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TITLE: Quantitative CT Biomarkers to Predict Metastatic RCC Response to Antiangiogenic Therapy

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14. ABSTRACT
Targeted therapies have transformed the treatment of advanced and metastatic renal cell carcinoma (RCC), but not all patients respond favorably. The Vascular Tumor Burden (VTB), a measure of vascularized tumor on CT images, has potential to be a predictive biomarker for metastatic RCC response to targeted agents. The VTB can be easily measured using an augmented intelligence image viewer to standardize image evaluation, capture multiple CT metrics, and generate data for machine-learning algorithms. The study aimed to validate the VTB as a quantitative CT biomarker and develop a machine-learning algorithm that utilizes patient CT images. Patients classified as VTB criteria nonresponders were more likely to experience progression of disease than responders across all treatments. Intraobserver and interobserver agreement for assessing VTB were good. The machine-learning algorithm achieved a C-index of 0.78 for predicting PFS >1 year using patient data and images from those treated with Sunitinib. When applied to axitinib and sorafenib cohorts, the algorithm had slightly reduced predictive accuracy (C-index values of 0.67 and 0.69, respectively). These results suggest that the VTB biomarker has the potential to aid in clinical decision-making for patients with metastatic RCC.

15. SUBJECT TERMS None listed.					
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1. INTRODUCTION:

Targeted therapies have improved treatment for advanced and metastatic renal cell carcinoma (RCC), but not all patients respond well. CT scans can predict response to targeted therapies, with the Vascular Tumor Burden (VTB) measuring the amount of vascularized tumor on CT images. The VTB can be easily measured using an augmented intelligence image viewer, which standardizes image evaluation and generates data for machine-learning algorithms. The proposal aims to validate the VTB as a predictive biomarker for metastatic RCC response to anti-angiogenic therapy, and to develop a machine-learning algorithm that uses CT images to make these predictions.

2. KEYWORDS:

Renal cell carcinoma
Kidney cancer
Anti-angiogenic therapy
Targeted therapy
Computer Tomography
CT
Vascular Tumor Burden
Biomarker
Machine Learning
Artificial Intelligence

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Tasks	Months	% Complete
Aim 1 - Validate the performance of eMASS v2 and the VTB as a CT imaging biomarker for predicting PFS and OS in patients with metastatic RCC treated with different anti-angiogenic agents.		
Major Task 1: Establish the accuracy of the VTB as a predictor of PFS and OS in patients with metastatic RCC treated with different anti-angiogenic agents by conducting post-hoc analyses of 2 landmark phase III trials.		
1. *IRB approval and collection of de-identified data and images from Sunitinib vs. Interferon-alfa trial (N=275; See **Table 2** below)	0	100%
2. Regulatory review by the USAMRMC Human Research Protection Office (HRPO)	0-3	100%
2. Quarterly team meetings to discuss study progress	1-12	100%
3. Receipt of de-identified data and images from the Axitinib vs. Sorafenib trial (N=271 and N=272 respectively; See **Table 2** below)	4-5	100%
4. Organization and preparation of de-identified images (N=275+271+272=818) for reading	4-6	100%
5. Organization of de-identified clinical data and data preparation (N=818) for statistical analysis	4-6	100%
6. Primary analysis of de-identified CT images using eMASS v2 (N=818)	4-30	100%
7. Statistical coding and set up for handling output data from eMASS v2	6-12	100%
8. Oversite of image analysis, database development, and statistical design	1-12	100%

