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The Attenuation Distribution Across the Long Axis (ADLA): Preliminary Findings for Assessing Response to Cancer Treatment

Nikita Lakomkin, Hakmook Kang, PhD, Bennett Landman, PhD, M. Shane Hutson, PhD, and Richard G. Abramson, MD

Department of Radiology and Radiological Sciences, 1161 21st Ave. Nashville, TN 37232, Vanderbilt University, Nashville, TN 37235-3779, USA (N.L., R.G.A.); Department of Biostatistics (H.K.); College of Arts and Science, Vanderbilt University, Nashville, Tennessee, USA (B.L., M.S.H.); Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee, USA (R.G.A.)

Abstract

Rationale and Objectives—Novel image analysis methods may be useful adjuncts to standard cancer treatment response assessment techniques. The attenuation distribution across the long axis (ADLA) is a simple measure of lesion heterogeneity that can be obtained while measuring the long axis diameter of a target lesion. The purpose of this study was to obtain preliminary validation of the ADLA method for predicting treatment response in a small clinical trial.

Materials and Methods—Under an Institutional Review Board waiver, we obtained de-identified imaging and clinical data from a phase 2 trial of an investigational anticancer therapy at our institution. We retrospectively analyzed all patients with at least one liver metastasis measuring ≥ 15 mm on baseline contrast-enhanced computed tomography. For each patient at every imaging time point, up to two target liver lesions were evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and ADLA measurements. The ADLA was obtained as the standard deviation of the post-contrast computed tomography attenuation values in the portal venous phase across a linear function spanning the long-axis diameter. Using Kaplan-Meier survival analysis, the log-rank test was used to evaluate the ability of RECIST 1.1 and ADLA measurements to discriminate patients with longer overall survival (OS).

Results—Fifteen patients met inclusion criteria. Median survival was 149 days (range 57–487). Best overall response by the ADLA method successfully separated patients with longer OS ($p = .04$). Best overall response by RECIST 1.1 did not discriminate patients with longer survival ($P > .05$).

Conclusion—In retrospective data analysis from a phase 2 clinical trial, the ADLA method was more predictive of OS than RECIST 1.1. Further studies are needed to explore the utility of this measurement in predicting response to cancer treatment.

Address correspondence to: R.G.A. richard.abramson@vanderbilt.edu.

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Keywords

Imaging biomarker; response assessment; overall survival; bevacizumab; cancer imaging; quantitative imaging

INTRODUCTION

In recent years, a number of imaging techniques have been proposed for the assessment and prediction of response to anticancer therapy. These proposals span multiple modalities and range from fully quantitative to semiquantitative approaches (1–6). They are linked by the common goal of assessing response earlier or more accurately than traditional lesion size-based response techniques, with the end objective of triaging patients quickly to more beneficial therapies and sparing patients harmful side effects from ineffective regimens (7). In order for new response assessment techniques to be successfully translated into clinical trials and routine clinical practice, the data extraction methods must not create an unreasonable workflow burden. Many fully quantitative techniques require significant time and resources for image processing and analysis. Although such techniques may be appropriate for a dedicated imaging core laboratory, their workflow requirements make their incorporation into routine clinical practice unlikely.

This paper introduces the attenuation distribution across the long axis (ADLA) as a simple and easily extracted semiquantitative imaging biomarker for assessing treatment response in solid malignancies. The ADLA, described in more detail later, is a measure of intralesional heterogeneity that can be obtained while measuring the long axis diameter of a target lesion on cross-sectional imaging. ADLA measurements may be easily obtained as part of the typical radiologist's work-flow. As a measure of intralesional heterogeneity, we hypothesize that the ADLA measurement is promising as a biomarker for treatment response under the assumption that viable tumors will have a heterogeneous distribution of postcontrast computed tomography (CT) attenuation values reflecting healthy perfused soft tissue, whereas tumors responding to therapy will have a more homogeneous attenuation distribution reflecting decreased tumor perfusion and intralesional necrosis. We believe that with proper validation, this metric may be incorporated into clinical trials and into routine clinical evaluation to help assess tumor response across a wide range of anticancer therapies. The purpose of this preliminary study was to illustrate the ADLA technique and to provide preliminary biomarker validation against survival end points using imaging data from a phase 2 clinical trial.

MATERIALS AND METHODS

Patient Selection and Data Collection

Under an Institutional Review Board waiver from our institution, we obtained de-identified imaging and clinical data from a phase 2 trial of linifanib, an orally activated multi-targeted tyrosine kinase inhibitor, in KRAS positive metastatic colorectal cancer. We included all scans from the trial in which there was at least one liver metastasis measuring at least 15 mm

at baseline. This inclusion criterion was established to minimize the effects of partial volume averaging through small lesions.

