Efficacy and safety of radiotherapy to delay second-line systemic therapy in patients with oligoprogressive hepatocellular carcinoma: study protocol of a multicentre, single-arm, phase II trial

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Abstract

Background: Hepatocellular carcinoma (HCC) is a highly aggressive cancer with a paucity of efficacious treatment options, particularly in advanced stages following first-line systemic therapy (FLST).

Objectives: The objective of this trial is to assess the efficacy and safety of radiotherapy as a treatment option to prolong progression-free survival (PFS) and delay the necessity for second-line systemic therapy (SLST) in patients with oligoprogressive HCC following FLST.

Design: Multicentre, single-arm, phase II trial.

Methods and analysis: This prospective, multicentre, single-arm phase II clinical trial will enrol 36 patients with oligoprogressive advanced HCC following FLST. A comprehensive clinical imaging evaluation will be conducted to confirm the presence of oligoprogressive disease, categorized as metachronous oligoprogression, repeat oligoprogression or induced oligoprogression. Furthermore, patients must have demonstrated stability of the primary HCC for a minimum of 3 months during FLST. Eligible patients will receive radiotherapy for all oligoprogressive lesions with a biologically effective dose (LQ, $\alpha/\beta = 10$) of at least 60 Gy while continuing their current FLST until disease progression necessitates SLST. The primary endpoint is PFS, with secondary endpoints including objective remission rate, overall survival (OS), disease control rate, safety and duration of disease remission.

Ethics: The final protocol was approved by the Ethics Committee of the Affiliated Cancer Hospital of Shandong First Medical University.

Discussion: Given the greater number of options for FLST in advanced HCC, which have demonstrated improvements in PFS and OS, and the limited number and less effective SLST options, this phase II trial aims to evaluate the use of radiotherapy to extend PFS and delay the application of SLST in patients with oligoprogressive HCC after FLST. This approach may preserve SLST options for more aggressive, widespread metastatic disease in the future.

Trial registration: This study is registered on ClinicalTrials.gov identifier: NCT06261047.

Keywords: first-line systemic therapy, hepatocellular carcinoma, oligoprogression, radiotherapy, second-line systemic therapy

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Introduction

Hepatocellular carcinoma (HCC) is often diagnosed at an advanced stage due to its aggressive nature and insidious nature,[1] making radical treatment unsuitable for most patients. Recently, novel therapeutic modalities such as targeted therapy, immunotherapy and their combinations have transformed the systemic treatment of advanced HCC and significantly improved patient survival. Studies have shown that switching to second-line systemic therapy (SLST), such as nivolumab or pembrolizumab monotherapy, after oligoprogression during first-line systemic therapy (FLST) is less effective than continuing FLST like sorafenib in patients with advanced HCC.[2,3]

The term 'oligometastatic' describes an intermediate state of metastatic lesions, ranging from isolated to widespread. By contrast, 'oligoprogressive' refers to a similar but distinct state where limited progression occurs within otherwise well-controlled metastases. The term was first introduced in 2012[4] to describe this clinical scenario. The latest consensus from the European Society for Therapeutic Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC) identifies three subclassifications of oligoprogressive disease following active systemic therapy: metachronous oligoprogression, repeat oligoprogression and induced oligoprogression.[5]

Studies in other tumour types have shown promising results for radiotherapy combined with FLST, supporting its potential use in patients with oligometastatic disease. For example, the SABR-COMET,[6,7] SINDAS[8] and other trials[9,10] have demonstrated survival benefits, including improved median progression-free survival (PFS) and overall survival (OS). Despite these promising results, the benefits of radiotherapy may vary depending on tumour type and oligoprogressive subclassification. Research in oligoprogressive advanced HCC is currently limited and the decision to use local treatment in these patients remains controversial.[11] A recently published phase II clinical study investigating the efficacy of SABR in oligometastatic advanced HCC demonstrated that SABR is an effective and feasible treatment option. However, the study did not specifically investigate these three distinct subtypes of oligoprogression.[12]

Consequently, this phase II clinical trial was designed to evaluate whether maintaining current FLST and adding radiotherapy to oligoprogressive lesions can achieve comparable or even superior long-term local control, similar to other tumour types. To our knowledge, this is the first prospective study to evaluate radiotherapy in all three subclassifications of oligoprogressive advanced HCC. It is expected that this research will provide valuable insights that will inform the development of innovative strategies to optimize oncological outcomes.

