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A Multi-Reader MultiCase Controlled Clinical Trial to Evaluate the Performance Improvement from Computer -aided Tool for the Prognostic Prediction of Colorectal Liver Metastases.

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1. Synopsis

1.1. Introduction

This study aims to evaluate the performance improvement from computer-aided tool for the prognostic prediction of colorectal liver metastases (CRLM).

1.2. Prediction Model Summary

In 2024, Chen et al. [1] firstly developed clinical prognosis models utilizing the Random Forest (RF) approach, along with a web-based tool designed for practical application of these predictive models in clinical settings for patients with CRLM undergoing simultaneous resection. These models demonstrated excellent performance and can assist in facilitating accurate and individualized treatment for CRLM patients.

1.3. Study Summary

A multiple reader, multiple case (MRMC) clinical study including a concurrent reading design will be conducted to determine the impact of the CRLM tool on physicians' performance in predicting disease progression and death, as characterized by the designated endpoints, when the physician's evaluation is compared with the ground truth. A total of 12 readers will evaluate 166 patients' medical records, then made prediction of the risk of post-operative 1, 3, 5-years recurrence and death, and provide follow-up timelines and treatment recommendations with or without the aid of CRLM prediction tool, by a memory washout period of approximately 5 weeks. The study will utilize retrospective data that is independent from the training dataset of the prediction tool. The terms 'physicians' and 'reader' are used interchangeably in this protocol. The same applies to 'patients' and 'case'.

1.4. Indication

Patients with CRLM receiving simultaneous resection.

1.5. Hypothesis

This study aims to verify that the CRLM prediction tool improves clinician performance as measured by the designated endpoints, when physician's findings are compared to the ground truth. All the objectives and endpoints will be assessed independently. This is a pilot study, the hypothesis testing will be conducted only on the primary endpoint. All the other analyses are exploratory in nature.

1.6. Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
To compare aid versus without aid with respect to (improved) AUC-ROCs for post-operative prediction of post-operative 3-year mortality made by readers.	AUCs: Area Under the Receiver Operating Characteristic Curve (AUC-ROC)
Secondary Objective	**Secondary Endpoints**

To evaluate aid versus without aid with respect to (improved) AUC-ROCs for post-operative prediction of post-operative 1-year recurrence, 3-year recurrence, 5-year recurrence, 1-year mortality, and 5-year mortality made by readers.	AUCs: Area Under the Receiver Operating Characteristic Curve (AUC-ROC)
To evaluate aided versus unaided with respect to (improved) sensitivity for prediction of post-operative 1-year, 3-year, and 5-year recurrence and mortality made by readers.	*Sensitivity*: the ratio of true positives to total (actual) positives.
To evaluate aided versus unaided with respect to (improved) specificity for prediction of post-operative 1-year, 3-year, and 5-year recurrence and mortality made by readers.	*Specificity*: the ratio of true negatives to total (actual) negatives.
To evaluate aided versus unaided with respect to (improved) inter-rater reliability for rating on the likelihood of post-operative 1-year, 3-year, and 5-year recurrence and mortality made by readers.	*Inter-rater reliability:* the consistency of ratings made by readers on the cases
Exploratory Objective	**Exploratory Endpoints**
To evaluate aided versus unaided with respect to inter-rater reliability for readers' recommendation on initiating surgical treatment; To evaluate aided versus unaided with respect to inter-rater reliability for readers' recommendation on the timing of the first post-surgery follow-up.	*Inter-rater reliability:* the consistency of ratings made by readers on the cases
To evaluate aided versus unaided with respect to (improve) decision-making confidence in predicting the disease progression and making recommendation for a case. The general confidence on prediction model in pre and post study will also be evaluated.	*Decision-making confidence:* confidence of a reader in completing the evaluation for a case
To evaluate aided versus unaided with respect to (reduced) decision-making time in completing a case evaluation.	*Decision-making time: duration of a reader in completing the evaluation for a case*

2. Background and Rationale

2.1. Clinical & Disease Background

Colorectal cancer is the third most commonly diagnosed cancer globally and the second leading cause of cancer-related deaths[2]. At the time of initial diagnosis, around 20% to 30% of colorectal cancer patients present with synchronous liver metastases[3]. This condition often results in more aggressive disease progression and poorer survival outcomes for those affected [4]. Therefore, improving the prognosis for individuals with synchronous CRLM has become a critical challenge and priority in clinical practice.

