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Fiducial **I**mage guided **S**tereotactic ablative body radiotherapy (SABR) for **H**epatocellular carcinoma **A**fter Interventional **R**adiology treatment (TACE) (**FISHAR** trial)

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BACKGROUND :

Hepatocellular Carcinoma And Current Therapies

Hepatocellular carcinoma (HCC) is a major health issue and the second leading cancer related cause of death in the world (1, 2). The current standard treatments for HCC are loco regional therapies - Microwave Ablation and Transarterial Chemoembolisation (TACE).

Microwave Ablation (MWA) - Typically, the outcomes for ablative therapies such as microwave ablation are excellent, with low risk of local recurrence. This is carried out by inserting a needle to the centre of the liver lesion, and ablating it with heat through the generation of microwaves. Despite excellent outcomes, the application of this therapy is limited to cancerous lesions less than 3cm in diameter and certain anatomical parts of the liver where it can tolerate thermo injury. HCC larger than 3cm, multifocal lesions, or HCC that are unreachable / not suitable to thermo injury (e.g. lesions near gallbladder and central bile ducts), are treated with TACE as an alternative.

Transarterial Chemoembolisation (TACE) - TACE involves puncturing the femoral artery to access the feeding arterial vessel of the HCC via catheterisation. This is achieved with the use of contrast under an image intensifier. Once the dominant feeding vessel is identified, a mixture of lipiodol and a chemotherapeutic agent (e.g. doxorubicin) is injected directly into the tumour. Following this, the feeding artery is occluded to cause tumour ischemia / necrosis. While TACE is commonly used as standard of care in large HCCs (5-10cm), unlike ablation, it is not considered a curative therapy. This is due to HCCs typically being fed by numerous arterioles, beyond a dominant feeding vessel. Therefore, while TACE does control HCC growth in the short term, local and distant recurrence is common. Hence, better treatment options that allow for curative outcomes are urgently required.

Stereotactic Ablative Body Radiotherapy (SABR) - There have been significant advances in external-beam radiation therapy that allow for more targeted and intense delivery of dose-fractionation to malignancies with minimal toxicity. SABR was initially developed to treat intracranial malignancies, however, there has been significant interest in adopting this technique for other tumours, including HCC. With the aid of fiducial markers, simulation

planning allows SABR to deliver intense radiation (typically 8-14Gy/fraction), without causing significant harm to the surrounding tissues. This is achievable even with moving targets such as lung or liver lesions during respiration.

The current data for SABR in HCC is limited, due to it being a relatively new treatment option for HCC. However, there have been a number of retrospective studies looking at the efficacy of SABR in heterogeneous populations. Yoon SM *et al*. investigated the use of SABR alone for smaller lesions 2-3cm (3). SABR is not current standard therapy for HCC management of lesions this size, according to the BCLC guidelines. Choi Bo *et al*. examined SABR combined with TACE for larger lesions 5-7cm with portal vein tumour thrombus. This cohort would normally be considered palliative by BCLC criteria (4). Hence, there are significant data gaps for those who are not eligible for curative ablative therapy and those receiving/failed TACE, with localised disease (no obvious lymphovascular invasion such as portal vein tumour thrombus). These large multi-institutional retrospective studies indicate SABR as a promising new therapy for HCC management; however, limitations of these investigations include radiation doses varying between institutions and heterogeneous patient groups (5, 6). While these studies add significantly to the literature and indicate potential for SABR being used to treat HCC, further prospective studies are clearly warranted. Takeda *et al.* published in Cancer this month the first investigation looking prospectively at the use of SABR (7). This study demonstrates that SABR provides high local control of HCCs that are not able to be treated with resection or ablation. However, their cohort of 90 patients had a median tumour range of 2.3cm and an inclusion criterion of tumours less than 4cm. Our prospective study aims to look specifically with curative intent at the application of SABR in treating larger lesions in patients (6cm or less) that have been unsuccessful with TACE. As such, our study will complement and provide further evidence for SABR becoming a standard treatment option for HCC.

EUS guided placement of fiducial markers - To further increase the accuracy of SABR in the treatment of HCC, placement of fiducial markers will be performed by endoscopic ultrasound (EUS). This has been shown to be a safe modality for insertion of fiducials, with greater than four years of experience in other areas of Gastrointestinal malignancy within our centre (8, 9).

PURPOSE OF STUDY

Hepatocellular cancer (HCC) is a major complication of cirrhosis and a leading cause of mortality. A large number of patients are only eligible for TACE for management of HCC, as their disease is beyond MWA therapy. As a result, their therapy is not considered curative, as repeat TACE procedures have a high chance of local recurrence or distal metastasis. This is particularly high in cases where the initial TACE did not adequately control tumour growth (based on restaging).