Patients and methods

Aim and study design

This is a prospective, multicentre, single-arm, phase II clinical trial. Experienced radiation oncologists will recruit a total of 36 patients from multi-tumour centres in China to ensure rigorous patient selection. Patients who meet the eligibility criteria will receive local radiotherapy for oligoprogressive lesions while continuing their previous FLST regimen. Progressive disease (PD) stage will be confirmed by imaging modalities including computed tomography (CT), positron emission tomography (PET)/CT and magnetic resonance imaging (MRI) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines. The study includes a 12-month enrolment period followed by a 24-month follow-up period to monitor patient outcomes. The overall study design, including the enrolment and follow-up periods, is shown in Figure 1. The reporting of this study conforms to SPIRIT guidelines[13] (see Supplemental Appendix 1).

Primary endpoints and definition

- PFS: defined as the time from the start of radiotherapy until disease progression according to RECIST 1.1 or death, whichever occurs first.

Secondary endpoints and definitions

- Objective remission rate (ORR): the proportion of patients who achieve a complete response (CR) or partial response (PR) as defined by RECIST 1.1.
- OS: defined as the time from the onset of oligoprogression to the date of death.

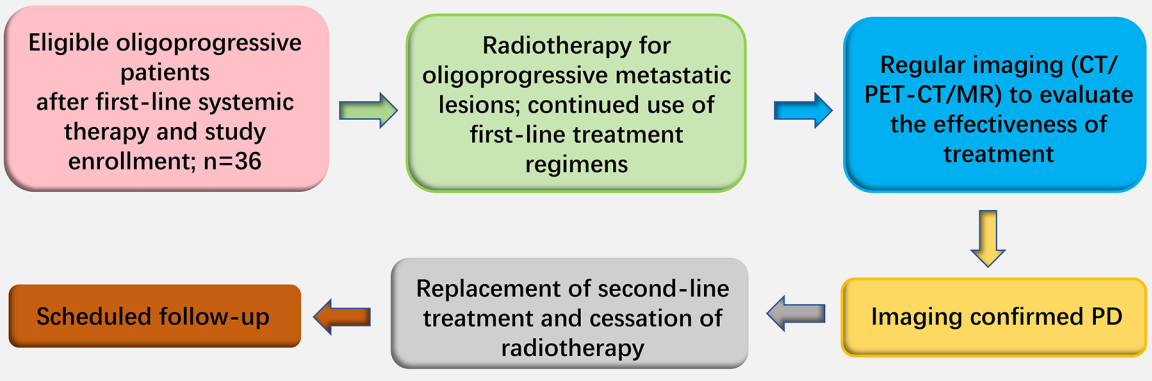

Figure 1. Study flow.
CT, computed tomography; MRI, magnetic resonance imaging; PD, progressive disease; PET/CT, positron emission tomography/computed tomography.

- Disease control rate: the proportion of patients who achieve CR, PR or stable disease (SD) as defined by RECIST 1.1.
- Duration of remission: the period from the first documented CR or PR until disease recurrence, progression or death occurs.
- Acute toxicity (Common Terminology Criteria for Adverse Events (CTCAE) v5.0).
- Late toxicity (LENT/SOMA score).
- Overall quality of life (QoL; QLQ-C30).
- QoL (QLQ-CR29).

Exploratory endpoints

- Radiomics: Quantitative imaging features will be extracted from PET-CT, CT and MRI scans and integrated with clinical factors to develop predictive models for PFS and OS in patients with oligoprogressive advanced HCC.
- Biomarker analyses: In addition, we will assess alpha-fetoprotein levels, circulating tumour DNA, immune markers and molecular profiling in both primary and metastatic lesions. These analyses are designed to identify potential predictive biomarkers of radiotherapy efficacy, refine patient stratification and provide deeper insight into treatment response.

