Histotripsy for Renal Cell Carcinoma: a pilot study for a novel focused therapy with an unmet need

Study Protocol

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Background

Renal cell carcinoma (RCC) is a significant contributor to cancer-related mortality worldwide, accounting for 2% of global cancer deaths (1). Despite advances in surgical management, targeted therapies, and immuno-oncology, long-term survival for patients with advanced or metastatic disease remains dismal at 12% 5-year overall survival rate (1). Current local ablative modalities, including radiofrequency ablation, microwave ablation and cryoablation are constrained by risks of thermal injury and procedural limitations associated with proximity to critical renal vasculature and collecting systems. The development of novel, non-thermal focal therapies that can be safely integrated with existing systemic treatment strategies is therefore of high clinical relevance.

Histotripsy is a non-invasive, non-thermal focused technique that utilizes precisely controlled high-intensity acoustic waves to mechanically fractionate tissue without the use of heat or ionizing radiation, enabling millimetre-scale precision under real-time ultrasound guidance. Preclinical investigations have identified the ideal acoustic parameters yielding the desired non-thermal damaging effect on kidney tissue without evidence of thermal coagulative necrosis (2-5). In addition, these studies also demonstrated a relative preservation of the collecting system and fewer bleeding events when compared with cryoablation. Furthermore, histotripsy be effective in producing fractionation of malignant tissue in various in vivo renal models (6, 7) demonstrating initial acute inflammatory responses followed by resorption of fractionated material within 60 days (8) and also with the potential of altering the tumour immune microenvironment (9, 10). Currently there are limited data on the safety and efficacy of histotripsy for the treatment of RCC, hence the unmet need of this pilot study, however the first patient treated with histotripsy for RCC with 12 months follow-up in the CAIN trial, only had procedure-related complications of grade 1 haematuria and lower abdominal pain and vomiting reported within the first couple of days post-procedure, which resolved without sequalae. The patient had no reported Clavien-Dindo Grade ≥3 complications, therefore the first ever global histotripsy of RCC with 1 year follow-up has shown preferable safety signal (11).

This proposal seeks to evaluate the safety, local tumour control, and immunomodulatory effects of histotripsy in renal cell carcinoma, establishing its potential as a novel local treatment modality capable of augmenting responses to contemporary systemic and immune-based therapies.

The HistoSonics Histotripsy System is now registered in the Medical Device Administration Control System from Department of Health in Hong Kong (HKMD no: 252842).

Hypothesis

Non-thermal histotripsy ablation is safe and feasible for renal cell cancers and induces a pro-inflammatory, immunogenic tumour microenvironment (TME) that augments systemic anti-tumour immunity.

Objective

The project will be a pilot study in localised or metastatic renal cell carcinoma, assessing safety, local control, and exploratory immune endpoints. Outcomes from this work will inform rational combinations with targeted agents and immune checkpoint blockade and may define a new, image-guided, non-invasive modality for renal cell carcinoma. If successful, histotripsy could become a new non-thermal, local therapy for renal cell carcinoma with dual benefits of debulking and immune activation achieving strong clinical and scientific impact.

Study Design and Methodology

This study will enrol 15 patients with localised or metastatic renal cell carcinoma. Patients will be identified from clinic, and undergo a comprehensive evaluation, including imaging studies and laboratory tests, to confirm the diagnosis and assess their eligibility for histotripsy.

Procedure

Histotripsy will be performed by dedicated team of oncologist, urologist and radiologist who have undergone accredited training on Histotripsy aiming to achieve the best clinical outcomes and ensure patient safety. Patients are typically placed under general anaesthesia (GA) or monitored anaesthesia care (MAC) with real-time monitoring. The component of the Histotripsy machine that generates sound waves is positioned within a soft, flexible membrane filled with specially treated water, which rests on the patient's abdomen and facilitates the transmission of sound waves to the targeted tissue. The procedure will be delivered in a single session or multiple sessions by ultrasound, depending on the size and location of tumours. Patient needs to be fit for general anaesthesia to start with.

Assessment

Patients will be invited to complete a questionnaire for pain score assessment before and after histotripsy.

Blood samples will be collected for clinical evaluation and laboratory tests at baseline, followed by 1-day, 30-day, 60-day, and 90-day after histotripsy, aligned with existing feasibility and trial schedules. Blood tests and cellular analysis such as complete blood profile, liver and renal function tests, tumour markers, immune markers and biomarkers etc. will be performed each time. Patients will be asked for consent for 15ml blood collection for the cellular analysis.

