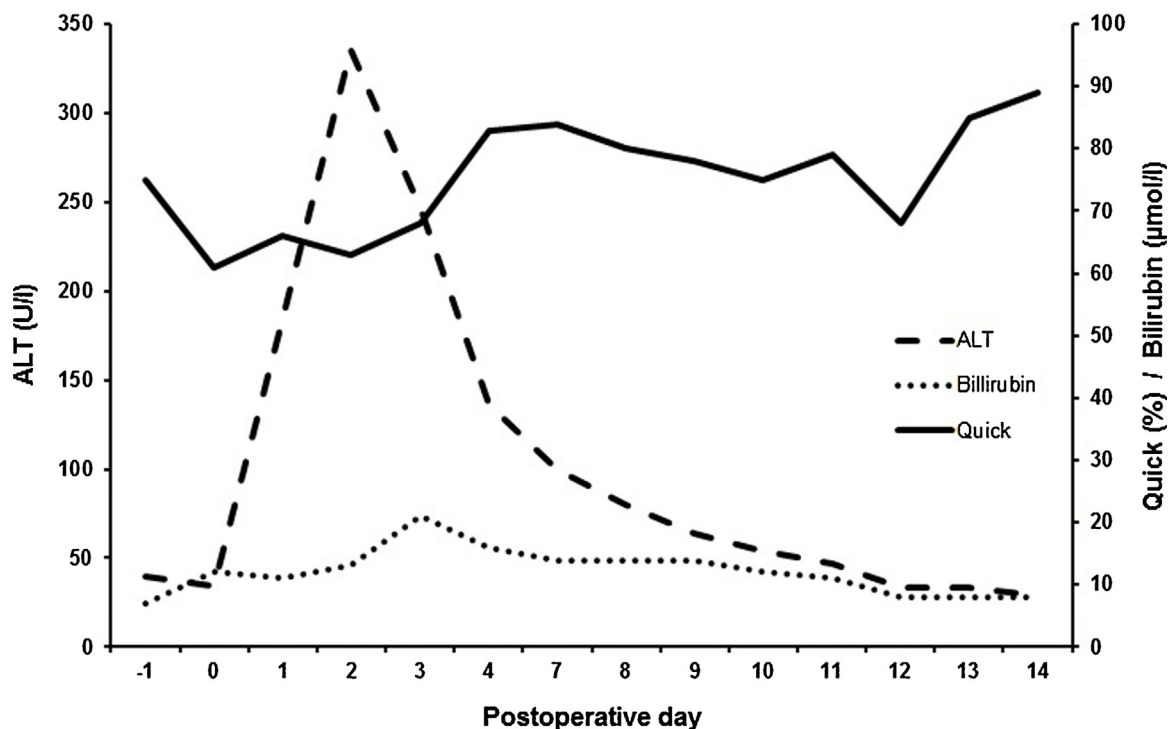


Fig. 4. Postoperative course of laboratory findings. ALT shows a peak on POD 2. Quick and bilirubin remain stable.

portal hypertension in this patient resulted in esophageal varicosis once. For these reasons resection of the suspected metastasis was interrupted once in a peripheral hospital.

Before undertaking another surgical approach, we searched for further diagnostics to minimize the risk of PLF in our patient. As other tests showed poor correlation with postoperative liver function, we relied on the LiMAX-test in this case. This is known to significantly correlate with sufficient postoperative liver function [8] also in cirrhotic liver disease [16]. It proved to be a predictor of postoperative liver function in patients with cirrhosis who had been rejected from surgery before in individual cases [8]. Jara et al. found significant decrease of PLF and PLF-related mortality after establishing a LiMAX-based algorithm [17].

In the present case, the tumor was related to the right hepatic vein which could have required right hepatectomy to achieve a tumor-free resection margin. But even with the minimal loss of liver tissue of only 15 ml the liver function capacity according to the LiMAX-test decreased significantly by $60 \mu\text{g}/\text{kg}/\text{h}$. The expected decrease would have been only $4 \mu\text{g}/\text{kg}/\text{h}$. Even under the supposition that bordering liver tissue mortified because of disturbed perfusion this indicated a seriously diseased liver. This can also be derived from the development of PHLF grade B.

However, LiMAX is a global liver capacity test. Therefore, it cannot give evidence on the regional distribution of functional liver tissue in the organ. This might become relevant if major liver resection is planned. By intraoperative decision to perform only atypical resection of the tumor, loss of functional liver tissue was minimized.

Another limitation of the test's predictive capability is intraoperative liver affection by Pringle maneuver or blood loss [8]. In our patient Pringle maneuver was not undertaken as it is controversial. This resulted in a higher blood loss but avoided the risk for reperfusion injury [18].

One may imagine that the LiMAX-test can be adulterated in tumors derived from liver tissue because of their ability to express cytochrome 1A2 themselves [19]. Our patient suffered from metastasis so there was little chance to overestimate the LiMAX-value.

Finally, the patient was able to leave our hospital free from tumor and with sufficient liver function. LiMAX-testing has helped to provide a safe and patient adapted therapy decision in this patient.

4. Conclusion

The LiMAX-test may represent a valuable diagnostic tool in case of ambivalent findings prior to liver resection in cirrhotic or critically ill patients.

Conflicts of interest

No conflict of interests to declare.

Funding

There was no sponsor involved in the presented Case Report.

Ethical approval

Retrospective analysis was approved by the institutional review board (ethic commission of Hannover Medical School; #3547-2017).

Consent

Informed and written consent has been obtained from the patient's wife as he died in the meantime.

Author contribution

SC: Data collection, Writing of the paper.

FO: Study conception (i.e. treatment of the patient), data collection.

KIR: Data collection, Data interpretation, Writing the paper.

WR: Data collection and interpretation.

KT: Data collection, Study conception (i.e. treatment of the patient).

MK: Writing the paper, Study conception (i.e. treatment of the patient).

JK: Data collection.

FL: Study conception (i.e. treatment of the patient).

HB: Study conception (i.e. treatment of the patient), Data collection, Writing the paper.

FV: Writing the paper, Data collection, Study conception (i.e. treatment of the patient).

Guarantor

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