2.2. Current Clinical Practice

The simultaneous resection of colorectal cancer along with liver metastases is the preferred strategy for selected patients with synchronous CRLM. This approach offers numerous advantages, such as reduced surgical burden, shorter anesthesia time, and improved survival rates compared to staged resections[5, 6]. However, it is important to note that not all patients benefit equally from this method. Research indicates that approximately 62.8% of CRLM patients experience postoperative recurrence, with relapse rates exceeding 50% within the first two years. Furthermore, the median progression-free survival is only 11.7 months, which correlates strongly with worse overall survival rates [5, 6].

Consequently, early identification of CRLM patients undergoing simultaneous resection who are at high risk for postoperative recurrence and mortality is critical for clinicians. This enables the development of tailored follow-up and treatment strategies. There is a pressing need for effective outcome prediction tools for CRLM patients undergoing simultaneous resection in specific clinical contexts, as this could significantly enhance clinical decision-making processes. Accurate prognostic assessments are essential for devising appropriate treatment and follow-up plans.

2.3. Prediction Model Background

High-performing predictive models are vital tools that can aid clinicians in developing treatment strategies and creating effective follow-up plans to improve the prognosis of patients with CRLM. Although several institutions have created prognostic nomograms to predict outcomes for CRLM patients[7-10], there is a lack of studies specifically addressing those undergoing simultaneous resection. In previous research, Chen et al. [1]firstly establish RF models that incorporate a wide range of variables, including demographic, clinical, laboratory, and genetic data, and to develop a web-based prediction tool designed to forecast long-term outcomes for CRLM patients undergoing simultaneous resection.

The RF models showed significant enhancements in predictive performance during both internal and external validation compared to traditional CRS scores. The AUC values for the survival model at 1 year, 3 years, and 5 years outperformed those of other models, such as CERR score, GAME score, and modified clinical score, reported in previous studies [11-13]. Furthermore, Chen et al. developed a user-friendly web-based prediction tool based on patients' baseline characteristics for clinical application. The practical implications of this prediction tool are considerable, as it provides clinicians with accurate risk assessments tailored to a patient’s tumor characteristics, ultimately facilitating personalized treatment interventions and follow-up plans.

2.4. Similar Studies

No similar study to evaluate the clinical benefit of a prognostic prediction model in clinical practice.

3. Study Design

3.1. Data Collection Procedure

This is a retrospective MRMC study which employs a fully crossed design in which all readers review medical records from all cases in two visits separated by a memory washout period of approximately 1 month. Readers are divided into two groups (A and B) roughly reflecting similar reader qualifications and experience. Training and instructions will be provided to each reader so that readers work from a set of given rules including a consistent process for recording their evaluations

3.2. Rationale for Endpoints

Primary endpoints:

The Area Under the Receiver Operating Characteristic Curve (AUC-ROC) for predicting post-operative 3-year mortality, comparing clinician performance with and without the aid of the prediction model according to risk scores: (low risk)＜10%, 2 (Moderate Risk)10%-30%, 3 (High Risk)30-70% and 4 (Critical Risk)＞70%.

Secondary endpoints:

The AUC-ROC for predicting post-operative 1-year recurrence, 3-year recurrence, 5-year recurrence, 1-year mortality, and 5-year mortality, comparing clinician performance with and without the aid of the prediction model according to risk scores: (low risk)＜10%, 2 (Moderate Risk)10%-30%, 3 (High Risk)30-70% and 4 (Critical Risk)＞70%.

