Study protocol for locoregional precision treatment of hepatocellular carcinoma with transarterial chemoembolisation (TACTida), a clinical study: idarubicin dose selection, tissue response and survival

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ABSTRACT

Introduction Hepatocellular carcinoma (HCC) is a common cause of cancer-related death, often detected in the intermediate stage. The standard of care for intermediate-stage HCC is transarterial chemoembolisation (TACE), where idarubicin (IDA) is a promising drug. Despite the fact that TACE has been used for several decades, treatment success is unpredictable. This clinical trial has been designed believing that further improvement might be achieved by increasing the understanding of interactions between local pharmacology, tumour targeting, HCC pathophysiology, metabolomics and molecular mechanisms of drug resistance.

Methods and analysis The study population of this single-centre clinical trial consists of adults with intermediate-stage HCC. Each tumour site will receive TACE with two different IDA doses, 10 and 15 mg, on separate occasions. Before and after each patient’s first TACE blood samples, tissue and liquid biopsies, and positron emission tomography (PET)/MRI will be performed. Blood samples will be used for pharmacokinetics (PK) and liver function evaluation. Tissue biopsies will be used for histopathology analyses, and culturing of primary organoids of tumour and non-tumour tissue to measure cell viability, drug response, multomics and gene expression. Multomics analyses will also be performed on liquid biopsies. PET/MRI will be used to evaluate tumour viability and liver metabolism. The two doses of IDA will be compared regarding PK, antitumour effects and safety. Imaging, molecular biology and multomics data will be used to identify HCC phenotypes and their relation to drug uptake and metabolism, treatment response and survival.

Ethics and dissemination Participants give informed consent. Personal data are deidentified. A patient will be withdrawn from the study if considered medically necessary, or if it is the wish of the patient. The study has been approved by the Swedish Ethical Review Authority (Dnr. 2021-01928) and by the Medical Product Agency, Uppsala, Sweden.

Trial registration number EudraCT number: 2021-001257-31.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary liver cancer, currently estimated to be the fourth most common cause of cancer-related death worldwide.1,2 Its incidence is expected to increase as the prevalence of liver diseases is rising in many parts of the world. According to the WHO, more than 1 million patients will die from primary liver cancer per year in 2030, and more than 80% of these are from...
HCC. An increasingly common risk factor for HCC is the occurrence of fatty liver disease. Other common risk factors include hepatitis infections and chronic alcohol intake. As HCC usually develops in the background of liver cirrhosis, these patients are burdened with several life-threatening conditions, since cirrhosis may cause portal hypertension and liver failure, which increase mortality rates and decrease the quality of life. The risk of developing HCC increases with progressing cirrhosis, regardless of the underlying aetiology.

The Barcelona clinic liver cancer (BCLC) staging system identifies 5 stages of HCC based on the number and size of the tumours, the patient’s performance status and the liver function. Treatment recommendations are made based on these stages. Treatments with curable intent for early stages of HCC include hepatectomy, liver transplantation and radiofrequency or microwave ablation. However, HCC is often detected in an intermediate stage, where only palliative treatment options are available. This is because discriminating between advanced cirrhosis and early-stage HCC is challenging.

The recommended therapies for intermediate-stage HCC, BCLC stage B, are intra-arterial therapies and stereotactic body radiation therapy and the standard of care is transarterial chemoembolisation (TACE), which has been used worldwide since the 1980. In TACE, a chemotherapeutic drug is delivered through a catheter placed in the liver artery, with or without the addition of an embolising agent (figure 1). The chemotherapeutic drugs can be delivered in an emulsion (conventional TACE, cTACE) or loaded into microspheres (drug-eluting bead TACE). In cTACE, the drugs are mixed with Lipiodol, a high-density oil with poppy-seed-derived ethyl iodinated esters, which is used as a carrier and for its contrast agent properties. A well-vascularised tumour is expected to respond to TACE and a good lipiodol accumulation correlates with increased overall survival and longer time to progression. However, not all well-vascularised tumours accumulate lipiodol. Early identification of these tumours would be desirable, to increase the precision of HCC treatment. Then TACE could be chosen only for tumours where it has an effect and other treatments could be chosen for other tumours, potentially within the same liver. This could be expected to increase the number of HCC patients responding to treatment.