Major Task 2: Assess intra- and inter-observer variability of VTB and other tumor metrics quantified by eMASS v2.		
1. Randomly select baseline and initial post-therapy de-identified CT images from 82 patients for intra- and inter-observer analysis	4	100%
2. Design and oversite of intra- and inter-observer reading sessions	1-30	100%
3. Prepare randomly selected images from 82 patients for reading session 1 for intra- and inter-observer analysis	12-24	100%
4. Conduct image analysis for reading session 1	5-24	100%
5. Prepare images for reading session 2 intra- and inter-observer analysis	24	100%
6. Conduct image analysis for reading session 2	13-30	100%
Major Task 3: Analysis of data from Aim 1		
1. Statistical preparations	12-18	100%
2. Final statistical analysis	16-18	100%
3. VTB manuscript preparations and submission	15-36	100%
Aim 3 - Train, validate, and test a machine learning algorithm that utilizes baseline clinical data and annotated data and images from eMASS v2 to accurately predict survival on an individual basis.		
Major Task 4: Train, validate, and test a machine learning algorithm using data and images from 2 completed landmark phase III trials that include 3 different targeted agents (sunitinib, axitinib, and sorafenib).		
1. Submit de-identified test images (N=40) to Innolitics to begin development of the machine-learning algorithm	4-6	100%
2. Begin development of the machine-learning algorithm, including establishment of the convolution neural network and testing with data sets	7-30	100%
3. Complete development of the machine-learning algorithm and pursue validation in the training/validation cohort (N=545), includes data augmentation, monitoring training progress, and combating under- and over-fitting.	12-32	100%

What was accomplished under these goals?

Our image viewer (eMASS v2) was independently upgraded to include artificial intelligence algorithms for tumor segmentation, anatomic labelling, and longitudinal tracking (**Figure 1**). eMASS v2 was designed to adhere to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 to improve standardization. Furthermore, eMASS v2 was upgraded to include PyRadiomics, an open-source python package for the extraction of radiomics features from medical images.

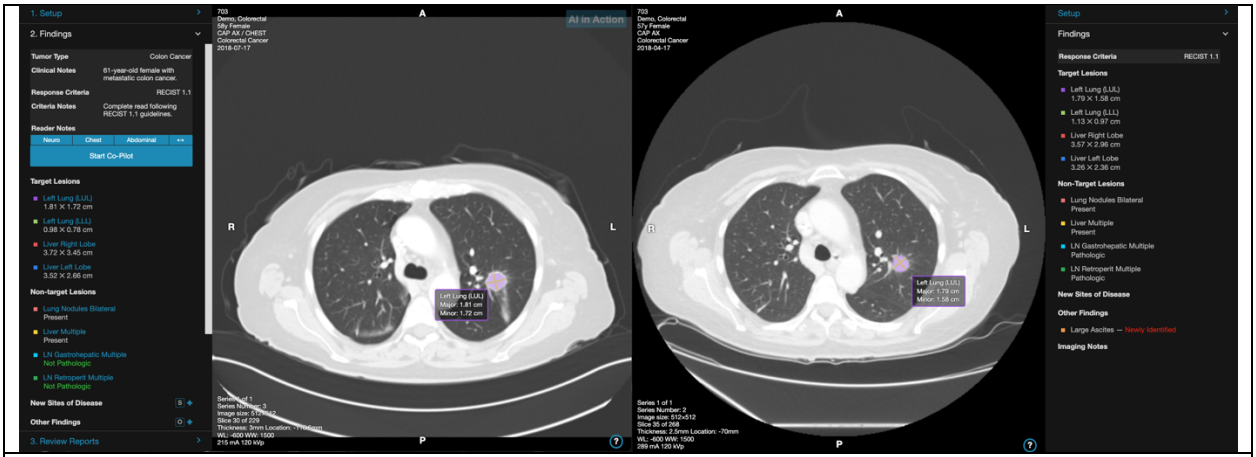

Figure 1. eMASS v2 displaying AI segmentation, labelling, and tracking of tumors.

Major Task 1:

Establish the accuracy of the VTB as a predictor of PFS and OS in patients with metastatic RCC treated with different anti-angiogenic agents by conducting post-hoc analyses of 2 landmark phase III trials. In patients treated with Sunitinib, VTB criteria nonresponders (n = 120) according to the initial posttherapy CT study were 5.7 times more likely to experience progression of disease (HR = 5.7; P < .001) than responders (n = 155). In patients treated with Axitinib, VTB criteria nonresponders (n = 115) according to the initial posttherapy CT study were 2.8 times more likely to experience progression of disease (HR = 2.8; P < .001) than responders (n = 156). In patients treated with Sorafenib, VTB criteria nonresponders (n = 135) according to the initial posttherapy CT study were 2.4 times more likely to experience progression of disease (HR = 2.4; P < .001) than responders (n = 137). See **Figure 2**.