After surgery, all patients were routinely monitored for recurrence through thoracic, abdominal, and pelvic computed tomography, magnetic resonance imaging of the liver, and serum carcinoembryonic antigen (CEA) measurements. The first postoperative assessment took place one month post-surgery, and subsequent evaluations were conducted in the outpatient clinic every three months. The rates of recurrence or mortality at one year, three years, and five years post-operation were determined based on these earlier follow-up reviews.

4. Sample Population

4.1. Reader Characteristics

A reader study with 12 participating physicians (4 Junior Physician, 4 mid-level Physician and 4 Senior Physician) from the Department of Surgical Oncology of the Digestive Tract will be conducted. The standardized training will be provided to all readers how to use medical record system to get patients data, and how to complete the questionnaire.

4.2. Case Population

The study will target 166 CRLM patients receiving simultaneous resection.
Inclusion Criteria:
- ≥ 18 years old
- confirmation of histologically diagnosed liver metastases of colorectal adenocarcinoma
- receiving colorectal resection with simultaneous liver resection.

Exclusion Criteria:
-presence of other malignancies
-absence of follow-up data
-patients who were followed up postoperatively for less than 5 years and had no occurrences of death.

5. Study Procedure

5.1. Ground Truth

The recurrent and modality status, and the date of experiencing the events of each patient have been documented. The readers will be blinded to the ground truth.