A differentiated tumour has a more advanced vascular structure than a lesser differentiated tumour. It has therefore been suggested that lipiodol would more easily pass through a well-differentiated tumour and thereby provide a larger immediate ischaemic effect. In addition, a correlation between the intensity of lipiodol remaining in peritumoural portal vessels during TACE and the degree of histopathological necrosis has been described. A better tumour response and survival have been observed in patients with, compared with those without, peritumoural portal lipiodol enhancement during TACE. It has been suggested that lipiodol accumulation would block peritumoural portal venules, thereby preventing tumour spread. A potential association between tumour differentiation and treatment response is yet to be explored.

Doxorubicin (DOX) is the most common among drugs used for TACE, although idarubicin (IDA), epirubicin, miriplatin and cisplatin are also used. Clinical studies have reported similar efficacy and safety for IDA and DOX when used in cTACE. Recent studies have indicated that IDA has a more effective permeability across biological membranes than DOX, as it forms a more stable emulsion (which might increase the contact time of the drug with the cancer cells). IDA has also been demonstrated to be more effective than 11 other tested chemotherapeutic drugs in vitro. Although different doses of IDA have been tested, it is still unclear which dose provides the best benefit-to-safety ratio and which patients will respond best to treatment.

Although TACE has been used for decades, treatment success is unpredictable. However, a recent Italian registry study of 7184 patients, reports an increased median survival time from 21 to 42 months over the past decades, which might be explained by improved patient selection and technical development. Further improvement might be achieved by increasing the understanding of interactions between drug delivery, local pharmacology, tumour targeting mechanisms, HCC pathophysiology, metabolomics and mechanisms of drug resistance. The interaction between the HCC and its
cirrhotic environment, which is largely unknown, might be of great importance for tumour response. Intermediate and advanced-stage HCC has a generally poor prognosis, causing a great medical need. Thus, HCC needs to be further explored to improve disease detection and to enable individualisation of precision treatments, such as TACE.

**Main objectives**
The main objective of this study is to evaluate and compare tumour response, safety and plasma pharmacokinetics (PK) of IDA and its active metabolite idarubicinol (IDAol) after 10 and 15 mg doses administered with TACE in patients with intermediate-stage HCC.

A second objective is to identify HCC phenotypes using imaging, molecular biology and multiomics techniques and to establish their relation to the plasma PK of IDA and IDAol and their correlation to treatment response and survival.

Primary and secondary end-points are listed in online supplemental table 1.

**Hypotheses**
The vast scope of this study is based on the belief that the anti-tumour effect of TACE on HCC can be improved by investigating the properties of the anticancer drug IDA and its formulation, as well as the tumour and its environment by using various techniques, assays and data analyses. Our hypotheses are that: (1) two different doses of IDA will be tolerated and safe; (2) the proportion of IDA that is metabolised into IDAol is not influenced by the IDA dose; (3) a higher proportion of IDAol is correlated to better treatment response (as these metabolites are formed intracellularly); (4) HCC phenotyping by using single or combined data from imaging techniques, plasma samples, and tissue biopsies can be used for assessment of antitumour effect and subsequent prediction of treatment response; (5) the HCC phenotype is correlated to PK and pharmacodynamics of IDA and IDAol and 6) that local lipiodol retention in the tumour can predict a poor time to progression and the overall survival.

**METHODS AND ANALYSIS**

**Patient selection**
The study population consists of women and men over 18 years of age, suffering from intermediate-stage HCC in one (unilobar) or both (bilobar) liver lobes, with Child-Pugh scores ≤ 7, which fulfils the inclusion criteria (table 1).

