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A pilot study of volumetric and density tumor analysis of ACC patients treated with vorinostat in a phase II clinical trial☆

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ABSTRACT

Rationale and objectives: Adenoid cystic carcinoma (ACC) is a rare salivary gland cancer. The vast majority of clinical trials evaluating systemic therapy efficacy in solid tumors use the Response Evaluation Criteria in Solid Tumors (RECIST) to measure response that is limited to 2 dimensional only evaluations, not taking volume or density into account. The indolent behavior ACC represents a challenge toward an appropriate evaluation of therapy response. Objectives: 1) To describe and contrast volumetric and density changes at each time-point, including changes noted from baseline to best response, to currently used 2 dimensional-only criteria (RECIST) and 2) To report the coefficient of variation in volume measurement among three reviewers on a subset of ACC patients.

Materials and methods: We retrospectively assessed a cohort of 18 prospectively treated patients with ACC in a phase 2 trial with vorinostat using a volumetric (viable tumor volume, VTV) and density criteria. Three independent and blinded observers segmented target lesions across a sample of randomly selected computed tomography (CT) exams to examine inter-observer variation.

Results: We found that the average coefficient of variation among observers for all target lesions was 16.1%, with lung lesions displaying a smaller variation at 14.0% (p-value >0.17). We

Abbreviations: ACC, Adenoid Cystic Carcinoma; SD, Stable Disease; CT, Computerized Tomography; VTV, Viable Tumor Volume.

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describe examples of decrease in volume and density in several lesions despite stable disease by RECIST.

Conclusion: This pilot study demonstrates that two-dimensional criteria such as RECIST may not be the best criteria to assess response to therapy, especially with evolving tools within picture archiving and communication system (PACS) that can assess volumetric size, density and texture, however, this should be prospectively studied.

1. Introduction

Adenoid cystic carcinoma (ACC) is a rare and slow-growing salivary gland cancer that has an indolent course but with a propensity to metastasize [1]. There is no Food and Drug Administration (FDA) approved systemic treatment for this malignancy. Most clinical trials evaluating systemic therapy to treat ACC reported stable disease (SD) by RECIST (Response Evaluation Criteria in Solid Tumors) as the most common outcome, irrespective of the treatment administered [2–8]. In this context, it is unclear whether SD is a surrogate of the indolent behavior of the disease or a limitation of two-dimensional criteria such as RECIST, thereby making the study of alternative methods to evaluate response in this malignancy of utmost importance [9]. RECIST was developed to assess tumor response (TR) from cytotoxic chemotherapeutic agents and may not be sufficient to characterize TR in patients treated with non-cytotoxic agents or in slow-growing tumors. Multi-slice computerized tomography (CT) is now widely available with routine volumetric acquisition of overlapping thin series that allow for volumetric analysis through lesion segmentation. By segmentation, we refer to the ability of advanced picture archiving and communication system (PACS) and third-party systems to outline a lesion by automated (or semi-automated) means on all images where a lesion is observed. Once the digital outline is visually confirmed, best represents the volumetric lesion sizeVolumetric analysis of lesions has emerged as a promising and comprehensive method to assess viable or necrotic tumor sizes (Folio, Sandouk, Huang, Solomon, & Apolo, 2013).

In a previously published phase 2 study of vorinostat in patients with metastatic and relapsed ACC, there was anecdotal (not based on formal quality of life questionnaires), however, obvious clinical improvement in patient symptoms without a corresponding partial response (PR) in tumor size [5]. We therefore retrospectively measured volumetric density and viable tumor volume (VTV) in selected patients treated on the above-mentioned trial, to describe the effect of vorinostat in tumor volume and densities. Additionally, we sought to determine inter-observer variation in volumetric segmentation since this has not been shown previously. To the best of our knowledge, there is no published information establishing expected ranges in this scenario. The objectives of this report were to (i) describe and contrast volumetric and density changes at each time-point, including changes noted from baseline to best response, to currently used 2 dimensional-only criteria (RECIST), and (ii) report the coefficient of variation in volume measurement among three reviewers on a subset of patients with AC treated with vorinostat.

2. Material and methods

2.1. Patient population and imaging

We retrospectively performed 191 segmentations on a total of 55 target lesions previously selected and measured using RECIST 1.1 criteria on 68 cross-sectional computed tomography (CT) scans (serial scans following the same lesion over time) from 18 ACC patients. Subjects were previously treated with vorinostat, a histone deacetylase inhibitor (HDACi) in the setting of a phase 2 clinical trial [5]. This study was approved by the National Cancer Institute IRB and informed consent was obtained from all parties. All patients were enrolled and treated with vorinostat according to the clinical trial protocol as published. Eighteen out of the 30 patients in the trial had available CT scans for volumetric measurement; therefore, not all the 30 patients in the phase 2 trial were included in this report. Patients with only MRI scans were excluded to control for consistency in the volumetric analysis of tumor volume and density.