Defining oligoprogression after systemic therapy

The use of a unified system for describing oligoprogressive disease in clinical trials facilitates a comprehensive understanding and interpretation of trial results and allows effective comparisons between trials, meta-analyses and systematic reviews. Based on the article that first introduced the concept of oligometastasis,[14] consensus statements from ESTRO and EORTC[5] and guidelines from the Red[15] and Green[16] journals, we define oligoprogression in advanced HCC for this clinical trial into three categories: metachronous oligoprogression, repetitive oligoprogression and induced oligoprogression. Figure 2 provides a comprehensive list of potential scenarios for these three types of oligoprogression, accompanied by detailed explanations. Oligoprogressive lesions are defined as radiologically confirmed and targetable lesions that are newly diagnosed or progressing. These lesions can vary from one to five metastases in up to three organs, including the primary tumour. For patients with lymph node and portal vein metastases, each lymph node metastasis site and macrovascular tumour embolism are counted separately. Bone metastases that do not manifest in soft tissue are eligible for inclusion but are not treated as measurable lesions. Conversely, if these metastases show soft tissue formation and meet the measurability criteria, they are considered measurable lesions.

Inclusion criteria

- Obtain written informed consent before implementing any trial-related procedures.
- Histological or cytological confirmation of primary HCC, or diagnosis according to the Clinical Diagnosis and Treatment Guidelines for Primary Liver Cancer (2019 edition) issued by the National Health Commission of the People's Republic of China.