**Study design**
This study is an open, non-randomised, two-step, active treatment single-centre clinical trial performed at Uppsala University Hospital, Sweden. Liver biopsies and positron emission tomography (PET)/MRI will be performed before and after the first TACE with the first dose of IDA as an intrahepatic intra-arterial IDA-lipiodol emulsion (study formulation details and IDA properties are presented in table 2).

| Table 1 | Inclusion and exclusion criteria for patients with intermediate-stage hepatocellular carcinoma (HCC) eligible for the TACTida study |
|-----------------|-------------------------------------------------|
| **Inclusion criteria** | **Exclusion criteria** |
| 1. Male or female adults (≥18 years) | 1. Portal vein thrombosis, with the exception of thrombosis of a segment branch of the portal vein |
| 2. Diagnosis of HCC: based on the Guidelines issued by AASLD | 2. Extra-hepatic cancer involvement |
| 3. HCC for which transplantation, surgical resection or percutaneous ablation are not indicated | 3. Contraindications to arteriography |
| 4. Child-Pugh ≤ 7p | 4. Use of IDA and/or other anthracyclines in the last 3 months prior to inclusion in the study |
| 5. Performance status: ECOG 0–2 (WHO) | 5. Previous or ongoing TACE treatment |
| 6. Life expectancy of at least 3 months in absence of treatments | 6. Known or suspect hypersensitivity to the investigational drug or to the investigational pharmacological class |
| 7. Has been vaccinated against COVID-19 or has a negative PCR-test | 7. Presence of localised or systemic infections (with the exception of HIV infection responsive to therapy, HBV and HCV) |
| 8. Signature of informed consent obtained from the patient | 8. Pregnancy |
| 9. Patients who are not capable of complying with the procedures established by the protocol and of signing the informed consent | 10. Patients evaluated for a liver transplantation |

AASLD, American Association for the Study of Liver Diseases; ECOG, European Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; IDA, idarubicin; TACE, transarterial chemoembolisation; TACTida, transarterial chemoembolisation.
TACE is performed according to local standard practice by experienced interventional radiologists at Uppsala University Hospital. The hepatic artery feeding the tumour/tumours is catheterised and the IDA-lipiodol emulsion is injected until the complete dose has been administered, or until stasis (Figure 1). If the full dose cannot be given, the given dose in each patient will be noted. The study has two parts: an experimental part (study part A) and an explorative part (study part B) (Figure 2).

In study part A, each tumour site will receive two doses of IDA on two separate treatment occasions; the first dose of 10 mg (which is the standard dose at our centre) will be given at the first TACE treatment and the second dose of 15 mg (expected to improve the benefit-to-safety ratio) will be given at the second TACE treatment. Thus, patients with unilobar HCC will receive two doses, and patients with bilobar HCC will receive four doses. For patients with bilobar HCC, TACE will be given to the liver lobe with the largest tumour(s) at the first treatment, and thereafter alternating between the liver lobes according to our clinical routine.

The maximum dose of IDA at dose event one is 10 mg/liver lobe. If this dose is tolerated by the patient, the maximum dose of IDA at dose event two and thereafter will be 15 mg/liver lobe. The decision is based on clinical observations of the tolerability of the 10 mg/liver lobe dose. The critical clinical observations are as follows: (1) intolerable adverse events during the TACE procedure such as severe abdominal pain, anaphylactic reactions, severe bradycardia; (2) deterioration in performance status, European cooperative oncology group (ECOG) 2 or more; (3) degraded liver function resulting in Child-Pugh >7p and (4) severe adverse events after the TACE procedure such as severe abdominal pain, sepsis, liver abscess, embolism, acute cholecystitis or gastrointestinal bleeding. In addition to PK, the effect of the treatment will be assessed with histopathology and multi-omics analyses (metabolomics, lipidomics, proteomics) of tissue and liquid biopsies, and with imaging techniques CT and PET/MRI.

In study part B, patients are continuously treated until disease progression or death according to local standard practice.

Biological specimens will be stored for analysis in the current trial and future use in ancillary studies.