3. Patients included in this report were treated in two different institutions in the United States

Patients had to have measurable disease by RECIST 1.1 and only CT exams for which intravenous contrast was given, were assessed with VTV. The CT scans evaluated included at least 3 time-points in the course of treatment with vorinostat (baseline, at time of best response to study drug, and most recent scan performed). A mid-treatment scan was also evaluated in patients that had more than 3 scans performed during the study duration. CT scan intervals ranged from 2 to 16 months apart. The target lesions analyzed in this study were the same target lesions pre-selected in the phase 2 trial and included lesions in the lung, liver, lymph nodes, pericardium, buccal space, mandible, soft tissue, diaphragm, and mediastinum. We also examined the inter-observer variation in nine randomly selected patients out of the 18 total patients with segmented lesions.

3.1. Volumetric tumor analysis and density measurement

A lesion segmentation PACS tool (VuePACS 12.1 Philips, Netherlands) was used to semi-automatically segment each target lesion to acquire volumetric size and density to determine VTV. The following CT scanners were used for the volumetric and density analysis: Siemens definition, biograph or flash (Siemens Healthcare USA; Malvern PA) or Philips Brilliance (Philips Healthcare; Andover, MA).

Research assistants segmented across the target lesions to acquire the volume of the lesion in cubic centimeters (cm^3) and densities (HU) through all imaging time-points (baseline, time of best response to study drug, most recent scan performed, and, in some cases, mid-treatment). Target lesions were previously measured and TR assessed by RECIST 1.1 as specified in the phase 2 trial. Select lesions, measurements, and segmentations were then evaluated independently by a radiologist (see Fig. 1).

Each target lesion was examined. The measurements included the sum of the longest diameter per each scan, i.e. RECIST response (cm), volume (cm^3), and HU mean as acquired through histograms. Average and standard deviation of HU was acquired by generating histograms in selected lesions to determine the density of the tumor in an attempt to differentiate tumor zones from tumoral necrosis zones as previously described by dividing into VTV-low: 0–50 HU (necrotic/cystic components) or VTV-high: 51–180 HU (mixed components/active tumor) (Figs. 2 and 3). Histograms had a threshold of a minimum value of 0 to ensure air from adjacent lungs was not included in the volumetric total as this would inappropriately skew the histogram toward the left. Similarly, the maximum value selected was 180 to avoid skewing from nearby bone or enhanced proportionally large vasculature. The histograms represented shifts in density over time; e.g. a shift to the left would suggest necrosis as exemplified in Fig. 2.

The patient's response to treatment by RECIST v1.1 was described as reported in the phase 2 clinical trial as seen in Table 1 *(Insert Table 1 here in publication)*. The percentage of volume (and density) change in lesions from baseline to best response for each tumor was calculated by adding the volume of all lesions at baseline for a given patient and again at best response. The difference was then calculated and described as a percentage. Changes in mean HU of all target lesions from baseline to best response were annotated (see Fig. 4).

3.2. Inter-observer segmentation variation

Three authors performed volumetric and density analysis on a randomly selected number of scans to determine inter-observer variation. Nine patients were randomly selected out of the study population where segmentations were performed in 25 lesions that were analyzed by the three raters: a research assistant, a general physician, and a radiologist. To avoid bias from previously segmented lesions, three copies of each exam were placed in separate folders to blind each observer from other segmentations to remain unaware of each other's analysis. Each lesion was surrounded by a line delimitating an oval for guidance as to which lesion to segment on each of the three research copies (separate from the original exam).

Variability in the measurement of lesion volume (cm^3) was determined using the coefficient of variation (standard deviation divided by the mean). The mean and standard deviations were estimated for each lesion segmented by three raters. In addition, the mean coefficient of variation was evaluated for each lesion type, e.g. lung, liver, lymph nodes.

4. Results

4.1. Description of volumetric tumor analysis and density measurement changes per patient

Overall, a decrease in volume of the lesions from baseline to best response was noted in 8/18 patients (12.7–52.5). A decrease in the density of the lesions from baseline to best response was seen in 13/18 patients (11.59–58.15). Most lesions were in the lung parenchyma (15 out of 18 patients). Among patients that had target lesions only in the lung (n = 10), a decrease in volume was seen in half of the cases. The patient that had a PR by RECIST (#12) had the largest decrease in volume change from baseline to best response, with a decrease of almost half in the size of the lesions (−48.93%). In this patient, the density of the lesions also showed a decrease of 33.3%. In contrast to patient #12, patient #13 lesions had a decrease in density of more than 50% (58.15%), along with a decrease in volume of almost 30% (−29.41), but was deemed to have SD by RECIST, whereas patient #12 had PR. Additionally, patient #16 lesions had an increase in volume of lung target lesions of 138.09% but was deemed to have SD by RECIST. This patient's lesions also