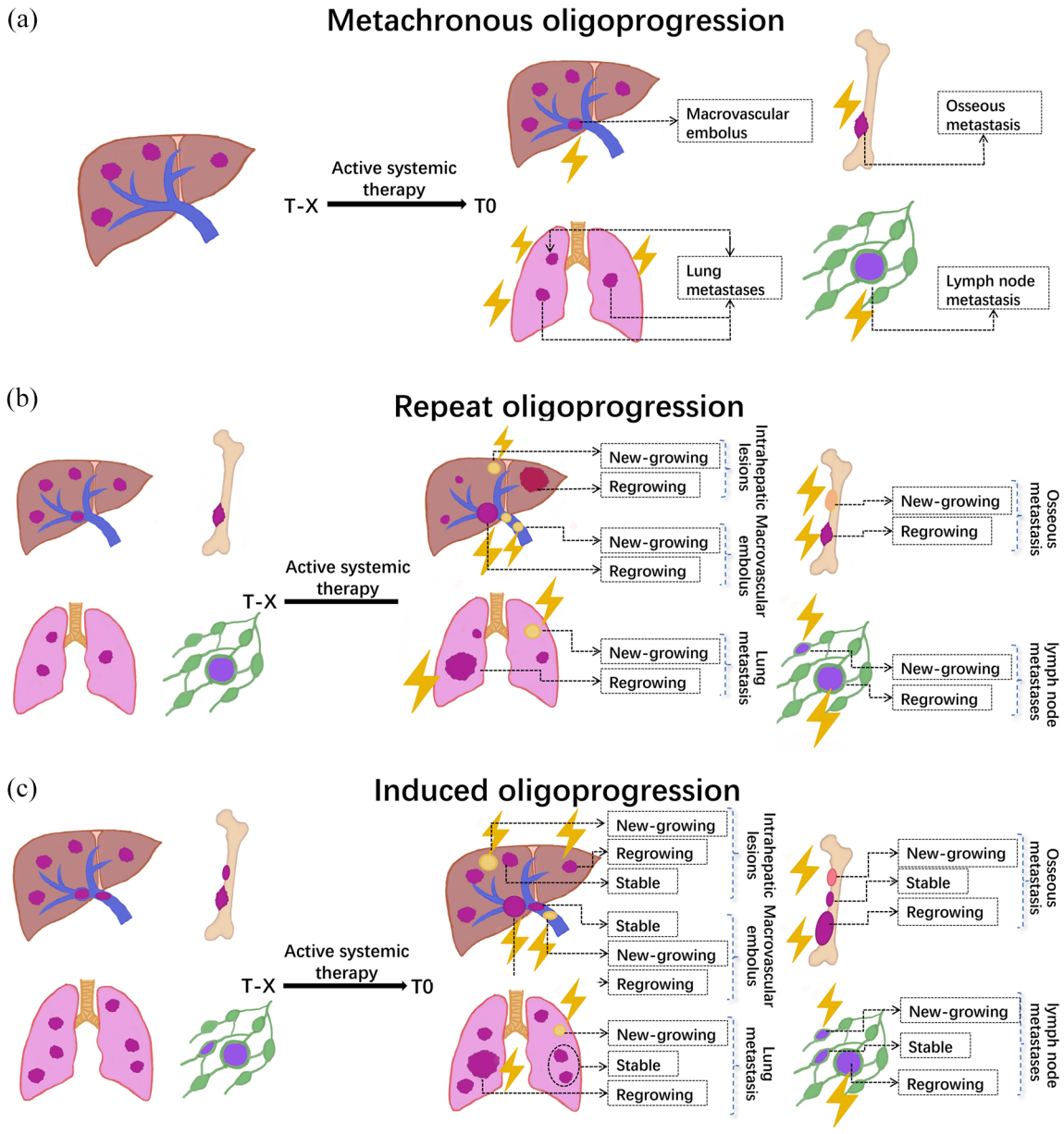

Figure 2. Comprehensive list of all possible scenarios for these three types of oligoprogression of advanced HCC. (a) Metachronous oligoprogression. T-X_a: diagnosis and treatment of primary cancer (left) in the non-metastatic state; $T0_a$: first diagnosis of new oligometastases (right) >6 months after cancer diagnosis; oligoprogression/oligometastases on the right includes, but is not limited to, the four types above (⩽5 metastases; ⩽3 metastatic organs). (b) Repeat oligoprogression. T-X^b: diagnosis of oligometastases followed by local or systemic treatment or both; $T0_b$: diagnosis of new and growing or regrowing oligoprogressive lesions; oligometastatic stage on the left include, but are not limited to, the four types above or any combination of them; oligoprogressive stage on the right include, but are not limited to, the types above or any combination of them; the newly diagnosed oligoprogressive lesions meet the following conditions: ⩽5 metastases and ⩽3 metastatic organs. (c) Induced oligoprogression. T-X_c: diagnosis of polymetastatic stage (>5 metastases or >3 metastatic organs or both); $T0_c$: diagnosis of new and growing or regrowing oligoprogressive lesions, possible residual non-progressive metastases (stable); polymetastatic stage on the left includes, but is not limited to, the types above or any combination thereof; oligoprogressive stage on the right include, but are not limited to, the types listed above or any combination of them; the newly diagnosed oligoprogressive lesions meet the following conditions: ⩽5 metastases and ⩽3 metastatic organs.
HCC, hepatocellular carcinoma.

- Prior to enrolment, patients should receive FLST and develop oligoprogression as defined in Figure 2; after enrolment, tumour stage should be BCLC stage C.
- Oligometastatic/oligoprogressive lesions should be eligible for radiotherapy and should have at least one measurable lesion that meets the RECIST v1.1 criteria for evaluable lesions.
- Liver function should be assessed by a Child-Pugh (CP) score ⩽7 points.
- Patients' Eastern Cooperative Oncology Group Performance Status should be 0–1.
- SD with systemic therapy for ⩾3 months and an anticipated survival period of ⩾6 months.
- Male or female, aged 18 years or older and 75 years or younger.
- Availability of tumour samples for biomarker assessment.

Exclusion criteria

- Oligoprogressive lesions are unsuitable for radiotherapy.
- Received traditional Chinese medicine or immunomodulatory drugs with antitumour indications within 2 weeks before enrolment (including thymosin, interferon and interleukin, except for local use to control pleural effusion).
- Active untreated hepatitis B (defined as HBsAg positive with HBV-DNA copy number exceeding the upper limit of normal value in the laboratory of the participating centre).
- Currently participating in interventional clinical research treatment, or received other investigational drugs or investigational device therapy within the past 4 weeks before enrolment.
- Received radiotherapy within 2 weeks before enrolment.
- Diagnosis of malignancy other than liver cancer within 3 years before enrolment (excluding curatively treated basal cell carcinoma, squamous cell carcinoma of the skin and/or in situ carcinoma).
- Experienced active autoimmune diseases requiring systemic treatment (such as disease-modifying drugs, corticosteroids or immunosuppressive agents) within 2 years before enrolment. Alternative therapies (such as thyroid hormone, insulin or physiological glucocorticoids used for adrenal or pituitary insufficiency) are not considered systemic treatment.