### Data collection and assessments

**PK sampling**

Plasma for quantification and population PK analysis of IDA and IDAol will be sampled from a peripheral vein during 24 hours in study part A. In study part B, plasma will be sampled at the end of the infusion and after 150 min for population PK data analysis. Sampling time points are presented in Table 3.

Population PK of the two doses IDA and IDAol will be evaluated using a model consisting of elements describing inter-patient variability in exposure as well as potential predictors of variability between patients, which could guide future individualised dosing. Based on the population PK model, individual exposure estimates such as maximal plasma concentration (Cmax) and area under the concentration vs time curve (AUC), of IDA and IDAol will be predicted and correlated to the anti-tumour effect (determined with different methods such as histopathology, metabolomics, CT and PET/MRI), and to the safety parameters described below. If the anti-tumour effect data allows, a pharmacodynamic response

### Table 2: Properties of the study composition, a water/oil (w/o) emulsion of lipiodol (LIP) drug delivery system, containing idarubicin (IDA) as the active drug

| Study drug delivery system |          |
|----------------------------|----------|
| Active pharmaceutical ingredient | IDA (molecular mass 497.5; Log P1=1.69) |
| Vehicle | water/oil (w/o) LIP emulsion. LIP consists of linoleic acid (50%–70%), oleic acid (~15%), palmitic acid (~10%), stearic acid (~5%). |
| Type of formulation | Emulsion, preferably w/o with higher LIP volume than aqueous IDA volume |
| Biodegradable | Yes, but LIP can be accumulated in tumour tissue for up to 3 months. LIP does not interact with transporters or enzymes important for doxorubicin (another anthracycline). |
| Loading mechanism | Emulsification of aqueous IDA solution in LIP |
| Common drug load | Variable |
| Maximum dose (per treatment) | 15 mg |
| Release mechanism | Diffusion and partitioning lipid/aqueous |
| Release rate | Dependent on type of w/o emulsion |
| Technique used for administration | Via image-guided insertion of catheter into hepatic artery via femoral artery |
| Site of administration | Whole-liver, lobar, segmental or subsegmental |
| Embolisation after administration | Partial and temporary |
| In vivo distribution | Dependent on tumour size and tumour vasculature |
model will be developed which can be used to explore the correlation between the plasma PK and the HCC phenotype. Thus, simulations based on the population PK model could guide TACE treatment recommendations for HCC. In addition, the data in this study will be used to build mechanistic physiology-based PK and pharmacological models to link the dynamic interactions between the biological systems and the drug on a local level, aiming to generate an increased mechanistic understanding of disease and drug response and to facilitate further optimisation of future HCC treatment with IDA.

Safety evaluation

Safety will be evaluated continuously. Data concerning biomarkers, previous treatments and aetiology of cirrhosis are collected, and a thorough physical examination is performed at baseline. Biomarkers (including blood samples analysing liver function, electrolytes, infection and kidney function) and the occurrence and severity of adverse events and postembolisation syndrome (pain, fever, nausea and/or vomiting) will be evaluated after each TACE. The Common Terminology Criteria for Adverse Events will be used to categorise adverse events. Correlational analyses between PK and safety will be performed, as well as estimation and comparison of safety at the different doses (10 and 15 mg).

In addition, quality of life will be evaluated before and after TACE using the Short-Form Health Survey (SF-36). SF-36 is a patient-reported survey of health using an 8-scaled score with 36 questions measuring vitality, physical functioning, bodily pain, general health perceptions, physical, emotional, and social role functioning, and mental health. Each section is transformed into a 0–100

Figure 2 Flow chart of study parts (A, B) for patients with unilobar and bilobar hepatocellular carcinoma (HCC). PET, position emission tomography; PK, pharmacokinetics; TACE, transarterial chemoembolisation.
scale where a lower score indicates a more advanced disability.28

**Positron emission tomography/MRI**

A PET/MRI will be performed before and after the first TACE treatment (or the second TACE if the patient has bilobar disease). PET is performed after a single intravenous bolus injection of 3 MBq/kg body weight $18^F$-fluorodeoxyglucose and MRI in several breath-hold sequences before and after a single intravenous bolus injection of 0.1 mL/kg body weight gadoxetic acid (0.25 mmol/mL, Primovist). The duration of the entire PET/MRI examination will be approximately 1 hour.