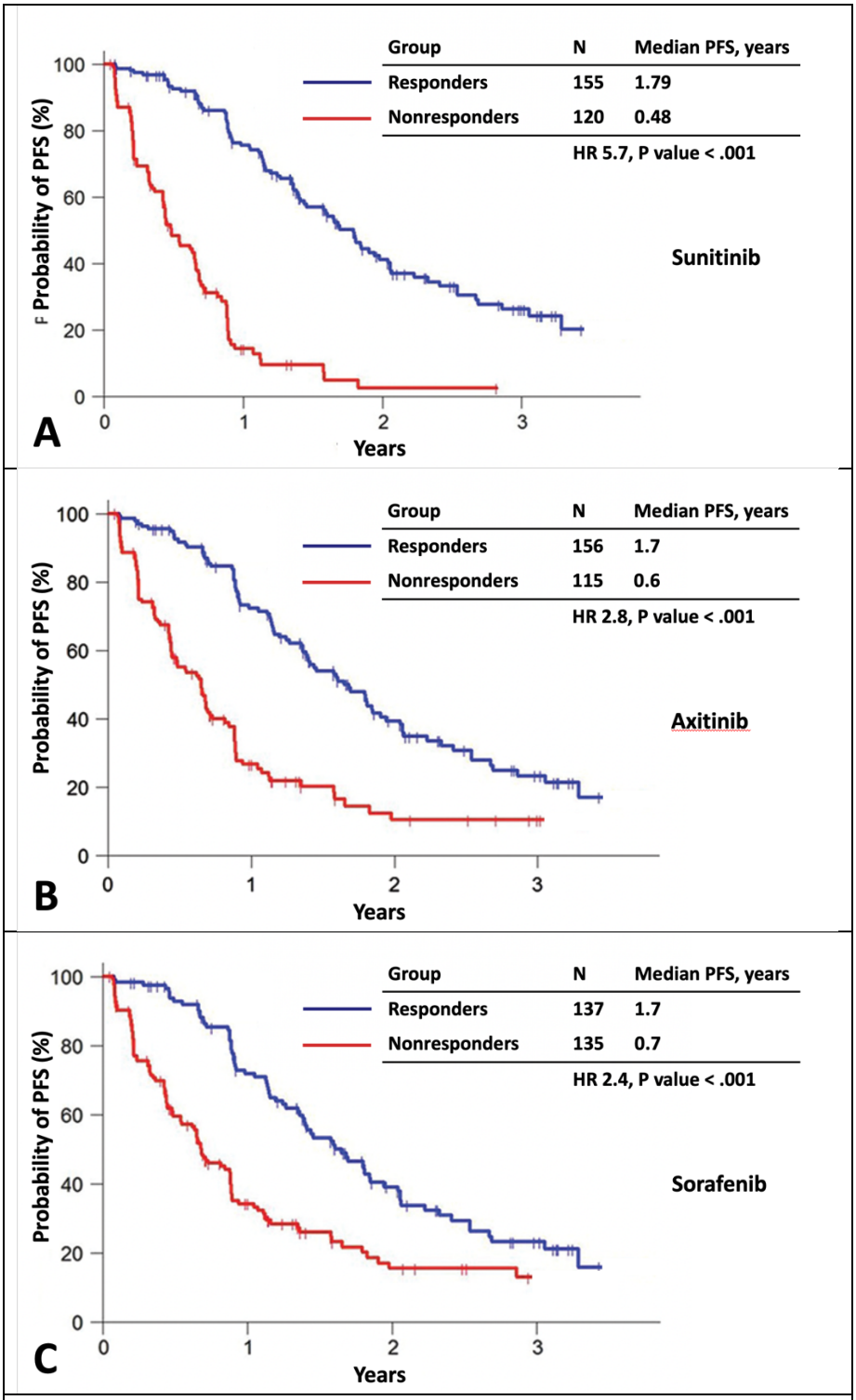

Figure 1. Kaplan-Meier plots show PFS of responders and nonresponders according to VTB criteria in patients treated with Sunitinib (A), Axitinib (B), and Sorafenib (C).