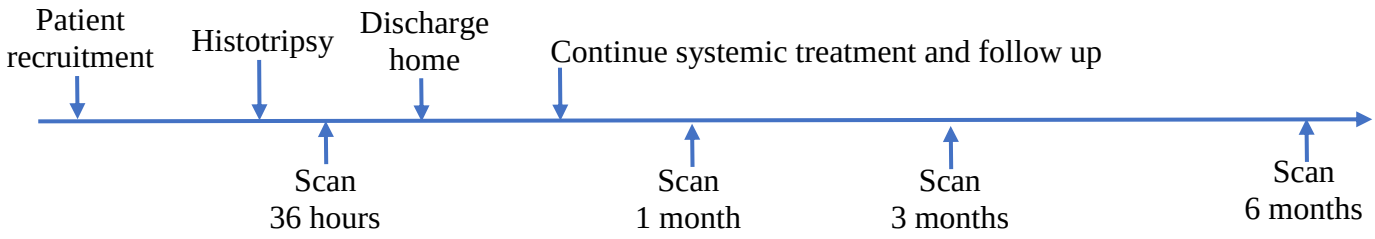
Serial post-histotripsy imaging (CT/MRI) will also be arranged. Imaging within 36-hour after histotripsy will be proceeded to confirm the ablation zone and assess complications. Post-procedure imaging at 1-, 3-, and 6-month will help to capture the sustainability of treatment effect, then per standard of care thereafter.

Admission and follow-up

Similar to other minimal invasive treatments, patients will be admitted one day prior, or on the day of procedure. After the procedure of histotripsy, patients may experience some discomfort in the treated area, but patients can often return to normal activities quickly. They could be discharged in few hours, or the next day after procedure depending on clinical conditions.

After discharge, follow-up consultations and assessments such as regular imaging and blood tests will be arranged accordingly.

Flowchart



Potential risk and discomfort

Blood drawn for laboratory tests can cause bruising at or near the site where the needle enters the vein and thus increase the risk of infection. Risks related to imaging scans will be explained prior to the procedures by the related doctors or medical professionals.

Procedure risk related to Histotripsy includes skin erythema or superficial burn injury, infection, bleeding, renal dysfunction, and abdominal wall injury or burn. Adverse post treatment event includes bleeding, infection, damage to surrounding structures etc. The medical team will monitor closely and response promptly.

Short-term effects

- Mild pain or soreness that usually responds to oral pain medication
- Low-grade fever and flu-like symptoms that typically resolve within 48 hours
- Temporary skin redness at the treatment site
- Mild abdominal discomfort
- Temporary changes in renal function tests
- Possible nausea or fatigue
- Transient haematuria

Potential serious complications

- Temporary decrease in kidney function
- Potential damage to surrounding organs (liver, lung, bowel, or stomach)
- Severe pain
- Need for extended hospital stay or additional treatment for serious complications
- Skin ulcer / necrosis requiring interventions
- Vascular thrombosis / dissection

Long-term complications

- Currently, there is no known long-term side effects from Histotripsy treatment. Ongoing research aims to evaluate the long-term outcomes.

In the event of complications arising from the study treatment, patients will be treated accordingly or referred for standard treatment and care.

Outcome

Primary outcome

- To assess treatment safety and efficacy
    - Safety
        - Clinical evaluation and laboratory tests
        - Imaging by MRI or CT within 36 hours post-procedure
    - Efficacy
        - Serial imaging by MRI or CT post-procedure (aside from the one within 36 hours)
        - RECIST, volumetric assessment of ablated and non-ablated tumour, local progression patterns

Secondary outcome

- Pain score assessment before and after histotripsy
- Explore immune endpoints

Selection and Withdrawal of Subjects

Inclusion criteria

- Age ≥ 18 years old
- Fit for general anaesthesia
- Histologically confirmed renal cell carcinoma; radiological diagnosis acceptable if biopsy is not feasible
- With or without distant metastases
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) grade 0-2
- Tumour visible and targetable by ultrasound with acceptable acoustic windows
- Adequate hematologic, hepatic, and renal function (eGFR ≥45mL/min, ≤14 days prior to the planned index procedure date).

Exclusion criteria

- Refusal to take part in clinical trial
- Not fit for general anaesthesia
- Poor general condition with limited life expectancy
- Uncontrolled coagulopathy
- The treatment of the tumour will not allow for an adequate margin as determined by the investigator

Treatment of Subjects

Resection remains the first line of treatment for localised renal cell carcinoma, while systemic treatment +/- cytoreductive nephrectomy is preferred for metastatic disease. Patients who decline to be involved in the study will continue with other standard treatment options.