Viable tumour volume before and after the first complete TACE will be evaluated on MR images using the modified Response Evaluation Criteria in Solid Tumours.29 On MRI, signal intensity, contrast enhancement and apparent diffusion coefficient (ADC) values will be evaluated. Liver metabolism will be assessed with a standardised uptake value (SUV) on PET before and after TACE. These collected data will be compared between HCCs within and between patients.

**CT and MRI**

In addition to the PET/MRI examinations described above, CT and MRI will be performed according to the clinical routine at Uppsala University Hospital. Thus, a CT will be performed 2–3 weeks after the first TACE for monitoring the tumour uptake of Lipiodol, and an MRI will be performed after every completed three TACE treatments (ie, after every third TACE in patients with unilobar and after every sixth TACE in patients with bilobar disease).

**Liver biopsies**

Liver biopsies with a diameter of 1.6 mm will be taken in local anaesthesia after each PET/MRI examination.

From each liver lobe, four liver biopsies will be taken using imaging guidance: 2 from viable tumour and two from non-tumourous liver parenchyma in the tumour proximity.

The samples from tumour and non-tumour tissue will be used for histopathology, molecular biology and multiomics analyses (metabolomics, lipidomics, proteomics). From the same tissue sample, 10 mg will be snap frozen for multiomics analyses, and approximately 5 mg will be used for establishing 3D organoids.

Organoid culture will be initiated by mechanically dissociating the tissue, followed by enzymatic digestion with collagenase type IV and subsequent purification steps of washing and centrifugation (figure 3). Organoids from tumour and non-tumour tissue will be embedded in hydrogels containing extracellular matrix components (figure 4) and left to proliferate for 3–5 passages, after which sufficient cell numbers will be reached for the planned experiments.30 These organoids will then be analysed and exposed to different concentrations of IDA or vehicle-control for 6, 24, 48 and 72 hours.

Cell growth and viability will be measured throughout, to quantify if ex vivo drug response correlates to the patient’s response to TACE treatment. The ex vivo data will also be compared regarding their predictive power on the overall treatment effect in each patient. In addition, RNA and protein samples will be taken from treated and untreated organoids for further molecular and multiomics assays, which will allow us to define underlying mechanisms that contribute to response and resistance. We will also collect cell culture medium to measure extracellular factors, such as exosomes. The results from these analyses will be used to identify potential non-invasive biomarkers for drug response.

**Liquid biopsies**

Liquid biopsies (plasma) will be collected before each TACE treatment and submitted to multi-omics analyses, which will be related to the antitumour effect searching for new biomarkers for HCC. IDA and IDAol will be quantified in the plasma samples using ultra-high-performance liquid chromatography-tandem quadrupole mass spectrometry (MS). The plasma and tissue samples for omics analysis will be analysed with ultra-high performance liquid chromatography—high-resolution full scan MS using the quadrupole-time-of-flight and Orbitrap techniques. If an association is detected between the antitumour effect and any of the omics parameters analysed in tissue biopsies, the same parameters analysed in liquid biopsies will be tested for associations.

**HCC phenotype**

An attempt will be made to identify different HCC phenotypes based on any differences detected in PK (IDA-metabolism), MRI (signal intensity, contrast enhancement and ADC-values), PET (SUV-values), histopathology, ex vivo data (from cultured cells) and metabolomics/lipidomics (on tissue and liquid biopsy and cultured cells).
In the search for associations or/and correlations between HCC-phenotype, PK and tumour response, the statistical evaluation will primarily be performed using descriptive statistics, with formal testing for the primary hypothesis, only. CIs will be presented and interpreted descriptively. For the primary analysis, a \( p < 0.05 \) will be considered statistically significant. Due to the exploratory nature of the study, no adjustments for multiplicity will be done. All variables will be presented in summary tables. Outcome variables will be summarised by dose, the number of treatments and tumour burden, and location as applicable. Frequency tables will be presented for qualitative variables and as the number of observations, means, SD, medians, and minimum and maximum values for quantitative variables. If possible, a model-based analysis of the correlations of exposure, HCC-phenotype and tumour response will be performed.