Study intervention/treatment and procedures

Systemic therapy

The FLST regimen, which was employed prior to the diagnosis of oligoprogression, will be continued to manage non-progressive lesions. Radiological evaluations will be conducted as scheduled or when patients exhibit discomfort. If the assessment reveals progressive lesions, the current FLST and radiotherapy regimen will be discontinued. Subsequently, the SLST regimen will be employed. All treatment regimens follow the protocols outlined in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in HCC (v.1.2024) and the China Guidelines for the diagnosis and treatment of primary liver cancer (2024 edition).

Dose/fractionation

During continued FLST, all oligoprogressive lesions will receive radiotherapy with a biologically effective dose (BED; LQ, $\alpha/\beta = 10$) of at least 60 Gy. The threshold of BED ⩾ 60 Gy for radiotherapy was chosen based on previous retrospective studies of oligometastatic radiotherapy.[17,18] These studies showed that patients who received BED ⩾ 60 Gy had better local control rates and improved survival outcomes. The radiotherapy technique, total dose and fractionation will be determined based on the location and characteristics of the oligoprogressive lesions. Given this individualized approach, it is not feasible to pre-specify fixed dose constraints for specific organs at risk (OAR). However, to ensure treatment safety and standardization, we have now incorporated a reference framework for OAR dose constraints. Specifically, depending on the location of the oligoprogressive lesion and the radiotherapy technique used, we recommend referring to the QUANTEC consensus for appropriate dose constraints.[19] In certain instances, a lower dosage than specified in the established protocol may be administered to ensure that the dose constraints for OAR are not exceeded.

Immobilization/localization/imaging

CT and/or MRI simulation will be performed with the fabrication of a customized radiotherapy

immobilization device for each patient. 4D CT will be used for motion management in patients with more mobile metastases, such as lung or adrenal metastases. For planning CT, the thickness of the CT slices should not exceed 3 mm, and the pixel size should not exceed 1×1 mm.

Treatment volumes

For all lesions, the gross tumour volume (GTV) is defined as the visible oligoprogressive lesions on CT and/or MRI imaging ± PET. The clinical target volume (CTV) includes the GTV plus margins for microscopic lesion spread, as determined by the clinician's judgement. To account for organ motion and set-up errors, a 2–5 mm expansion of the CTV will be applied to the planned target volume (PTV), depending on the irradiated site. CTV delineation for non-spinal bone metastases will follow consensus recommendations from international experts.[20] For bone lesions, a CTV of 5–10 mm is recommended, but a CTV of 3–5 mm is allowed at the investigator's discretion. For vertebral lesions, we follow the protocol of the SABR-COMET series of clinical trials[21–23] and the guidelines of the International Spinal Consortium,[24–26] defining the CTV as follows:

- If the vertebra is involved in GTV, the whole vertebra will be included in the CTV.
- If the ipsilateral pedicle and/or transverse processes is involved, then the whole ipsilateral posterior spine (pedicle, lamina and transverse process) ± the spinous process will be included in the CTV. Whether to include the spinous process is left to the discretion of the radiation oncologist.
- If the ipsilateral pedicle, lamina and/or transverse process has GTV, then the entire ipsilateral posterior segment (pedicle, lamina and transverse process) plus the spinous process will be included in the CTV.
- If there is bilateral involvement of the pedicles and/or transverse processes with GTV, then the posterior segment anatomy ± the spinous process will be included in the CTV. Whether to include the spinous process is left to the discretion of the radiation oncologist.
- If there is bilateral involvement of the pedicles and laminae and/or transverse processes with GTV, the entire posterior segment anatomy will be included in the CTV, including the spinous process.
- If only the spinous process is involved in GTV, then the bilateral lamina ± pedicles will be included in the CTV.