Stereotactic ablative body radiotherapy (SABR) is an emerging therapy for HCC, whereby intense radiation can be delivered to the desired target with the help of metal markers (gold fiducials), without causing significant toxicity to surrounding tissues or neighbouring organs. There is limited data for its use in small and large HCCs in research and palliative settings, respectively. However, to our knowledge, there is no current data for its use as an adjuvant therapy with best standard practice, to decrease recurrence in high-risk patients. We hypothesise that SABR will reduce the likelihood of recurrence with incurable HCCs.

In 2015 at the Royal Adelaide Hospital, conservatively 17 patients underwent repeat TACE procedures, whereby standard treatment for HCC was unsuccessful at least once. Apart from risking further treatment unsuccessful treatments with repeat TACE procedures leading to tumour progression, performing multiple TACEs can be associated with complications, from liver failure due to hepatic ischemia, through to death.

In this study, we hope to gather pilot data to assess the safety and efficacy of using SABR, instead of repeating TACE, in those who have failed TACE therapy at least once. With this pilot data, we hope to apply for further funding to perform a multicentre, randomised, controlled trial, to test the safety and efficacy of SABR and TACE in HCC patients.

AIMS

The aim of this study is to assess the safety and efficacy of SABR in a small cohort of HCC patients whom have failed TACE therapy, characterised by persistent tumour on radiological imaging. Patients recommended by the HCC multidisciplinary team to consider a further round of TACE treatment will be invited to participate in this study. ***The overall hypothesis to be tested in this proposal is: (i) The use of SABR in HCC patients with persistent/ recurrence of HCC despite previous failed TACE treatment is safe and more effective than repeated TACE and (ii) it is feasible and safe to place fiducial markers in cirrhotic patients who have HCC.***

SPECIFIC AIMS

1) To evaluate the effectiveness of SABR in the treatment of persistent/recurrent HCC where TACE (standard therapy) has failed based on tumour activity on restaging scans.

2) To evaluate the feasibility and safety of fiducial marker insertion by EUS and SABR on liver disease evident by decompensation of synthetic liver dysfunction or regional toxicity from radiation.

SUBJECTS

Twenty patients with HCC, previously treated with TACE, that have persistent or recurrent HCC will be invited to participate in this non-randomised trial.

INCLUSION CRITERIA

- Aged > 18 years
- Able to give informed consent
- ECOG 0-1

- Barcelona clinic liver cancer (BCLC) class A/B as determined by a Hepatocellular Carcinoma Multidisciplinary team (HCC MDT)
- HCC diagnosed by standard radiological criteria or histology
- HCC < 6cm which is amenable to SABR
- Pre-treated with TACE with incomplete response or re-occurrence
- Measureable disease on imaging defined by M RECIST criteria

EXCLUSION CRITERIA

- BCLC C (significant decompensated liver disease or HCC not amenable to TACE)
- Significant comorbidities unable to safely tolerate sedation/anaesthetic
- Expected life expectancy of < 24 months
- Prior radiotherapy to abdomen
- Pregnant or lactating (any woman of childbearing potential must have a pregnancy test prior to enrolment and must take adequate precautions to prevent pregnancy during treatment)

WITHDRAWAL CRITERIA

- Wish of a patient to discontinue
- Occurrence of serious adverse events

DESIGN AND PLAN FOR STUDY

Patients will be recruited for this study via the HCC Multidisciplinary (MDT) meeting from the Royal Adelaide Hospital. Twenty consecutive patients with HCC previously treated with TACE that have recurrence of tumour, and recommended by the HCC MDT to consider a repeat TACE, will be offered the opportunity to enrol in this non-randomised study. Patients will be given a patient information sheet and informed consent will be obtained. The information sheet will have details pertaining to EUS insertion of fiducials and the SABR

schedule, as well as any potential complications. Standard demographics (age, sex, ethnicity, BMI) along with aetiology and severity of liver disease, will be collected. These include Child's Pugh status and MELD score. Details of the tumour will be carefully recorded, including tumour volume and maximal diameter (mm), number of tumours, and presence or absence of vascular invasion on imaging along with biochemical markers such as AFP.

Patients recruited will receive SABR +/- fiducial placement to their HCC. The patients recruited will have ongoing follow up with RAH HCC MDT, to determine timing and type of radiological modality of restaging of their HCC. Those who progress on SABR based on M RECIST criteria will be offered salvage therapy based on standard of care as determined by the MDT, including repeat TACE or Sorafenib, should they be eligible.

