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Comparison of CT volumetric measurement with RECIST response in patients with lung cancer

S.A. Hayes [a,*], M.C. Pietanza [b], D. O'Driscoll [c], J. Zheng [d], C.S. Moskowitz [d], M.G. Kris [b], M.S. Ginsberg [a]

[a] Department of Radiology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, United States
[b] Department of Medicine, Memorial Sloan Kettering Cancer Center, 300 East 66th Street Breast & Imaging Center, NY 10065, United States
[c] Department of Radiology, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland
[d] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, 307 East 63rd Street, New York, NY 10065, United States

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ABSTRACT

Purpose: To examine the correlations between uni-dimensional RECIST and volumetric measurements in patients with lung adenocarcinoma and to assess their association with overall survival (OS) and progression-free survival (PFS).

Materials and methods: In this study of patients receiving chemotherapy for lung cancer in the setting of a clinical trial, response was prospectively evaluated using RECIST 1.0. Retrospectively, volumetric measurements were recorded and response was assessed by two different volumetric methods at each followup CT scan using a semi-automated segmentation algorithm. We subsequently evaluated the correlation between the uni-dimensional RECIST measurements and the volumetric measurements and performed landmark analyses for OS and PFS at the completion of the first and second follow-ups. Kaplan–Meier curves together with log-rank tests were used to evaluate the association between the different response criteria and patient outcome.

Results: Forty-two patients had CT scans at baseline, after the first follow up scan and second followup scan, and then every 8 weeks. The uni-dimensional RECIST measurements and volumetric measurements were strongly correlated, with a Spearman correlation coefficient (ρ) of 0.853 at baseline, $\rho = 0.861$ at the first followup, $\rho = 0.843$ at the 2nd followup, and $\rho = 0.887$ overall between-subject. On first follow-up CT, partial responders and non responders as assessed by an "ellipsoid" volumetric criteria showed a significant difference in OS ($p = 0.008$, 1-year OS of 70% for partial responders and 46% for non responders). There was no difference between the groups when assessed by RECIST criteria on first follow-up CT ($p = 0.841$, 1-year OS rate of 64% for partial responders and 64% for non responders).

Conclusion: Volumetric response on first follow-up CT may better predict OS than RECIST response.

Clinical relevance statement: Assessment of tumor size and response is of utmost importance in clinical trials. Volumetric measurements may help to better predict OS than uni-dimensional RECIST criteria.

1. Introduction

Accurate radiological measurement of treatment response is imperative in both clinical practice and clinical trials, and ultimately, also may help predict overall outcome.

The response evaluation criteria in solid tumors (RECIST 1.0) was first introduced in 2000 [1] and established uni-dimensional measurement of target lesions on cross-sectional imaging as the standard method for evaluating treatment response. These guidelines were updated in 2009 when RECIST 1.1 was published, with the aim of improving ease of use and providing more accurate assessment of tumor response [2]. World Health Organization (WHO) guidelines published in 1985 also used linear measurements, but recommended two perpendicular measurements [3]. These guidelines were practical to use, particularly in the past when many radiologists used printed film images for reporting, and were widely adopted in oncologic research. However, both systems have limitations in the assessment of treatment response. RECIST

* Corresponding author. Fax: +1 212 794 4010.
E-mail addresses: hayess@mskcc.org (S.A. Hayes), pietanzm@mskcc.org (M.C. Pietanza), deemeagle@gmail.com (D. O'Driscoll), zhengj@mskcc.org (J. Zheng), moskowc1@mskcc.org (C.S. Moskowitz), krism@mskcc.org (M.G. Kris), ginsberm@mskcc.org (M.S. Ginsberg).

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guidelines exclude the use of lesions smaller than 1.0 cm. Linear measurements have been shown to be subject to significant intra- and inter-observer variation [4,5]. For irregularly-shaped non-small cell lung cancers (NSCLC), inter-observer variation resulting in response misclassification has been found to be as high as 45% for uni-dimensional measurements and 53% for bi-dimensional measurements [4].

More recent advancements in multi-detector row computed tomography has allowed for the volumetric measurement of tumors [6,7]. Studies have indicated that CT measurements are accurate for determining volume [8], possibly with better repeatability and reproducibility than for linear measurement [9,10]. Dinkel et al. found that using computer-assisted size assessment of lung tumors reduced interobserver variability to about half to one third compared with traditional manual measurements [11]. Published literature has suggested that volumetric measurements can better predict response and outcome than linear measurements [12]. CT volumetry, as well as other advanced methods such as CT perfusion, dynamic contrast-enhanced and diffusion weighted MR and metabolic tumor volume in PET CT, have all shown potential for the assessment of tumor response, but standardization and validation of these newer techniques is needed before they can be widely adopted [13].

Here, we assess volumetric measurements on CT to examine the correlations between uni-dimensional RECIST and volumetric measurements in patients with lung adenocarcinoma receiving first-line chemotherapy in the setting of a clinical trial and to assess their association with overall survival (OS) and progression-free survival (PFS).