Radiotherapy quality assurance

The contours of the GTV, CTV, PTV and any relevant OAR will be evaluated and approved by two radiation oncologists to ensure accuracy and consistency. All radiotherapy plans will be reviewed and approved by planning dosimetrists, physicists and radiation oncologists. This process will determine the optimal dose fractionation scheme and assess dose constraints for the OAR. Additionally, the institution's quality assurance department may evaluate the radiation plans and the delivery of radiotherapy for oligoprogressive lesions.

Evaluation of therapeutic efficacy

The scheduled time points for imaging assessments will be closely adhered to as per the protocol throughout the study to ensure consistent and accurate monitoring. The initial tumour imaging assessment will be conducted after radiotherapy. Subsequent assessments will occur 1 month post-radiotherapy and then every 2 months (within a margin of ±7 days) thereafter. The efficacy of imaging will be assessed according to the RECIST v.1.1.[27] The primary evaluation criteria and their respective definitions are as follows:

- CR: the disappearance of all target lesions, with all pathological lymph nodes (both target and non-target) reduced to <10 mm in small diameter. The short diameter of all pathological lymph nodes (including target and non-target nodes) must be reduced to <10 mm.
- PR: The sum of target lesion diameters must decrease by at least 30% from baseline.
- PD: a relative increase of at least 20% in the sum of target lesion diameters measured throughout the study, relative to the minimum of the sum of target lesion diameters measured throughout the study (or the baseline value if the baseline value is the smallest); in addition, an absolute increase in the sum of target lesion diameters of at least 5 mm must be achieved (the presence of one or more new lesions is considered progression).

- SD: the target lesion has not decreased to the level of PR, has not increased to the level of PD and has not progressed to the level of PD in between; the minimum value of the sum of diameters can be used as a reference for the study.

Follow-up

A safety follow-up visit will be scheduled 30 days (±7 days) after the last radiotherapy treatment. During the trial, the investigator will observe for any potential adverse events (AEs) and record their severity using the National Cancer Institute CTCAE version 5.0. Additionally, the investigator will analyse the AEs, considering their cause, toxicity grade and response to treatment. Safety follow-up includes monitoring for acute AEs during and up to 1 month post-treatment, while late AEs occurring after the first month were assessed at 3 months, 6 months, 1 year and 3 years using the LENT-SOMA scoring system.

After enrolment, patients will undergo QoL assessments using the EORTC QLQ-C30 and EORTC QLQ-CR29 at 3 months, 6 months, 1 year and 3 years. Changes in QoL will be compared to each patient's pre-treatment baseline QoL.

Survival visit

Following the safety visit, subjects will be monitored for survival, with contact every 60 days (±7 days; telephone visits are acceptable) to collect information on survival and any subsequent systemic antineoplastic therapy. Information on disease progression will also be collected for patients who discontinue the study for reasons other than disease progression. Long-term follow-up will continue until the patient's death or the conclusion of the study. If a safety visit is not conducted, the survival visit should be calculated from the end of treatment. Supplemental Appendix 2 provides a comprehensive list of the study procedures, including screening activities, for all trials.

Discontinuation/withdrawal/loss to follow-up

If a patient discontinues or withdraws from the study, the occurrence of AEs and the patient's survival will be monitored. For those who discontinue but attend study visits, the procedures outlined in Supplemental Appendix 2 will be completed. Withdrawals that are not due to disease progression will require end-of-treatment imaging. If a patient fails to attend a scheduled visit, the investigator will attempt to contact the patient to arrange a new appointment and document the outcome.

Statistical analysis

The primary endpoint of the study is PFS. Based on the guideline-recommended standard of care, SLST with regorafenib has a median PFS of 3.1 months. In our previously published multicentre retrospective study in *The Red Journal*,[28] we evaluated the role of radiotherapy in delaying the initiation of SLST. Our findings showed that patients who continued FLST with additional radiotherapy for oligoprogression achieved a median PFS of 8.6 months, whereas those who transitioned directly to SLST had a median PFS of only 3.1 months. However, given the inherent limitations of retrospective studies, we have conservatively set the expected improvement in median PFS for this prospective clinical trial at 5 months.