Major Task 2:

Assess intra- and inter-observer variability of VTB and other tumor metrics quantified by eMASS v2. In a patient-level analysis across all three treatments (n = 82), intraobserver agreement was good for assessing percentage change in length and VTB (ICC = 0.88 [95% CI: 0.81, 0.95] and 0.89 [95% CI: 0.83, 0.95], respectively; **Table 1**). In a patient-level analysis across all three treatments (n = 82), interobserver agreement (N=3 readers) was good for assessing percentage change in length and VTB (ICC = 0.81 [95% CI: 0.69, 0.91] and 0.83 [95% CI: 0.71, 0.94], respectively; **Table 2**).

Table 1. Intraobserver Agreement

Metric	**No. of observations**	**ICC**
Length (cm)	82	0.95 (0.86, 0.98)
VTB (cm^2)	82	0.95 (0.85, 0.98)
% change in length	82	0.88 (0.81, 0.95)
% change in VTB	82	0.89 (0.83, 0.95)
Intraclass correlation coefficient, ICC; 95% CIs in parentheses		

Table 2. Interobserver Agreement

Metric	**No. of observations**	**ICC for 3 Readers**
Length (cm)	82	0.94 (0.85, 0.98)
VTB (cm^2)	82	0.93 (0.84, 0.98)
% change in length	82	0.81 (0.69, 0.91)
% change in VTB	82	0.83 (0.71, 0.94)
Intraclass correlation coefficient, ICC; 95% CIs in parentheses		

Major Task 3:

Analysis of data from Aim 1. The statisticians completed the statistical analysis as described above.

Major Task 4:

Train, validate, and test a machine learning algorithm using data and images from 2 completed landmark phase III trials that include 3 different targeted agents (sunitinib, axitinib, and sorafenib). Using the patient data and images from patients with metastatic RCC treated with Sunitinib as the training cohort (N = 275), a machine-learning algorithm was created that incorporated the percent change in VTB, baseline MSKCC risk scores, and percent change in 5 radiomic metrics. The resulting machine-learning algorithm achieved a C-index of 0.78 in the training cohort (**Figure 3**A), indicating good predictive power for PFS >1 year. To evaluate the performance of the algorithm, it was applied to the axitinib (n =271) and sorafenib (n = 272) cohorts, respectively. The C-index values for these cohorts were moderate at 0.67 and 0.69 (**Figure 3B and 3C**), respectively, indicating that the algorithm had somewhat reduced predictive accuracy when applied to external cohorts treated with different anti-angiogenic agents. These are highly promising results.

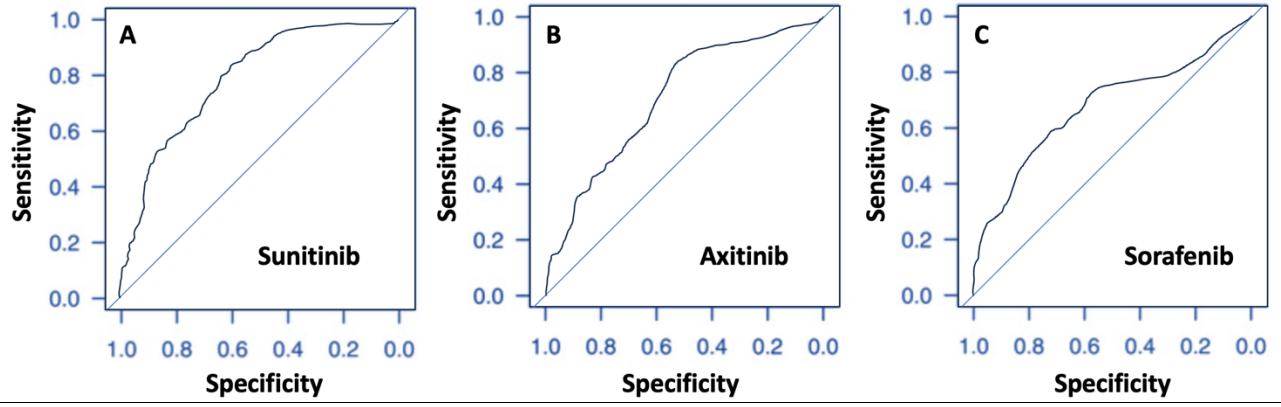

Figure 3. C-index displaying the accuracy of a machine learning model for predicting PFS >1 year for Sunitinib (A), Axitinib (B), and Sorafenib (C).