2. Materials and methods

Patients included in this study were all successfully accrued to a single-arm, open-label, phase II single-institution study evaluating chemotherapy for stage IV lung cancer (ClinicalTrials.gov ID: NCT00807573) that had been reviewed and approved by the institutional review board. Written informed consent was provided by all patients. All patients had pathologically confirmed lung adenocarcinomas with stage IV disease at diagnosis or evidence of metastatic recurrence after definitive local therapy. Inclusion in the study also required Karnofsky performance status of $\geq$70%, and measurable disease per RECIST 1.0. Adequate organ and marrow function were necessary. Patients were excluded if they had received systemic therapy for advanced lung cancers or radiation therapy to greater than 25% of the bone marrow within 30 days of starting treatment. While prior neoadjuvant or adjuvant chemotherapy was permitted if it did not contain paclitaxel, pemetrexed or bevacizumab, at least 6 months had to have elapsed from last administration. Additional exclusion criteria included squamous cell carcinoma, small cell carcinoma, hemoptysis; symptomatic brain metastases with evidence of hemorrhage; history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess; and myocardial infarction or stroke within 6 months.

Forty-four patients were treated with a chemotherapeutic regimen including paclitaxel, pemetrexed, and bevacizumab. Each patient had a thin section CT scan of the chest and other relevant sites of disease at baseline, following cycles 1 and 2 of chemotherapy, and every 8 weeks thereafter. Cycles of therapy consisted of 28 days each. Response to chemotherapy was assessed based on uni-dimensional RECIST 1.0 measurements. Retrospectively, we obtained institutional review board approval to assess tumor volumes on each CT scan and correlated these to the previously measured RECIST. Target lesions for measurement were selected based on RECIST 1.0 guidelines [1], as the study was written and opened to accrual in 2008, prior to the publication of RECIST 1.1 guidelines [2].

Table 1
CT scanning parameters.

Parameter	Value
Detector row configuration	16 × 1.25
Pitch/table speed	1.375/27.50 mm
Collimation	2.5 × 2.5 mm
Reconstruction algorithm	1.25 mm slice thickness, lung and soft tissue windows

Multidetector CT was performed using LightSpeed 16CT scanners (GE Medical Systems, Milwaukee, Wis). Chest, abdomen and pelvis were scanned from the supraclavicular regions to symphysis pubis, using a single breath hold for the chest. Scan parameters are listed in Table 1. The images were obtained with intravenous and oral contrast, unless the patient had a contraindication to iodinated contrast. CT images were reconstructed at 1.25 mm slice thickness. These thin-section images were directly downloaded from the CT workstation onto a research server, where de-identified DICOM (Digital Imaging and Communications in Medicine) images were stored. The images were then transferred onto an Ultra 10 workstation (Sun MicroSystems, Santa Clara, California) for segmentation.

The target lesions in the lung were measured using a novel semi-automated segmentation algorithm, as described previously [7], which had been adapted in house from a program used for the segmentation of pulmonary nodules which had been developed by Zhao et al. [14]. Other segmentation algorithms also developed by these authors were used to assess target lesions in other organs, such as lymph nodes and liver [15,16]. The initial automated segmentation of the target lesions was performed by a technologist. All segmentation results, included the longest diameters and segmented target lesions, were visually inspected for errors by a board-certified cardiothoracic radiologist (M.S.G.) with >15 years of experience in CT interpretation. An example of the segmentation, showing the volumetric outline and the axial measurements recorded are shown in Fig. 1. The RECIST uni-dimensional measurements, as well as other patient data, were recorded prospectively by the same radiologist in a novel computer software system designed to enable real-time collection and review of clinical data during trials, as previously described by Pietanza et al. [17]. Volumetric measurements of the target lesions were performed using the segmentation algorithms. The sum of the volumes of the target lesions was recorded for each CT scan, similar to a RECIST read. RECIST reads were performed separately to the volumetric segmentation and the radiologist was blinded to the RECIST results at the time of volumetric segmentation.

2.1. Response assessment

Treatment response was assessed on follow-up CT scans using uni-dimensional RECIST and two different methods of three-dimensional volumetric response assessment, as a consensus for volumetric response criteria is still lacking. For the first volumetric method, volumetric spherical, we used volumetric response cut-offs based on simple mathematical extrapolation of RECIST to spherical volumes, as initially described by Therasse et al. in the 2000 RECIST guidelines [1]. Here, follow-up CT scans were categorized as complete response (CR, disappearance of the lesions), partial response (PR, 30% decrease in diameter, correlating geometrically to 65% decrease in volume), progressive disease (PD) (20% increase in diameter, correlating geometrically to a 73% increase in volume), or otherwise stable disease (SD). For the second method, volumetric ellipsoid, we utilized an alternative criteria proposed by Schiavon et al. in 2012 [18], who found that extrapolating RECIST