Axial CT scans were retrieved from our medical image archive for each patient at every imaging time point while on trial. All patients received iohexol 350 mg/mL (Omnipaque 350; GE Healthcare, Waukesha, WI) as intravenous contrast using weight-based dosing according to our institutional protocol, and we selected the portal venous phase acquisition for subsequent analysis. The display field of view for each scan varied between 335 and 500 mm. A standard matrix of 512×512 was used, for a resultant pixel size of 0.65–0.96 mm. All scans were reconstructed at 3-mm slice intervals.

On each scan, up to two target liver lesions were evaluated using both traditional Response Evaluation Criteria in Solid Tumors (RECIST) criteria (ie, with measurement of long axis diameters) and ADLA measurements. In cases where more than two lesions were present, the two with the largest long-axis diameter were selected as target lesions. Each ADLA measurement was obtained as the standard deviation of the postcontrast CT attenuation values in the portal venous phase across a linear function spanning the long-axis diameter of the lesion (Fig 1). Attenuation measurements were made at each pixel along the line. For each long axis measurement, we created attenuation histograms plotting the frequency of the sampled attenuation values, thus enabling derivation of the standard deviation of the attenuation distribution as a quantitative variable. Composite weighted average ADLAs were then computed at each time point using tumor long axis diameters as the weighting factor. All measurements were performed by a student alongside a board-certified diagnostic radiologist using publicly available ImageJ software (National Institutes of Health, available at <http://imagej.nih.gov/ij/>) (8).

Data Analysis

A treatment response by RECIST was defined as a decrease in the sum of long axis diameters of at least 30% from baseline. A treatment response by ADLA was defined as a decrease in composite ADLA measurement of at least 40% from baseline. This threshold was determined by examining cutoff values at 5% increments between 0 and –50% and selecting the threshold at which ADLA was determined to be most predictive of survival. Best overall response (BOR) for each patient over the course of the trial was recorded using both RECIST and ADLA criteria.

Statistical Methods

Using Kaplan-Meier survival analysis, the log-rank test was used to evaluate the ability of BOR by RECIST and BOR by ADLA to discriminate patients with longer overall survival (OS). Statistical analyses were performed in IBM SPSS Statistics 21 (IBM, Armonk, NY). Because this study was performed retrospectively on preexisting clinical trial data, an a priori power analysis was not performed. The threshold for statistical significance was established at $P < .05$.

RESULTS

A total of 30 patients were enrolled in the clinical trial. Fifteen were excluded from this study due to the lack of a liver metastasis measuring at least 15 mm, leaving a total of 15 patients for analysis.

Median survival for these patients was 149 days (range 57–487) days. Table 1 shows maximum change in RECIST and ADLA measurements, BOR by RECIST and ADLA, and OS for all patients.

BOR by RECIST 1.1 did not discriminate patients with longer OS ($P > .05$). However, the ADLA technique did discriminate patients with longer OS ($P = .04$). Figure 2 shows Kaplan-Meier survival curves for responders and nonresponders as defined by ADLA measurements. The log-rank test outcomes for ADLA cutoff thresholds between 0 and –50% are presented in Table 2.

DISCUSSION

In this preliminary study using retrospective data from a cancer clinical trial, ADLA measurements successfully discriminated patients with longer OS, whereas RECIST measurements did not. This result is potentially significant for two reasons. First, it adds to the increasing body of literature suggesting that conventional imaging-based response criteria, including RECIST, may underestimate or lag behind true biological response (Fig 3) (9–13). Second, it offers early evidence that ADLA measurements may be a useful adjunct to traditional size-based response evaluation methodologies.

Among the wide range of novel imaging biomarkers that have been proposed for assessing and predicting tumor response, the ADLA technique is one of a handful of approaches that require little additional time and effort on the part of the interpreting radiologist. The ADLA measures lesion heterogeneity using a single linear function across the long axis; because linear tumor measurements are already a component of the radiologist's typical workflow, we believe ADLA measurements could be easily incorporated into standard clinical practice. This could be done by incorporating image feature analysis functions into commercial Picture archiving and communication system (PACS) software. By contrast, advanced quantitative imaging techniques like contrast-enhanced perfusion CT and dynamic contrast-enhanced magnetic resonance imaging (3,14–17) are complex and resource-intensive and may be difficult to use in a standardized manner across different institutions. The demand for semiquantitative biomarkers that are readily extractable from standard-of-care scans has already been made evident; in the ACRIN 6657/I-SPY trial of magnetic resonance imaging for the prediction of breast cancer response to neoadjuvant chemotherapy, for example, investigators chose a simple, semiquantitative, three-point signal enhancement ratio method over more complex pharmacokinetic modeling approaches, citing the need to standardize image acquisition and data processing across different system platforms at multiple institutions (18).