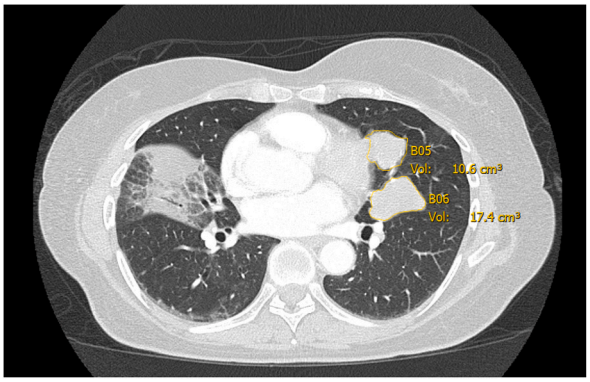

Fig. 1. Segmented Lung Lesions
An illustrative post-treatment computed tomography (CT) axial slice of two left lung masses segmented around lesion borders showing volumetric sizes of 10.6 cm^3 and 17.4 cm^3. Right middle lobe atelectasis is incidentally noted.

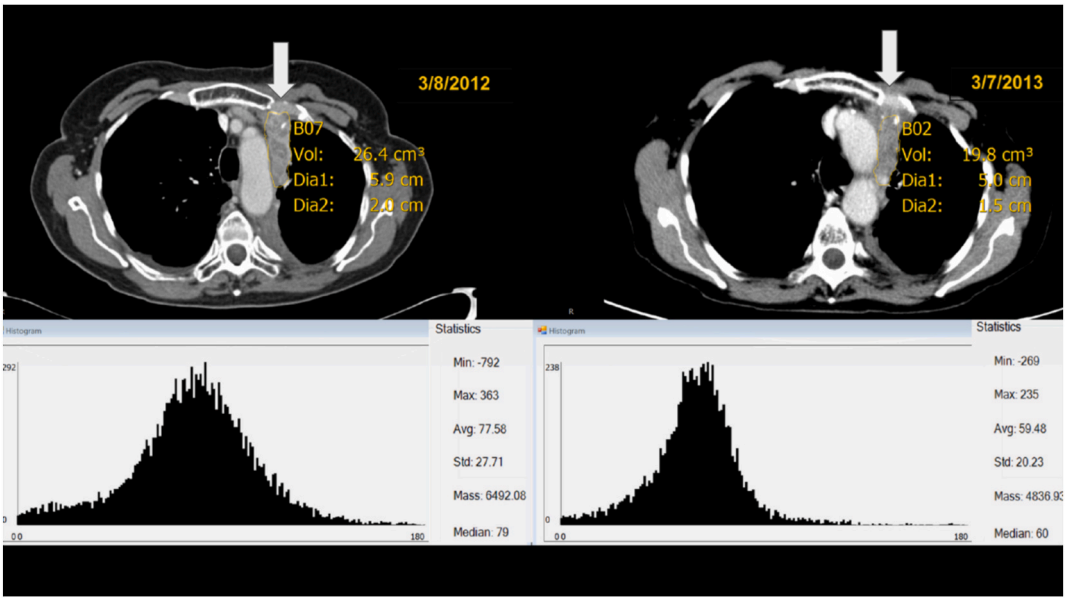

Fig. 2. Histograms of a Mediastinal Mass
Axial CT (computerized tomography) baseline scan (top left) of an enhancing mediastinal mass compared to post-treatment CT (top right). Volumetric density histograms (bottom images) are associated with each CT above them. Note the decreasing size in volume (from 26.4 cm^3 to 19.8 cm^3) and left shift of the post-treatment exam histogram (bottom right) compared to the baseline histogram (bottom left), likely representing tumor necrosis.

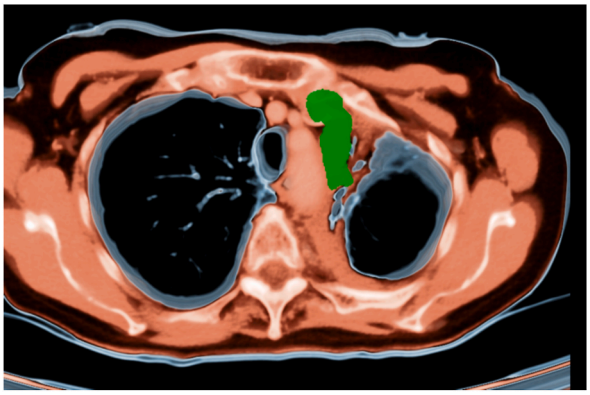

Fig. 3. Axial slab of the same lesion seen in Fig. 2.
Lesion shown in MPVR (Multiplanar Volume Rendered). Note the segmented mediastinal lesion in green as a discrete object that lends itself to further analytics and visualization incidentally noted.