Statistical assumptions include unilateral $\alpha = 0.05$, power = 0.80, H0 = 3.1 and H1 = 5. Assuming a dropout rate of 10%, calculated using the one-sample log-rank test procedure in PASS 15 with a total sample size of 36 cases. R language version 4.0.2 (or higher) will be used for analyses, using a one-tailed 0.05 superiority test and reporting group comparisons with 95% confidence intervals and p values. Measurement data are reported as the mean ± standard deviation or median (minimum, maximum), and count data are reported as frequencies (percentages).

Patients in this study received different FLST regimens, which may influence their response to radiotherapy. To account for these potential differences, we have planned stratified analyses based on FLST type, with patients divided into three groups: targeted therapy, immunotherapy and combination targeted therapy plus immunotherapy. This approach will help reduce the impact of treatment heterogeneity and increase the robustness of our results.

Trial quality assurance

The investigator will implement and maintain a quality assurance and quality control system in

Figure 3. Comparison of survival benefit between first-line systemic therapy and second-line systemic therapy.
Order of words: drug, corresponding clinical trial, months of survival benefit; Grey curvilinear bars are the second-line treatment regimens; Orange ring: ICIs; Blue ring: ICIs + Targeted; Red ring: Targeted.
ICIs, immune checkpoint inhibitors; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; Targeted, targeted therapy.

accordance with the principles of good clinical practice (GCP) and the standard operating procedures that are appropriate for the trial in question. This will ensure that the trial is conducted and the data are collected, recorded and reported in accordance with the protocol, GCP and the applicable regulatory requirements.

Data collection and management

Clinical trial documentation will be in accordance with GCP requirements. The Department of Radiation Oncology Research Centre will archive and manage relevant data for 5 years to ensure accessibility. Safety and environmental risks should be considered in the storage of documents.

Discussion

For oligoprogression in advanced HCC, switching systemic therapy to the next line of treatment is a major strategy. However, this may not result in a survival benefit. Figure 3 illustrates the results of the survival benefits[3,29–32] of FLST versus SLST in advanced HCC, including the ORR, median OS and median PFS. The FLST and SLST are from the NCCN Clinical Practice Guidelines in HCC (v.1.2024). As can be seen, patients with advanced HCC have a superior survival benefit with more options for FLST compared to SLST.

Current staging practices generally uniformly classify metastatic HCC as M1, overlooking nuances in disease behaviour and response to treatment. A subset of patients with oligoprogressive disease may benefit from metastasis-directed therapies in combination with ongoing FLST. Further understanding of biomarkers of inactive versus aggressive HCC is essential to guide these decisions, particularly in the absence of robust comparative trials.[33]

Proper selection of CP-B stage patients is essential to avoid iatrogenic deterioration of residual liver function, which could prevent the continuation of FLST as planned. Specifically speaking, the prognosis of CP-B patients may differ significantly depending on whether they have re-compensated cirrhosis following a previous episode of decompensated cirrhosis. In CP-B patients with a history of decompensated cirrhosis, special care must be taken during radiotherapy to prevent further decompensation. Based on these considerations, our study inclusion criteria restricted CP-B patients to those with a maximum CP score of 7. CP-B7 patients often have relatively well-compensated cirrhosis, whereas CP-B8 or CP-B9 patients are more likely to have decompensated cirrhosis with significant ascites, encephalopathy or jaundice and may therefore be more adversely affected by HCC treatments.[34] In addition, when staging CP-B7 patients and determining appropriate treatment options, it is critical to carefully evaluate the specific factors contributing to their CP score. In the CP classification model,[35] the minimum score possible is 5. However, certain clinical conditions can raise a patient's score to

CP-B7 even if overall liver function is not severely impaired. For example, a serum albumin level of 3.5 mg/dL (within normal limits) adds two points to the CP score, resulting in a CP-B7 classification. Therefore, some CP-B7 patients may respond to treatment in a similar way to CP-A patients. For CP-B7 patients with evidence of more severe liver dysfunction, we will consider prescribing dose reductions and stricter liver dose constraints; liver dose constraints should at least meet the standard of $D_{\geqslant 700\ cc} \leqslant 15$ Gy.[36]