Clinically relevant laboratory abnormalities will be described. The absolute values and changes from baseline will be described. Relative change in tumour size and Statistic
percentage of necrosis will be defined as the difference between baseline and post-TACE measurements.

Sample size calculation

The primary aim is to detect a difference in plasma exposure (AUC) between the 10 mg dose/liver lobe and the second 15 mg dose. The sample size has been determined by the experimental part of the study (part A), that is, to empower the detection of differences in plasma exposure of IDA and its active metabolite (safety surrogate parameter) between the two doses of IDA. A recent study of patients with HCC presented AUC<sub>0-24h</sub> data of 149.9 (±64.8) ng/mL·hour (mean±SD) for 15 mg of IDA administered with TACE and suggested a linear dose–exposure correlation between 10 and 25 mg. Thus, we expect a mean (±SD) AUC<sub>0-24h</sub> of 100.4 (±43.4) ng/mL/hour for 10 mg. The interindividual and intraindividual variability are expected to be similar in our cohort compared with theirs. The sample size needed to compare the two expected means (149.9±64.8 vs 100.4±43.4 ng/mL/hour) has been calculated using the following equation, expecting 80% of the patients to tolerate the higher IDA dose:

\[
\eta_A = \left( \sigma_A^2 + \sigma_B^2 + \frac{\sigma_1 a + \sigma_1 b}{\mu_A - \mu_B} \right) \Phi \left( \frac{\mu_1 - \mu_B}{\sigma_1} \right)^2
\]

Absolute numbers used in the one-sided power calculation are: \(\alpha=0.05\), \(\beta=0.1\) and \(K=0.8\).

\(
\kappa=nA/nB \) is the matching ratio.

\(\sigma_A\) is the SD in Group ‘dose event 1’.

\(\sigma_B\) is the SD in group ‘dose event 2’.

\(\Phi\) is the standard normal distribution function.

\(\Phi^1\) is the standard normal quantile function.

\(\alpha\) is a type I error.

\(\beta\) is a type II error, meaning \(1-\beta\) is power.

Thus, to detect a difference in AUC between the 10 mg and the 15 mg of IDA, an initial sample population of 25 patients is required. To get 25 evaluable patients, with an expected error margin of 30%, up to 30 patients will be included.

Novel and highly specialised bioanalytical and imaging techniques are used and combined in the explorative part of the study (part B) for a large number of secondary endpoints. If the sample size turns out to be too small to reliably test the hypotheses of study part B, this part of the study will be regarded as a pilot study.

Total run time of the study

The total run time of the study is based on the number of HCC patients receiving their first treatment at Uppsala University Hospital. At least 30 patients will need to be included to obtain 25 evaluable HCC patients from the treatment centre at Uppsala University Hospital. The estimated total time to include a sufficient number of patients is 18 months. The inclusion started in January 2022 and is expected to stop in August 2023.

Patient and public involvement

None.

Ethics and dissemination

The study has been approved by the Swedish Ethical Review Authority (Dnr. 2021-01928) and is conducted under the tenets of the Declaration of Helsinki. It has also been approved by the Medical Product Agency, Uppsala, Sweden (EUDRA: 2021-001257-31). All participants sign an informed consent after having received written and oral information about the study. The informed consent is collected by a physician from the research group.