It is biologically plausible that a decrease in lesion heterogeneity should correlate with treatment response. Indeed, this notion forms the basis for other proposed semiquantitative

treatment response biomarkers including Choi and Morphology, Attenuation, Size, and Structure (MASS) criteria (19,20). It should be noted that the ADLA approach is even less time-intensive than Choi and MASS measurements because it does not require placement of a dedicated region of interest on the lesion to obtain CT attenuation values.

Despite our promising results, this preliminary study has several limitations that set the stage for further investigation. First, our sample size was quite small; as a next step in its evaluation, the proposed technique must be validated with a larger dataset, ideally one collected within a clinical trial that also has survival data available for clinical endpoint correlation. Second, the scope of this study was limited to liver metastases from colorectal cancer treated with linifanib, an investigational antivascular endothelial growth factor inhibitor; future work must be carried out to understand the anatomical sites, tumor types, and drug agents for which the ADLA approach is relevant. Third, our threshold of a 40% decrease to define a response by ADLA measurements was chosen by examining various cutoff thresholds at 5% intervals; within a larger clinical trial, a more formal analysis could be performed to establish the optimal threshold for defining an ADLA response. Fourth, this study did not compare the ADLA technique to Choi and MASS criteria; such comparisons could be performed in the future as part of a larger evaluation.

In conclusion, this preliminary study offers early evidence of the ADLA measurement as a potentially useful imaging biomarker for assessing treatment response in solid tumor liver metastases. Because ADLA measurements may be easily obtained as part of a typical radiologist's workflow, this approach may be more amenable to broad clinical adoption than other more complex and resource-intensive methods. This technique merits further study in larger clinical trials as an easily extractable biomarker for assessing response to anticancer treatment.

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ADLA Function	Contrast Histogram	Standard Deviation of Attenuation Distribution
19.50
10.48
4.64

Figure 1.

Depiction of the ADLA function drawn across the diameters of three lesions of varying heterogeneity along with the accompanying contrast histogram and standard deviations (lesions obtained from different patients for illustrative purposes). The ADLA measurement was obtained as the standard deviation of the postcontrast CT attenuation values in the portal venous phase across a linear function spanning the long-axis diameter of the lesion. The y -axis of the contrast histogram represents the number of pixels representing each contrast shade (shown on the x -axis).

ADLA, attenuation distribution across the long axis; CT, computed tomography.

Figure 2. Kaplan-Meier survival curves demonstrating the ability of ADLA to discriminate patients with longer survival. ADLA, attenuation distribution across the long axis. (Color version of figure available online).

Figure 3.

A 51-year-old female with KRAS-mutated adenocarcinoma of the colon. CT imaging at baseline (a) and follow-up imaging (b) demonstrate a decrease in intralesional heterogeneity (ADLA measurements 18.2 and 7.71, respectively). Note that the lesion did not change significantly in size.

ADLA, attenuation distribution across the long axis; CT, computed tomography.

TABLE 1

Best Overall Response by ADLA and RECIST 1.1

Patient Number	Maximum Change in Diameter (RECIST) Ψ	Maximum Change in Weighted Average (ADLA) Ψ	Best Overall Response RECIST 1.1	Best Overall Response ADLA	Overall Survival (Days)
1	+17.9%	+32.4%	Nonresponse	Nonresponse	126
2	+33.9%	-35%	Nonresponse	Nonresponse	59
3	+26.5%	+42%	Nonresponse	Nonresponse	89
4	-2.5%	-43.9%	Nonresponse	Response	172
5	+17.5%	+37%	Nonresponse	Nonresponse	95
6	+13.45%	-53.8%	Nonresponse	Response	174
7	+41%	-29.8%	Nonresponse	Nonresponse	149
8	+6.2%	-42.4%	Nonresponse	Response	461
9	+22.4%	+73.6%	Nonresponse	Nonresponse	131
10	+14.3%	-14.1%	Nonresponse	Nonresponse	57
11	-16.3%	-44.8%	Nonresponse	Response	367
12	-24.7%	-40.9%	Nonresponse	Response	487
13	+38.9%	-5.5%	Nonresponse	Nonresponse	71
14	+30%	+15.9%	Nonresponse	Nonresponse	281
15	+24.7%	+20.5%	Nonresponse	Nonresponse	183

 Ψ Negative values represent a decrease in diameter or weighted average ADLA measurements.

ADLA: attenuation distribution across the long axis; RECIST: Response Evaluation Criteria in Solid Tumors.

TABLE 2

Log-Rank Test Outcomes for Various ADLA Cutoff Thresholds

ADLA Cutoff Threshold	Log-Rank Test <i>P</i> Value
0	0.228
–5%	0.228
–10%	0.081
–15%	0.081
–20%	0.081
–25%	0.081
–30%	0.053
–35%	0.012
–40%	0.012
–45%	0.973
–50%	0.973

ADLA, attenuation distribution across the long axis.