Evaluating the cost-effectiveness of radiotherapy for oligoprogressive HCC is essential to understanding its impact on both patient QoL and the healthcare system. First, prolonging PFS has the potential to prolong OS, providing a meaningful clinical benefit. In addition, maintaining patients on their current systemic anti-cancer therapy (SACT) with radiotherapy may delay the need for more toxic second-line treatments, reduce treatment-related adverse effects and preserve a higher QoL. A recent review[16] highlighted that radiotherapy for oligoprogression not only aims to improve survival but also delays the initiation of further SACT and its associated toxicity, reducing both the physical and economic burden. While prospective cost-effectiveness studies in oligoprogressive HCC remain limited, data from oligometastatic disease provide relevant insights. For example, the cost-effectiveness analysis of the SABR-COMET trial showed that although stereotactic ablative radiotherapy increased treatment costs, it significantly improved quality-adjusted survival, making it a cost-effective strategy.[37] Similarly, an analysis in oligometastatic non-small-cell lung cancer found that local treatments, including radiotherapy, were cost-effective due to improvements in quality-adjusted life years, even without an OS benefit.[38] However, the cost-effectiveness of radiotherapy for oligoprogressive HCC requires further validation through prospective studies, and given the variability in healthcare policies worldwide, cost-effectiveness analyses should be tailored to specific national healthcare systems. In addition to economic considerations, radiotherapy provides effective local tumour control, alleviating pain and other symptoms that significantly impact patient well-being. For HCC patients, pain relief is critical to maintaining daily activities, improving adherence to treatment and reducing psychological distress. Finally, this strategy can help preserve additional therapeutic options for patients in anticipation of future disease progression, ensuring that more aggressive interventions remain available if needed.

Limitations of this study include the heterogeneity of patients and tumour characteristics, which may influence the results and limit the generalizability of the findings to broader populations. We acknowledge that the lack of a randomized control group is a major limitation of our study, which limits the ability to definitively determine the added value of radiotherapy with continuation of FLST versus switching to SLST alone, and we recognize that a randomized controlled trial remains the gold standard for establishing causality. Therefore, if the results of this phase II study are promising, we plan to conduct a large, randomized phase III study to provide more definitive evidence and strengthen the clinical applicability of our approach. Another limitation is that the variation in FLST regimens may influence the response to radiotherapy and potentially impact the overall study results. To address this, we have planned to perform stratified analyses based on FLST type, categorizing patients into targeted therapy, immunotherapy and combination targeted and immunotherapy groups.

We hypothesize that radiotherapy targeting oligoprogressive lesions will prolong the duration of FLST efficacy by eliminating drug-resistant lesions, thereby delaying the need for SLST and preserving these SLST options for potentially more aggressive, widespread metastatic disease in the future.

Declarations

Ethics approval and consent to participate

The final protocol (Grant No. SDZLE C2023-389-02) was approved by the Ethics Committee of the Affiliated Cancer Hospital of Shandong First Medical University, Jinan, Shandong Province, China, on 22 December 2023 in accordance with the Declaration of Helsinki and GCP principles. Formal approval is required for any change to the protocol that affects the conduct, patient benefit or safety of the trial. The trial will adhere to local regulations. Consent to participate: Patients will provide written informed consent after receiving a thorough explanation of the rationale, benefits and potential side effects.

Consent for publication
Not applicable.

Author contributions
Haohua Wang: Data curation; Investigation; Methodology; Validation; Visualization; Writing – original draft.

Xiang Zhang: Conceptualization; Investigation; Methodology; Resources; Visualization; Writing – original draft; Writing – review & editing.

Kunli Zhu: Conceptualization; Investigation; Methodology; Project administration; Writing – original draft.

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Jinbo Yue: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The datasets used and/or analysed during the current study were available from the corresponding author upon reasonable request.

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Supplemental material
Supplemental material for this article is available online.

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