Primary end points in this study include :

(1) Persistent tumour or local recurrence

(2) New development of distant metastasis during this study

Secondary end points in this study include :

(1) Progression of MELD

(2) Progression of Child's Pugh Score. Follow up will continue up to 24 months after completion of randomised intervention (i.e. after completion of I-131 or SABR) or primary end point is reached

To evaluate the effect of SABR + EUS guided fiducial as adjuvant therapy in patients with local recurrence of HCC who have previously received TACE

Pre-treatment Investigations

i) Imaging including triple phase CT or MRI

ii) Liver function including coagulation studies

iii) AFP

iv) Complete blood examination

Intervention

Imaging of patients will be reviewed by investigating EUS Endoscopist and Radiation Oncologist. If required, radiotherapy fiducial markers will be placed by EUS in four quadrants of the ablated site, or surgical margin to outline its peripheral borders. EUS and fiducial placement will be carried out in accordance with Gastroenterology and Hepatology Unit protocol at the Royal Adelaide Hospital. CT simulation will be performed within five days after fiducial placement. Simulation will employ full body immobilization (Omni V SBRT system), multi-detector 4DCT with 3mm slices and IV contrast (late arterial phase scan). Simulation tumour motion study will be assessed to determine the degree of tumour excursion. Treatment planning is determined by imaging (CT or MRI) to ensure accurate delineation of the target volume on the 4DCT maximum intensity projection. SABR will be scheduled to commence within two weeks from simulation. The planning criteria will be as follows: Planning Target Volumes (PTV): In ablated lesions, PTV will be determined by gross tumour volume (GTV) plus uniform 5mm margin. In resected lesions, PTV will be determined by the clinical target volume (CTV) plus uniform 5mm margin.

The absorbed dose will be 42-45Gy in three fractions to each PTV (BED10 = 100.8Gy). The prescription isodose should encompass at least 95% of the PTV. The maximum dose within the PTV should not exceed 140%. Treatment delivery will be in three fractions, with a maximum of two fractions per week at least 48 hours apart. Online image matching process of the gold seed fiducial markers to the reference image will be carried out.

Follow up: The clinical outcomes of tumour size, AFP and survival will be collected at 1, 3, 6, 9, 12, 18 and 24 months after the completion of treatment. The exact modality of radiological restaging (CT or MRI) will be at the discretion of the HCC MDT, to allow for the best method of assessing efficacy of therapy. Any subsequent therapy due to progression of HCC (if needed), will be determined by the HCC MDT.

To evaluate the feasibility and safety of fiducial marker insertion and SABR on liver disease evident by decompensation of synthetic liver dysfunction or regional toxicity from radiation - weekly blood tests (CBP, EUC, LFT and INR) will be performed from commencement and

up to four weeks after completion of SABR, to assess for deterioration of liver impairment/failure. Side effect profile will be carefully documented including any pain, discomfort, nausea or vomiting during or post SABR. Complications related to EUS insertion of fiducials will be recorded, including fiducial migration, bleeding, and organ perforation.

PATIENT RECRUITMENT

We plan to recruit patients from the Royal Adelaide Hospital Hepatocellular Cancer multidisciplinary meeting, or during their subsequent follow up at Outpatient clinics.

PATIENT CONSENT

Specific consent will be sought from participants for the duration of the FISHAR trial. Patients will have the option to withdrawa from the trial.

SAMPLE SIZE

- 20 Patients

ETHICAL CONSIDERATIONS

All aspects of this study will be discussed with each patient during the recruitment process. An information sheet will be provided and each patient will be given the opportunity to discuss this study with a medical practitioner, friends or family prior to involvement. Each participant will be give written, informed consent and will be free to withdraw from the study at any time.

The study protocol will be submitted to the Royal Adelaide Hospital Research Ethics Committee for approval. This study will be performed in accordance with the National

Statement on Ethical Conduct in Human Research 2007. The Chairman of the Research Ethics Committee will be notified within 72 hours should any serious adverse event occur. Confidentiality will be maintained beyond study parameters.

DATA

Data collected will include patient information (age, gender, medical history), treatment regimens and results of relevant tests (including blood, radiology and biopsy results). Data will be de-identified on completion of this study (expected duration 24 months) and patients will be assigned an identification number. Data will be stored electronically in the department of Gastroenterology and Hepatology at the Royal Adelaide Hospital. It will be password protected. The data and specimens will be kept for a maximum of 15 years after which they will be erased / destroyed.

ANALYSIS

Statistical Methods: Statistical analysis will be carried out using SPSS version 22.0.0 for Windows. Categorical variables will be compared using Chi-square and Fisher's exact test where appropriate. Quantitative variables will be tested by t-test. Univariate analysis for survival will be performed using the Kaplan Meier method and differences in Kaplan Meier curves will be tested for statistical significance using the log rank test.

OUTCOMES

Outcomes will be measured via the following criteria:

- Local recurrence: RECIST criteria
- Distant metastasis: RECIST criteria
- Progression of MELD

- Progression of Childs Pugh Score

The outcomes for patients who have undergone SABR will be compared to historic controls at the RAH, as well as those who decline this trial and have had repeat TACE treatment. Long term this trial aims to improve treatment options and management of non-resectable HCC and to ascertain if the addition of SABR to current best practice will reduce the rate of reoccurrence of high risk HCC. Data obtained from this study will be used for future grant applications for a multicentre, randomised, controlled study.

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