Personal information remains confidential, and data are deidentified using participant numbers. Only the research group will have access to study data. A patient will be withdrawn from the study treatment if it is considered medically necessary, or if it is the wish of the patient. The reason for withdrawal will be clearly described, and the patient will not be replaced. Study participants do not get any economic provision, and any harm will be compensated by regular patient insurance. It was not appropriate to involve patients or the public in the design, conduct, reporting or dissemination plans of our research. The research group holds monthly monitoring meetings. The results of the study will be published in peer-reviewed scientific journals, authored by the research group.

DISCUSSION

HCC is often detected in the intermediate stage (BCLC stage B), where TACE is the best treatment option. Although TACE has been the standard of care for several decades it still has many limitations. HCC is a heterogeneous cancer with a large variety of genotypes and phenotypes necessitating further research to understand the complexity of the disease and to pave the way for precision medicine. Thus, to improve the therapeutic effect it is essential to increase the understanding of the complex interactions between drug delivery, local pharmacology, tumour targeting mechanisms, liver pathophysiology, metabolomics, patient and tumour heterogeneity and resistance mechanisms.

A large Italian study reveals, that in real-life practice, TACE is used more extensively than what is recommended by the BCLC guidelines. Thus, a majority of patients in BCLC stage B who are recommended to receive treatments with curable intent, and a large number of patients in BCLC stage C, who are recommended systemic treatments, received TACE. This further highlights the complexity of identifying patients who will benefit from TACE compared with other treatment options, and the need for more reliable predictors to increase treatment precision. Providing an ineffective treatment not only brings unnecessary suffering and potential harm to the patient but also strains the limited resources available in the healthcare system.

Our study aims to increase the knowledge of HCC in general, and its response to TACE with lipiodol and IDA specifically, to improve patient prognosis and enable precision medicine. Our cross-disciplinary team has vast experience with various established and recently
developed highly specialised techniques for data analysis and interpretation. These techniques will be used to investigate whether the differences between HCCs detected with histopathology correlate with those detected with PET/MRI and/or any of the multomics techniques aiming to determine HCC phenotypes and to investigate whether such phenotypes correlate with PK and tumour response. Ideally, a single or combined imaging and multi-omics biomarker might be identified which could be used to predict short and long-term treatment responses. Such a tool would be helpful to identify patients who would benefit from TACE and, thus, enable personalisation and increased precision of HCC treatment.