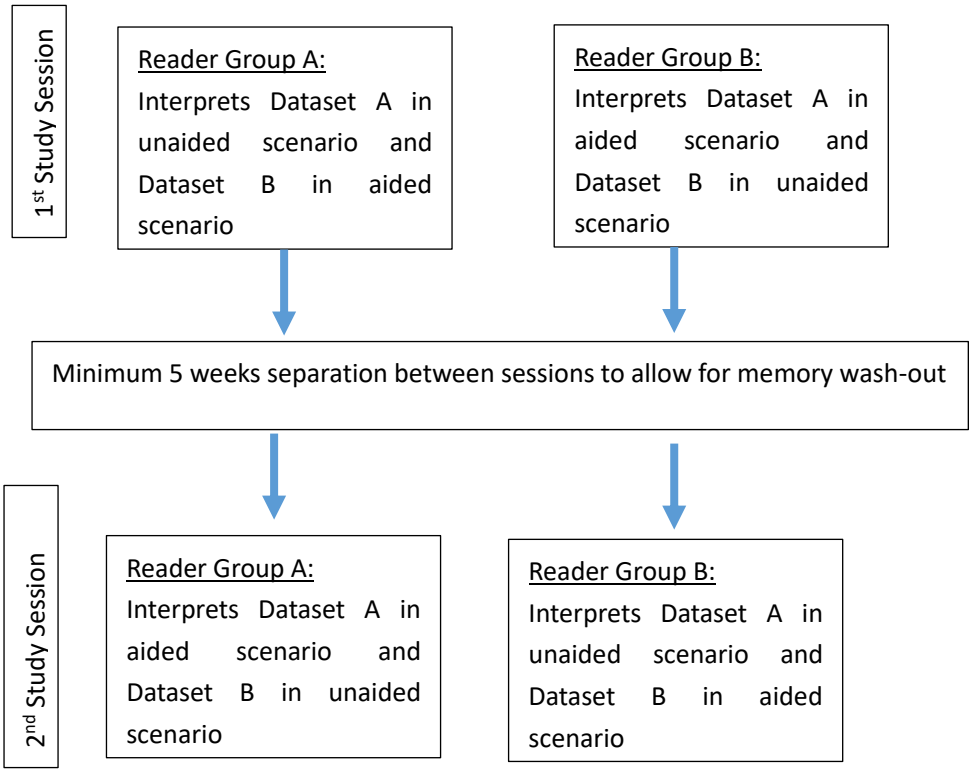
5.2. Reading Procedure

The standardized training will be provided to all readers how to use medical record system to get patients data, and how to complete the questionnaire. Reading will be conducted in a blinded fashion in the sense that the readers will not have access to the identification information and post-operative recurrence and modality status during either the aided or unaided portion of the reading. During the reading process, whether aided or unaided, the readers will only have access to anonymous medical information relevant to surgery, as well as information pertaining to the period prior to the surgical procedure. This includes medical records, demographics, imaging examinations, preoperative biochemical markers, surgery-related variables, tumor pathological characteristics, genetic markers, and treatment information from the medical records system. In the aided session, the individualized predicated KM curves and landmark survival probabilities based on prediction models for the case will be presented in addition to the information provided in unaided session.

Each reader will be asked to complete a questionnaire about the risk score of post-operative 1-year, 3-year, and 5-year recurrence or mortality, their confidence of the making the decision and the recommended timing for the first follow-up examination after surgery. Time from starting to read the medical history to completing the questionnaire will be recorded.

Patient cases will be equally and randomly split between Dataset A and Dataset B. The readers are also equally and randomly split between Group A and Group B. During each session each reader reads all the cases assigned to the group they belong to in that session. There will be at least a one-month washout period between sessions.

Study Schema like below



5.3. Study discontinuities

Several extenuating circumstances exist where readers may not be able to read all cases expected of them. Table below summarize several such scenarios and responses.

Study Discontinuity Scenarios and responses

Scenario	**Protocol**
A reader is not able to complete all the cases assigned to his group in session 1, but remains committed to continue reading in session 2.	Additional cases will be assigned to either existing readers or new readers to supplement the cases that reader could not complete.
A reader withdraws after session 1 and is not able to participate in session 2.	A new reader will be identified to replace this reader. This new reader will complete both session 1 and 2.
A reader completes session 1 but can only partially complete session 2.	Depending on the number of unread cases in session 2, investigator will opt to either (1) forego the unmatched cases

	which will reduce sample size and statistical power, or (2) assign unmatched cases to new or existing readers. In the latter scenario, the replacement reader will need to complete both session 1 and 2 with the assigned cases, including the washout period.

5.4 Safety Assessment

There are no safety concerns of physicians on using the prediction tools and making evaluation for patients. As cases are retrospectively evaluated, patients would not experience safety concern through incorrect evaluation or action of a reader in this study.

5.5. Data Security

All case data used in this study is completely anonymized. This includes any identifying information (e.g. patient name) displayed to readers. All data collected in this reader study will be securely maintained by Cancer Hospital, Chinese Academy of Medical Sciences.

6. Statistical Plan

Study Design Overview	A retrospective, MRMC study, employs a fully crossed design in which all readers (physicians) review medical records from all cases (patients) in two visits separated by a memory washout period of approximately 5 weeks.
Analysis Population	The intention-to-treat (ITT) population will serve as the population for primary efficacy analysis. All randomized participants (readers and cases) will be included in this population.
Primary Endpoints	AUC-ROC
Secondary Endpoints	Sensitivity Specificity Interrater reliability
Statistical Methods	The primary endpoints, between reading conditions, will be compared using the standard MRMC analysis of variance (ANOVA) method of Obuchowski and Rockette (OR)[14], where both reader and case are random effects.
Interim Analyses	No interim analysis of study endpoints is planned.
Multiplicity	Other analyses will be exploratory in nature. No multiplicity adjustment will be implemented. Nominal p-value will be reported.
Sample Size and Power	A sample size of 166 cases (90 experienced OS events within 3 years),

	and 12 readers was selected for this study. The AUC for predicting 3-year mortality is designed for two-sided $\alpha = 0.05$ and power of at least80% to detect a 0.05 absolute advantage in AUC for reading with an assistant of the CRLM prediction tool.