Duration of Study

The study duration is approximately 2 year for 15 successful recruitments.

Statistical analysis

Analysis will be performed for the 15 participants recruited, with basic demography (age, sex, medical history etc.), clinical evaluation, laboratory tests, imaging, treatment outcome with associated complication.

DATA AND BIOLOGICAL SAMPLES HANDLING

Patients will be invited to register on the Histotripsy (HistoSonics®) Registry in Gleneagles Hospital Hong Kong for data collection. Collected personal and study data will be anonymised and stored in a password protected, encrypted database with the principal investigator and delegated staff in the long run. The principal investigator will be responsible for the safekeeping. Only investigators and delegated staff can have right to gain access to the data. All collected data and biological samples will be stored permanently for future review in histotripsy related research. Unused biological samples will be destroyed and discarded upon request, however, the results will remain a part of the overall research data if part of the sample has been proceeded.

Cost and Benefit

Patients may receive some advantages from non-invasive surgical procedure. If the disease is inoperable initially, this treatment approach would be another feasible treatment.

The package fee of histotripsy in Gleneagles Hospital Hong Kong may be supported by a designated research fund from Gleneagles Hospital Hong Kong and The University of Hong Kong, subject to availability. Patients can also pay for the fee on their own.

Details of package coverage are listed below, according to the website of Gleneagles Hospital Hong Kong:

Inclusions

- Room charge including accommodation
    - 2-bedded standard room
    - One basic set meal per meal time
    - Overnight ends at 12:00 noon on the core package end day
- Doctor's fees (including daily attendance fee, doctor's procedure fees and anaesthesiologist's fees if applicable) related to package procedure
- Treatment charges
    - Basic equipment and instrument charges
    - Related and basic medication fee, consumables, materials, and implant charges
    - Related and essential basic diagnostic procedure charges (including laboratory testing and X-ray imaging)
- Nursing procedure charges

Exclusions

- Accommodation related:
    - Additional room charge may apply for late checkout
    - Changing bed within the same grade of accommodation
    - Companion bed or guest meals
- Additional operation charges, medication, diagnostic procedures, professional fees and sundries charges unrelated to the Histotripsy treatment procedure
- Any treatment, medication, procedures fee related to pre-existing condition
- Pre-operative advanced diagnostic procedure charges (Biopsy, CT, MRI etc.)
- Advanced equipment, instruments, consumables and materials, and non-designated implant charges
- Any charges or services before actualisation of the trial and after patient discharge (pre-admission consultation, post-consultation etc.)
- Any imaging eg. pre-procedure ultrasound screening, post-procedure scans (CT/MRI, etc.)

Notes

- The package applies only to patients staying in standard room, and expires upon discharge or on the end date of the package (or that of an extension package, if applicable), whichever earlier.
- There will not be any refund for discharge earlier than the end date of the package.
- Should the duration of Histotripsy exceeds the stipulated timeframe due to actual clinical needs, additional charges will be applied.
- If the patient is diagnosed with a disease which deviates from the original diagnosis and requires a different course of treatment subsequent to the hospital admission, the hospital may void the package and charge according to the new treatment required. In that case, patients (or their next-of-kin / authorised persons) will be informed of the new charges with consent sought before the new course of treatment is administered.

- The package only applies to surgical procedures performed and confirmed by designated doctor of Gleneagles Hospital Hong Kong. Advance appointment is required.
- The package cannot be used in conjunction with other promotional offers; it cannot be exchanged for cash or other product. The package offer is non-transferrable and non-refundable.
- Gleneagles Hospital Hong Kong reserves the right to amend any of the above terms and conditions without prior notice. In case of any dispute, Gleneagles' decision is final.

Consent

Written voluntary consents will be obtained after full explanation of the study to patients before agreement of the histotripsy procedure.

Funding

A designated research fund from Gleneagles Hospital Hong Kong and The University of Hong Kong, and / or private donation will support the trial, subject to availability. The trial will also be covered by the master HKU-CTC insurance and Gleneagles Hospital Hong Kong insurance. Individual clinician will be covered by MPS subscription as per usual practice. The cost of each patient's procedure (Histotripsy package) will be covered by the designated research around HKD 6,160,000 (i.e. HKD 308,000 per patient), subject to the availability. Investigation, cellular analysis costs to evaluate response, staff cost for data collection, database maintenance as well as study administration, will be supported by additional fund under the research fund.

Conflicts of interests

All investigators and funding bodies have no financial interests in the study.

Research ethics

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Patient data protection.

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