What opportunities for training and professional development has the project provided?

During the project, opportunities for training and professional development were provided to Asser Abou Elkassem MD, the post-doctoral research fellow responsible for image analysis. The grant proposal supported his development in a variety of areas, including research methodology, image preparation, data organization, image analysis, machine learning, grant management, team science, leadership, and innovation. These skills have equipped him with the knowledge and expertise needed to work toward his independence as a clinician scientist.

How were the results disseminated to communities of interest?

Dr. Andrew Smith MD PhD (PI) prepared a video titled, "The Broad Impact of Kidney Cancer Research" that was placed on the Kidney Cancer Advocacy website. The video is based on his kidney cancer research and was targeted to patients, patient advocates and the public. The video was also targeted to promote the CDMRP for Kidney Cancer and shown to legislators from the U.S. Congress and Senate.
https://www.youtube.com/watch?v=U8iZkKcQgE8

An original research manuscript is being prepared for submission to *Radiology*.

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to Report.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The AI-based image viewer has been adapted for broad use in advanced cancer clinical trials.

What was the impact on other disciplines?

The AI Metrics system applies to all solid advanced cancers and lymphoma and all therapies. AI Metrics currently applies to clinical trials and radiomics research and is being adapted to clinical practice.

What was the impact on technology transfer?

eMASS v2 was licensed to AI Metrics Inc, an Alabama startup company. The software was commercialized and now incorporates artificial intelligence, guided workflows for clinical trials (e.g. RECIST 1.1, iRECIST, Lugano, etc.), advanced reports, and radiomics tools to support similar projects. The AI metrics viewer achieved FDA clearance in Dec of 2020 and is currently in use in 4 different NIH cancer centers in the United States. This augmented intelligence CT/MRI viewer and reporting system is being adapted to a clinical practice environment for broader deployment.

What was the impact on society beyond science and technology?

The AI Metrics platform was validated in a multi-institutional comparative effectiveness study with 24 radiologists and 20 oncologic providers and increased accuracy by 25%, reduced major errors by 99%, cut image assessment time in half, and increased inter-reader agreement by 45% compared to current practice with manual image assessment and dictated text reports. In this study, 96% of radiologists and 100% of oncologic providers preferred AI Mass over current practice methods. The AI Metrics image viewer has redefined the standard of care in advancer cancer imaging and reporting.

5. CHANGES/PROBLEMS:

A no-cost extension was applied for due to delays in receiving all images. All images were eventually received, and image analysis, machine learning, and biostatistical analysis have been completed.

There were not changes to the approach.

6. PRODUCTS:

- **Publications, conference papers, and presentations:**

  Nothing to report

  Journal publications.

  A manuscript targeting Radiology is under development.

  Books or other non-periodical, one-time publications.

  Nothing to Report.

  Other publications, conference papers and presentations.

  Nothing to Report.

- **Website(s) or other Internet site(s)**

  Dr. Andrew Smith MD PhD (PI) prepared a video titled, "The Broad Impact of Kidney Cancer Research" that was placed on the Kidney Cancer Advocacy website. The video is based on his kidney cancer research and was targeted to patients, patient advocates and the public. The video was also targeted to promote the CDMRP for Kidney Cancer and shown to legislators from the U.S. Congress and Senate.
  https://www.youtube.com/watch?v=U8iZkKcQgE8

- **Technologies or techniques**

  As described above, eMASS v2 was licensed to AI Metrics Inc, an Alabama startup company. The software was commercialized and now incorporates artificial intelligence, guided workflows for clinical trials (e.g. RECIST 1.1, iRECIST, Lugano, etc.), advanced reports, and radiomics tools to support similar projects. The AI metrics viewer achieved FDA clearance in Dec of 2020 and is currently in use in 4 different NIH cancer centers in the United States.

- **Inventions, patent applications, and/or licenses**

  There were no patent applications associated with this proposal. eMASS v2 was licensed to AI Metrics Inc; however, eMASS v2 was created prior to the proposal.

- **Other Products**

  Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Andrew D. Smith MD PhD – No change
Asser Abou Elkassem MD – No change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Pfizer Medical has partnered on this project and provided the imaging data sets. No financial support was provided by Pfizer Medical.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. APPENDICES: N/A