6.1. Response for Analyses/Blinding

The readers will be blinded to the ground truth of the cases' recurrence or mortality status they will be asked to review. Readers will also not have access to results from other readers or information that could influence the diagnosis decision. The statistical analysis of the data obtained from this study will be the responsibility of the Sponsor and conducted by an unblinded statistician.

6.2. Analysis Endpoints/Objectives

The following endpoints are used to compare the reader's performance for assessing patients' disease progression and death under two reading scenarios (i.e. with the aid of the CRLM prediction tool vs. without aid).

6.2.1 Primary Endpoint

AUCs: Area Under the Receiver Operating Characteristic Curve (AUC-ROC)

Objective: To compare aid versus without aid with respect to (improved) AUC-ROCs for post-operative prediction of post-operative 3-year mortality made by readers.

6.2.2 Secondary Endpoints

AUCs: Area Under the Receiver Operating Characteristic Curve (AUC-ROC)

Objective: To evaluate aid versus without aid with respect to (improved) AUC-ROCs for post-operative prediction of post-operative 1-year recurrence, 3-year recurrence, 5-year recurrence, 1-year mortality, and 5-year mortality made by readers.

Sensitivity: the ratio of true positives to total (actual) positives.

Objective: To evaluate aided versus unaided with respect to (improved) sensitivity for prediction of post-operative 1-year, 3-year, and 5-year recurrence and mortality made by readers.

Specificity: the ratio of true negatives to total (actual) negatives.

Objective: To evaluate aided versus unaided with respect to (improved) specificity for prediction of post-operative 1-year, 3-year, and 5-year recurrence and mortality made by readers.

Inter-rater reliability: the consistency of ratings made by readers on the cases

Objective: To evaluate aided versus unaided with respect to (improved) inter-rater reliability for rating on the likelihood of post-operative 1-year, 3-year, and 5-year recurrence and mortality made by readers.

6.2.3 Exploratory Endpoints

Inter-rater reliability: the consistency of ratings made by readers on the cases

Objective: To evaluate aided versus unaided with respect to inter-rater reliability for readers' recommendation on initiating surgical treatment; To evaluate aided versus unaided with respect to inter-rater reliability for readers' recommendation on the timing of the first post-surgery follow-up.

Decision-making confidence: confidence of a reader in completing the evaluation for a case

Objective: To evaluate aided versus unaided with respect to (improve) decision-making confidence in predicting the disease progression and making recommendation for a case. The general confidence on prediction model in pre and post study will also be evaluated.

Decision-making time: duration of a reader in completing the evaluation for a case

Objective: To evaluate aided versus unaided with respect to (reduced) decision-making time in completing a case evaluation.

6.3. Randomization/Treatment Assignment

This is a retrospective MRMC study, which employs a fully crossed design in which all cases will be evaluated the same way by all study readers, such that there are no treatment assignments or treatment groups.

The 12 readers will be randomly allocated into two groups, reader group A and B. The 166 cases will be randomly allocated into two subsets of 83 cases each, case subsets A and B. The cases within a case subset will be assigned to each reader in a randomized case order. Each reader will read one case subset with prediction tool aided and another case subset as unaided during Session 1, and the complementary unaided and aided during Session 2.

Study case identification numbers and study reader numbers will be assigned to all cases and readers and used to protect their identities in statistical analysis and in reporting of results.

6.4. Statistical Methods

6.4.1 Statistical Methods for Efficacy Analyses

6.4.1.1 Primary Endpoints

AUC-ROCs for 1-year, 3-year, 5-year of recurrence and mortality will be estimated for each reader in **each review condition** (aided or unaided, and the difference between them) based on the reader's interpretations of all cases. The account for right-censor data, the inverse probability of censoring weighting estimate was used for the cumulative/dynamic time-dependent ROC curve approach by Blanche et al. [15].

AUC-ROCs between reading conditions will be compared using the standard MRMC analysis of variance (ANOVA) method of Obuchowski and Rockette (OR), where both reader and case are random effects, to ensure generalization of the study results to both the population of readers and the population of cases.

