ClinicalTrials.gov Document Cover Page

Study Protocol

Official Title of the Study:	Prospective Multicenter Observational Evaluation of a Risk-Adapted Surveillance Strategy for First-Site Lung and Bone Metastasis in Hepatocellular Carcinoma
NCT Number:	NCT07444905
Document Date:	January 2, 2022
Document Type:	Study Protocol
Protocol ID:	MLEHM-010
Version:	Version 1.0; pre-live frozen operative package
Institution:	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

The substantive study document begins on the next page.

Prospective Multicenter Observational Evaluation of a Risk-Adapted Surveillance Strategy for First-Site Lung and Bone Metastasis in Hepatocellular Carcinoma

Study Protocol

Protocol ID MLEHM-010
Version 1.0; pre-live frozen operative package
Version / effective date January 2022
Institution Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

1. Administrative synopsis

Field	Summary
Study type	Observational; prospective multicentre cohort / patient registry embedded in routine care.
Overall design	Linked programme comprising retrospective model development with held-out internal validation and international external evaluation, followed by a planned two-wave domestic prospective implementation programme.
Retrospective phase	20,139 patients from 65 centres in 13 countries (domestic retrospective cohort n=15,688; international external-evaluation cohort n=4,451).
Prospective programme	Fifteen domestic centres are planned for the primary implementation programme: wave 1 in 11 centres and wave 2 independent new-centre replication in 4 additional centres. Final analytic counts are determined after data lock according to this protocol and the SAP.
Planned prospective enrolment window	February 2022 to February 2023.
Comparative framework	Centre- and calendar-epoch-aligned usual care is the primary observational comparator; contemporaneous eligible no-tool episodes are retained for sensitivity analyses only.
Population scope	Adults with hepatocellular carcinoma without baseline extrahepatic metastasis across routine treatment pathways represented at the eligible index assessment.
Outcome hierarchy	Primary outcome for the prospective implementation analysis: stratum-specific pathway-action fulfilment within 60 days after the eligible index assessment, defined as completion or formal scheduling/documentation by day 60 of the stratum-specific prespecified pathway action assigned at that assessment. Secondary implementation, patient-important, detected-event, disease-event/model-evaluation, and supportive long-term outcomes are specified below.
Version status	This version 1.0 protocol fixes the design, threshold table, SOP-linked pathway logic, endpoint hierarchy, and principal analytical framework before first live implementation.

This protocol specifies the prespecified risk-adapted surveillance strategy intended for routine clinical use at the first post-diagnostic, pre-treatment surveillance-planning assessment. The programme evaluates transportability, implementation fidelity, clinically actionable detection pathways, patient-important downstream outcomes, supportive long-term survival, and economic translation across routine HCC management pathways rather than within a postoperative-only population.

2. Background and rationale

Hepatocellular carcinoma carries a meaningful risk of subsequent extrahepatic metastasis, especially lung metastasis and bone metastasis. Earlier identification of participants at increased near-term risk may support more appropriate surveillance intensity, earlier multidisciplinary review, and more timely downstream management.

3. Objectives

- To evaluate transportability, discrimination, calibration, and threshold stability of the lung-metastasis and bone-metastasis risk modules in international and prospective settings.
- To evaluate implementation performance, including stratum-specific pathway-action fulfilment within 60 days, time to first prespecified action, and downstream management activation within 60 days after the eligible index assessment.
- To evaluate clinically meaningful detection patterns, including asymptomatic actionable lung- or bone-metastasis detection, symptom-driven detection, and detection while still clinically actionable at first discovery.
- To evaluate patient-important downstream outcomes, including metastasis-related acute deterioration, metastasis-related emergency care or hospitalisation, BM skeletal-related events, and supportive long-term survival.
- To describe workflow, resource, and health-economic implications of risk-adapted surveillance in routine practice.

4. Study design and setting

This is a multicentre prospective observational cohort study conducted in routine care. The study does not assign treatment or surveillance strategies on a protocol basis. Treating clinicians retain responsibility for all diagnostic, surveillance, and management decisions.

The live implementation programme is structured in two waves. Wave 1 introduces the version 1.0 package into 11 domestic centres. Wave 2 is prespecified independent new-centre replication in 4 additional domestic centres from a distinct health-system setting within the same national context, using the unchanged v1.0 package. No retraining, threshold revision, or SOP remapping is permitted during the primary implementation phase.

5. Study population

Adults aged 18 years or older with hepatocellular carcinoma and without baseline extrahepatic metastasis at the first post-diagnostic, pre-treatment surveillance-planning assessment are eligible for prospective enrolment and follow-up under routine clinical practice at participating centres.

