TITLE: AI-powered volumetric and radiomic biomarkers for predicting recurrence-free and overall survival after liver transplantation for unresectable colorectal liver metastases.

ABSTRACT Liver transplantation (LTx) for unresectable colorectal liver metastases (u-CRLM) shows promise, with 5-year survival rates between 60-80%, contingent on careful patient selection. However, post-transplant recurrence, particularly non-lung relapse, significantly limits long-term success, highlighting the urgent need for better predictive biomarkers. Current selection methods, including response assessment using RECIST 1.1 during bridging systemic therapy, often underestimate dynamic tumor volume changes and heterogeneity, suffer from inter-observer variability, and correlate weakly with pathology and outcomes. This project proposes leveraging Artificial Intelligence (AI) for a more accurate assessment. We will utilize the validated COALA AI model for automated CRLM segmentation on CT scans, enabling robust Total Tumor Volume (TTV) and single lesione volume tracking. We aim to develop and validate novel AI-powered biomarkers integrating dynamic volumetric (TTV, Metabolic Tumor Volume from PET-CT), spatial (tumor-vascular interface), radiomic, and deep learning features from widely vailable imaging. These biomarkers are hypothesized to capture tumor biology more accurately than standard criteria, improving the prediction of post-LTx recurrence patterns, recurrence-free survival (RFS), and overall survival (OS), thereby refining patient selection for LTx.

RESEARCH QUESTION: How can AI-derived imaging biomarkers predict recurrence-free and overall survival in post-LTx patients with u-CRLM, surpassing the prognostic accuracy of RECIST 1.1 criteria?

SPECIFIC AIMS AND OBJECTIVES

1. Evaluate the prognostic value of AI-derived Total Tumor Volume dynamics during bridging therapy for post-LTx recurrence pattern, recurrence-free (RFS) and overall survival (OS), benchmarking against RECIST 1.1.
2. Develop an automated vessel segmentation tool and assess the predictive power of tumor-vascular interface dynamics for post-LTx recurrence pattern, RFS and OS.
3. Adapt AI models via transfer learning for PET-CT analysis to determine the prognostic significance of Metabolic Tumor Volume dynamics for post-LTx recurrence pattern, RFS and OS.
4. Investigate the prognostic potential of radiomic and deep learning features (from CE-CT/PET-CT, intra- and peri-tumoral regions, tumor-vascular interface) combined with molecular data for predicting post-LTx recurrence pattern, RFS and OS.

METHODOLOGY

Population: Retrospective cohort study of patients who underwent LTx for u-CRLM following bridging systemic therapy at Oslo University Hospital (OUH) and Padova University Hospital (PDH). Ethics approvals will be secured/confirmed for data access and analysis. **Data Collection:** CE-CT scans and available PET-CT scans obtained during bridging therapy, along with relevant clinical data (demographics, therapy, pathology, outcomes like RFS/OS), will be collected for the patient cohorts; Segmentation models will be trained/fine-tuned leveraging datasets from partner institutions (CAIRO5 from PHAIR consortium), host institutions(e.g. OSLO-COMET, CAMINO from OUH, MELODIC from PDH) and publicly available datasets (e.g., 3D- IRCADb-01, LiTS, LiVS). **Image Analysis & modeling:** The validated COALA model will segment CRLM on all CTs to calculate TTV and individual lesion volumes. Their dynamics (e.g., absolute/relative change, slope) will be computed and analyzed as time series. An automated deep learning model (e.g., nnU-Net) will be trained/validated for hepatic vessel segmentation. Tumor-vessel interface volume dynamics will be quantified. Transfer learning will adapt segmentation models for automated Metabolic Tumor Volume (MTV) calculation and dynamic analysis. Standardized radiomic features (IBSI-compliant) and deep learning features (from CNNs, Visual Transformer-based algorithms) will be extracted from segmented intra- and peri-tumoral regions, and tumor-vascular interface regions on CE-CT and PET-CT. Survival analysis will correlate imaging biomarkers with RFS and OS, adjusting for clinical factors and molecular markers. Predictive performance will be assessed and compared against RECIST 1.1. Predictive XGBoost models integrating features will be and model explainability will be investigated using techniques like SHAP. **Project feasibility** is strongly supported by confirmed access to well-curated LTx patient cohorts with imaging and clinical data from OUH and PDH, supplemented by extensive datasets for robust model training and tuning, and by the team's comprehensive expertise in AI, medical imaging, and HPB oncology.

SIGNIFICANCE Current LTx selection for u-CRLM is hampered by RECIST 1.1's inability to capture dynamic tumor biology and its variability. This project introduces quantitative, reproducible AI-powered biomarkers from serial imaging to assess volumetric and spatial dynamics, aiming for significantly improved prediction of post-LTx recurrence and survival, thus refining patient selection. While prerequisites for our analyses, these AI models and methodology are designed for broad applicability, usable directly or via transfer learning for diverse liver imaging studies, regardless of pathology or treatment- not only for patients considered for transplant for uCRLM. By open-sourcing these foundational tools, we intend to enable the HPB research community to accelerate future AI-driven liver tumor analysis through efficient large-scale annotation, thereby enhancing clinical decisions and potentially expanding access to advanced image analysis

TIMELINE: **Months 1-2:** Protocol finalization, IRB, data agreements. **Months 3-7:** Imaging/clinical data collection & curation (Oslo/Padova LTx cohorts). **Months 8-9:** Segmentation model training/tuning/application; TTV/MTV dynamics calculation; **Months 10-11**: Data analyses and results integration; explainability analysis; **Month 12**: End of manuscript drafting & dissemination planning.