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REFERENCES
1 Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, et al. Global, regional, and National cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA Oncol* 2017;3:524–48.
2 Yang JD, Hainaut R, Gores GJ, et al. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol* 2019;16:589–604.
3 European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;64:1388–402.
4 Projections of mortality and causes of death [Internet]. Available: https://www.who.int/healthinfo/global_burden_disease/projections/en/
5 Blachier M, Leleu H, Peck-Radosavljevic M, et al. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol* 2013;58:136–47.
6 Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2015 update. *J Hepatol* 2015;62:578–88.
7 European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;69:182–236.
8 Galle PR, Tovili F, Foerster F, et al. The treatment of intermediate stage tumours beyond TACE: from surgery to systemic therapy. *J Hepatol* 2017;67:173–83.
9 Aguina CT, Eskander MF, Pawlik TM. Liver-directed treatment options following liver tumor recurrence: a review of the literature. *Front Oncol* 2022;12;10:102815.
10 Suzuki K, Kono N, Ono A, et al. Transcatheter arterial chemoembolization for humoral hypercalcaemia of hepatocellular carcinoma. *Gastroenterol Jpn* 1988;23:29–36.
11 Fairev S, Rimassa L, Finn RS. Molecular therapies for HCC: looking outside the box. *J Hepatol* 2020;72:342–52.
12 Chen C-S, Li F-K, Guo C-Y, et al. Tumor vascularity and lipiodol deposition as early radiological markers for predicting risk of disease progression in patients with unresectable hepatocellular carcinoma after transarterial chemoembolization. *Oncotarget* 2016;7:7241–52.
13 Miyayama S, Mitsui T, Zen Y, et al. Histopathological findings after ultraselective transcatheter arterial chemoembolization for hepatocellular carcinoma. *Hepatology Research* 2009;39:374–81.
14 Nyman SS, Creussen AD, Johnsson U, et al. Peritumoral portal enhancement during transarterial chemoembolization: a potential prognostic factor for patients with hepatocellular carcinoma. *Acta Radiologica* 2021;62:11041321.
15 Lencioni R, de Baere T, Soulen MC, et al. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. *Hepatology* 2016;64:106–16.
16 Roth GS, Teissyer Y, Abouassaliha M, et al. Idarubicin vs doxorubicin in transarterial chemoembolization of intermediate stage hepatocellular carcinoma. *World J Gastroenterol* 2020;26:324–34.
17 Favelier S, Boulin M, Hamza S, et al. Lipiodol trans-arterial chemoembolization of hepatocellular carcinoma with idarubicin: first experience. *Cardiovasc Intervent Radiol* 2013;36:1039–46.
18 Padia SA. Is idarubicin the future of TACE? *Radiology* 2019;291:809–10.
19 Favoulet P, Cercueil JP, Faure P, et al. Increased cytotoxicity and stability of Lipiodol-pirarubicin emulsion compared to classical doxorubicin-Lipiodol: potential advantage for chemoembolization of unresectable hepatocellular carcinoma. *Anticancer Drugs* 2001;12:801–6.
20 Boulin M, Guiu S, Chauffert B, et al. Screening of anticancer drugs for chemoembolization of hepatocellular carcinoma. *Anticancer Drugs* 2011;22:741–8.
21 Guiu B, Jouve J-L, Schmitt A, et al. Intra-arterial idarubicin-lipiodol without embolisation in hepatocellular carcinoma: the LIDA-B phase I trial. *J Hepatol* 2018;68:1163–71.
22 Pelizzaro F, Haxhi S, Penzo B, et al. Transarterial chemoembolization for hepatocellular carcinoma in clinical practice: temporal trends and survival outcomes of an iterative treatment. *Front Oncol* 2022;12.
23 Chen Z, Xie H, Hu M, et al. Recent progress in treatment of hepatocellular carcinoma. *Am J Cancer Res* 2020;10:2993–3036.
24 Khaled J, Kopsida M, Lennernäs H, et al. Drug resistance and endoplasmic reticulum stress in hepatocellular carcinoma. *Cells* 2022;11:632.
25 Lilienberg E, Dubbelboer IR, Karalli A, et al. In Vivo drug delivery performance of lipiodol-based emulsion or drug-eluting beads in patients with hepatocellular carcinoma. Mol Pharm 2017;14:448–58.
26 Yarchoan M, Agarwal P, Villanueva A, et al. Recent developments and therapeutic strategies against hepatocellular carcinoma. Cancer Res 2019;79:4326–30.
27 UDo H, Services H. Common terminology criteria for adverse events, version 4.0. Bethesda, MD: National Institutes of Health, 2010.
28 Ware JE, Sherbourne CD. The mos 36-item short-form health survey (SF-36), I. conceptual framework and item selection. Med Care 1992;30:473–83.
29 Lencioni R, Llovet J. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. In: Seminars in liver disease, 30. . Thieme Medical Publishers, 2010: 30. 052–60.
30 Broutier L, Mastrogianni G, Verstegen MMA, et al. Human primary liver cancer-derived organoid cultures for disease modeling and drug screening. Nat Med 2017;23:1424–35.
31 Ebeling Barbier C, Heindryckx F, Lennernäs H. Limitations and possibilities of transarterial chemotherapeutic treatment of hepatocellular carcinoma. Int J Mol Sci 2021;22:13051.
32 Lin D-C, Mayakonda A, Dinh HQ, et al. Genomic and epigenomic heterogeneity of hepatocellular carcinoma. Cancer Res 2017;77:2255–65.
33 Lu L-C, Hsu C-H, Hsu C, et al. Tumor heterogeneity in hepatocellular carcinoma: facing the challenges. Liver Cancer 2016;5:128–38.