The cohort is not restricted to postoperative or curative-intent populations and may include participants entering follow-up from surgical, ablative or transplantation, locoregional, systemic, or supportive-care pathways, as applicable in routine care.

6. Prespecified strategy package

Field	Summary
LM thresholds	T1 = 8%; T2 = 12%.
BM thresholds	T1 = 4%; T2 = 6%.
Low-risk pathway	Routine surveillance at the usual interval; no automatic MDT; no immediate directed lung- or bone-metastasis work-up unless symptoms or new abnormalities emerge.
Intermediate-risk pathway	Reassessment within 4-8 weeks; MDT if imaging changes or symptoms occur; directed evaluation as indicated.
High-risk pathway	Expedited imaging and MDT review within the prespecified window, with endpoint-specific directed evaluation and downstream management planning.
Discordant LM/BM strata	Overall pathway intensity follows the higher operational stratum; directed work-up remains endpoint specific.

7. Version chronology and implementation milestones

Milestone	Timing	Interpretation
Pre-live freeze dossier	January 2022	Protocol framework, thresholds, SOP-linked pathway rules, endpoint hierarchy, and SAP-level analytical framework are frozen before first live implementation.
v1.0 release	Before first wave-1 go-live	Prespecified package released for live use in routine care.
Prospective implementation window	February 2022 to February 2023	Two-wave programme to operate under the unchanged package.
Wave 2 replication	Within the prospective enrolment window	Independent new-centre replication in a distinct health-system setting within the same national context uses the unchanged v1.0 package.
Monitoring review	During the primary implementation phase	Review points are descriptive only; no deployment change is allowed during the primary implementation phase.

8. Outcomes and assessment windows

- Primary outcome for the prospective implementation analysis: stratum-specific pathway-action fulfilment within 60 days after the eligible index assessment, defined as completion or formal scheduling/documentation by day 60 of the stratum-specific prespecified pathway action assigned at that assessment. Qualifying fulfilment comprised documented continuation or scheduling of routine review for low-risk episodes, earlier focused reassessment or formal scheduling/documentation for intermediate-risk episodes, and expedited LM/BM-directed imaging, MDT review, referral, or formal scheduling/documentation thereof for high-risk episodes.
- Secondary implementation outcomes: time to first prespecified pathway action within 60 days; downstream management activation within 60 days; low- or intermediate-risk strategy-nonconcordant intensified action, excluding symptom-driven overrides; and post-detection treatment-changing action within 60 days after qualifying LM/BM detection as a pathway-linked detected-event outcome.
- Key patient-important comparative outcomes within 12 months: asymptomatic actionable LM/BM detection; symptom-driven LM/BM detection; metastasis-related emergency-department visit or hospitalisation; metastasis-related acute deterioration; detection while still clinically actionable at discovery; and BM skeletal-related events.
- Disease-event and model-evaluation endpoints: first LM and first BM are the endpoint-specific model-evaluation outcomes. Incident EHM and non-target EHM events are retained for event ascertainment, competing-risk classification, descriptive clinical context, and site-specific disease-event analyses, but are not the primary implementation success endpoint.
- Supportive long-term outcomes: overall survival and restricted mean survival time are assessed from the prespecified day-60 landmark through 36 months. These analyses are supportive translations and are not interpreted as causal survival-effect estimates or the primary causal claim.

9. Comparative analysis framework

Comparative implementation analyses are observational and use centre- and calendar-epoch-aligned usual-care episodes as the primary comparator under a TARGET-aligned observational framework. Time zero is the eligible index assessment, defined as the first post-diagnostic, pre-treatment surveillance-planning assessment at which the strategy could be applied or, for aligned usual-care comparisons, the corresponding usual-care decision point. A 0-7-day implementation grace period is allowed. The primary implementation outcome and secondary 60-day implementation outcomes are assessed through day 60; patient-important outcomes through 12 months; and supportive long-term survival analyses are anchored to the 60-day landmark. All comparative estimates are observational and should not be interpreted as randomised treatment effects.

10. Ethics, registration, and dissemination

Prospective implementation is conducted only after applicable institutional review board or ethics-committee approval at participating centres. Written informed consent is obtained according to local requirements. Retrospective analyses of de-identified multicentre data are conducted under applicable institutional approvals and data-governance requirements. All study procedures are to be conducted in accordance with the Declaration of Helsinki. Public registry linkage is administrative and does not define, revise, or replace the frozen version 1.0 strategy, thresholds, endpoint hierarchy, or analysis framework.

11. Companion documents

This protocol should be read together with the Statistical Analysis Plan, Endpoint Definitions and Adjudication Charter, Model Freeze and Version Governance Note, and the companion timeline document.