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Quantitative CT Biomarkers to Predict Metastatic RCC Response to Antiangiogenic Therapy

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TECHNICAL ABSTRACT

Background: During the last decade, treatment of advanced and metastatic renal cell carcinoma (RCC) was revolutionized with the advent of targeted therapies (e.g., anti-angiogenic agents, mTOR inhibitors, immunotherapy agents), but not all patients respond favorably. Computed tomography (CT) has the potential to be an ideal biomarker for predicting metastatic RCC response to targeted agents. The Vascular Tumor Burden (VTB) is a measure of the amount of vascularized tumor on CT images and is directly related to tumor devascularization caused by anti-angiogenic targeted agents. The VTB can be easily measured by eMASS, an image viewer that performs computer-assisted response evaluation and that is designed to standardize image evaluation, reduce errors and variability, capture multiple quantitative CT metrics, generate annotated data and images for development of machine-learning algorithms, and improve display and archival of data and images.

Objectives and Hypotheses: The first objective is to use eMASS to validate the VTB as an accurate and reproducible quantitative CT biomarker for predicting metastatic RCC response to three different anti-angiogenic agents. We hypothesize that changes in the VTB on initial post-therapy CT images are highly reproducible and accurately predict survival in patients with metastatic RCC treated with different anti-angiogenic agents. A second objective is to develop and validate a machine-learning algorithm to accurately predict survival on an individual basis (also known as precision medicine). We hypothesize that a machine-learning algorithm that utilizes the baseline clinical data and annotated images from eMASS will be highly reproducible and accurately predict survival in patients with metastatic RCC treated with different anti-angiogenic agents.

Specific Aims:

Aim 1: Validate the performance of eMASS and the VTB as a CT imaging biomarker for predicting survival in patients with metastatic RCC treated with different anti-angiogenic agents.

(1) Establish the accuracy of the VTB as a predictor of survival in patients with metastatic RCC treated with different anti-angiogenic agents by conducting post-hoc analyses of two landmark phase III trials.

(2) Assess intra- and inter-observer variability of VTB and other tumor metrics quantified by eMASS.

Aim 2: Train, validate, and test a machine-learning algorithm that utilizes baseline clinical data and annotated data and images from eMASS to accurately predict survival on an individual basis.

(1) Train, validate, and test a machine-learning algorithm using data and images from two completed landmark phase III trials that include three different targeted agents (sunitinib, axitinib, and sorafenib).

(2) Assess accuracy and intra- and inter-observer variability of the machine-learning algorithm.

Study Design: We will conduct post-hoc secondary analyses of two completed, landmark, multi-national, multi-institutional, randomized, prospective phase III trials of metastatic RCC treated with various anti-angiogenic targeted agents (N=818 patients). We have the data and images from the first trial and a signed transfer agreement with Pfizer for the data and images from the second trial. We will use eMASS to measure the VTB on the baseline and initial post-therapy CT studies and associate the percent change in the VTB with progression-free survival (PFS), objective response rate (ORR), and overall survival (OS). We will also compare to other common CT biomarkers (e.g., tumor length) and multiple other tumor response criteria. In addition, we will use the baseline clinical data and annotated data and images from eMASS to develop a machine-learning algorithm to predict PFS >1 year and OS >2 years. We have partnered with Innolitics, commercial software engineers who built eMASS in collaboration with PI Andrew Smith, MD, PhD, and who have extensive experience developing and validating machine-algorithms that utilize medical images. For both objectives, we will assess intra- and inter-observer agreement.

Applicability: The VTB biomarker directly captures the devascularization effects of anti-angiogenic agents and is applicable to metastatic RCC and other advanced cancers treated with anti-angiogenic therapy. The machine-learning algorithm will first be validated in patients with metastatic RCC treated with anti-angiogenic therapy but could be replicated with any advanced cancer and any therapy.

Impact: A quantitative biomarker that can predict targeted therapy efficacy in patients with metastatic RCC is critically needed to guide individualized therapy and avoid unnecessary increases in tumor burden, drug toxicities, and costs from an ineffective treatment. The long-term impact of our research is to alter cancer treatments and outcomes in both metastatic RCC and other tumors treated with targeted agents. The impact of this research is far-reaching and could improve therapy for patients with many different cancer types and therapies, both for civilians and Veterans with advanced cancer.

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