The average AUCs within each reading condition, as well as its standard error and two-sided 95% confidence intervals (CIs) will be reported. The average difference in AUCs, its standard error, corresponding two-sided 95% CIs, and statistical inference will be computed, referencing to the approach in Obuchowski and Rockette. No adjustments for covariates are planned.

Sensitivity analysis may be conducted using OR approach with only reader (sensitivity analysis 1) and only case (sensitivity analysis 2) as random effects.

6.4.1.2 Secondary Endpoints

Analyses of sensitivity and specificity will also use standard MRMC ANOVA methods to compare reader performance under different reading condition and use two-sided 95% CIs to quantify uncertainty. Sensitivity and specificity each provide additional information needed to understand the expected impact of using the prediction tool on clinical practice. Their analysis and reporting, including confidence intervals, is thus required to provide a complete description of reader performance.

Analysis of Inter-rater reliability or other ordinal outcomes collected under different reading condition will use generalized linear mixed model (for appropriate link function) with reading condition as a covariate and both reader and case are random effects.

6.4.1.3 Missing Data

Readers are required to complete evaluating all cases in the two sessions, and missing reader data will be prevented. If any, missing reader data will be reviewed and reported (considered as protocol deviations). No imputation is planned for any study data. The analysis methods would accommodate missing reader data under missing at random assumption.

6.4.2 Statistical Methods for Safety Analyses

No adverse events are anticipated in this study using retrospective cases. Readers are not expected to report any adverse events.

6.4.3 Summary of Baseline Characteristics

The demographic and baseline characteristics of the cases will be assessed by the use of tables

and/or graphs. The baseline characteristic of readers (e.g. confidence on prediction aided tool) will also be assessed in the same way. No statistical tests will be performed on these characteristics.

6.5. Interim Analysis

No interim analysis of study endpoints are planned. The final analysis will be triggered when all the readers complete and record their findings for all the assigned cases at Session 2.

6.6 Multiplicity

The study allocated two-sided $\alpha = 0.05$ to test AUC for 3-year mortality between reading conditions. All the other analyses are exploratory in nature. No multiplicity adjustment will be implemented. The nominal p-value will be reported.

6.7. Sample Size and Power Calculation

This study is well powered for the primary endpoint AUC of 3-year mortality prediction. A sample size of 166 cases and 12 readers was selected for this study. The method of Obuchowski[14] is used to determine the number of readers required in a fully crossed design to provide at least 80% power to detect a 0.05 absolute advantage in AUC for reading, at statistical significance level $\alpha = 0.05$ (two-sided). The disease cases to non-disease cases (for 3-year mortality) will be randomly selected with an approximately 1:1 ratio from the patient dataset pool, which is independent from the dataset used to training the prediction tool. A balanced disease vs non-disease design may not reflect the actual disease prevalence in the real-world setting but enhance statistical efficiency in assessing the accuracy of diagnostic tests. The sample size calculations conservatively assume that both readers and cases are random effects.

Due to this being a pilot study, there were no estimate of variance components. Variance component estimates (via Obuchowski and Rockette approach using jackknife method) from previous MRMC studies that use a similar study design as the proposed (regardless of the original endpoint types) were leveraged in the power and sample size calculation of this study. All power estimates are dependent upon the appropriateness of the assumed variance components.

6.8. Subgroup Analysis

To determine whether the advantage of a prediction tool in assisting physicians is consistent across various subgroups, the between reading conditions differences in AUCs (with a nominal 95% CI) will be estimated within each category of the following classification variables:

- Reader Subgroups
    - Reader expertise (junior physician, mid-level physician, senior physician)
- Case Subgroups
    - Age at baseline (<60, >=60)
- Primary Tumor site Subgroups

- Primary tumor site (right half-colon, sigmoid colon, and rectum)

Appendix: Patient Evaluation Questionnaire

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