Table 1
Description of response categories by RECIST version 1.1

RECIST 1.1	
Evaluation of target lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions compared with nadir (this includes the baseline sum, if that is the smallest on study). The sum must also demonstrate an absolute increase of at least 5 mm. One or more new lesion(s) is also considered PD.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference, the smallest sum of diameters, while on study.

showed a decrease in density of 33.3%. Patient #8, with liver target lesions, despite a decrease in volume and density of over 40%, was also deemed to have SD by RECIST. Changes in volume and density were congruent, i.e. decreasing or increasing similarly, in 7/18 patients. Finally, it should be acknowledged that volumetry has contributed to changes dependent on variable chemotherapy strategies. This study was retrospective and did not change therapy, however, the treatment course may affect therapy for future patients with ACC with the potential to determine response earlier.

Table 2 describes the volume and density changes of each tumor from baseline to the time of best response *(Insert Table 2 here in publication)*.

4.2. Inter-observer segmentation variation

The average coefficient of variation among the three authors (Cov) for all lesions was 16.1%. If one assumes that the lesions are spherical, where the volume goes as the third power of the radius, then the overall CoV of 16.1% would correspond to a CoV in diameter measurement of 5.1%. The CoV for lung lesions was 14.0% and for liver lesions, CoV was 30.7%. The CoV for all lesions excluding the liver was 14.3%. A paired *t*-test was performed on all log-transformed lesion volume measurements to determine if there was a significant reduction in lesion size between pre and post-treatment (at best response). A p-value of 0.17 indicates a non-significant trend in reduction of lesion volume, considering all types of lesions. We found that there was more consistency among segmentations in lung lesions (CoV 14.0%) which had clear identifiable margins. In lesions that did not have such margins, such as the liver lesions, the CoV was higher (30.7%).

5. Examples of volume and density changes

Fig. 1 shows an example of semi-automatically segmented lesions used to generate the volume of each lesion.

Fig. 2 displays an example of volume and histogram changes from a patient treated with vorinostat (over 1 year), showing a decrease in the size of the volume of the lesions along with histogram changes suggestive of tumor necrosis. This patient was qualified as having SD by RECIST.

Fig. 3 shows an axial slab of the same lesion depicted in figure 2, but with green contrast rendering the lesion to be more easily identified.

Fig. 4 illustrates one of the advantages of using VTV, as it clearly shows a decrease in volume and histogram shift to the left, corresponding to cavitation of such lesion.

6. Discussion

We describe changes in volume and density of pre-selected target lesions of patients with ACC treated on a phase 2 trial with vorinostat. In that trial, patients experienced anecdotal (not evaluated by formal quality of life questionnaires) clinical improvement of symptoms related to ACC despite having SD as best response by RECIST. In medical oncology, PR is usually a surrogate of clinical benefit and it is often a "go, no-go" parameter on a clinical trial, as drugs that lead to a PR are considered to have efficacy against a particular malignancy. Response rate by RECIST is one of the parameters used by the FDA for drug approvals. As mentioned before,

Table 2
Description of changes in lesions (volume and density) per patient from baseline to best response imaging.

Patient #	Total # of scans (n)	Location of target lesions	Total # of target lesions (n)	Best response by RECIST on phase 2 trial	Volume (%) change from baseline to best response	Density (%) change in from baseline to best response from a representative target lesion
1	5	Lung	2	SD	−12.7	35.71
2	4	Lung	2	SD	+43.75	−17.94
3	4	Lung	4	SD	−18.6	+18.72
4	3	Lung	3	SD	−12.9	−45.18
5	3	Lung	3	SD	+9.1	252.95
6	5	Lung	4	SD	+17.5	−45.03
7	3	Lung, pericardium	4	SD	−21.5	−29.16
8	3	Liver	3	SD	−52.5	−40.56
9	4	Liver, lung	8	SD	+24.5	−6.31
10	4	Lung	3	SD	+9.92	+23.31
11	2	Oral, mandible, lung	5	SD	−23.27	+16.81
12	4	Lung	3	PR	−48.93	−33.30
13	4	Lung	1	SD	−29.41	−58.15
14	4	Lung and liver	2	SD	+17.6	−22.89
15	4	Soft tissue, lung	3	SD	+18.85	−27.90
16	4	Lung	2	SD	+138.09	−33.48
17	2	Lymph node, liver, diaphragm	3	SD	+6.18	−27.05
18	4	Mediastinal	4	SD	+13.63	−11.59

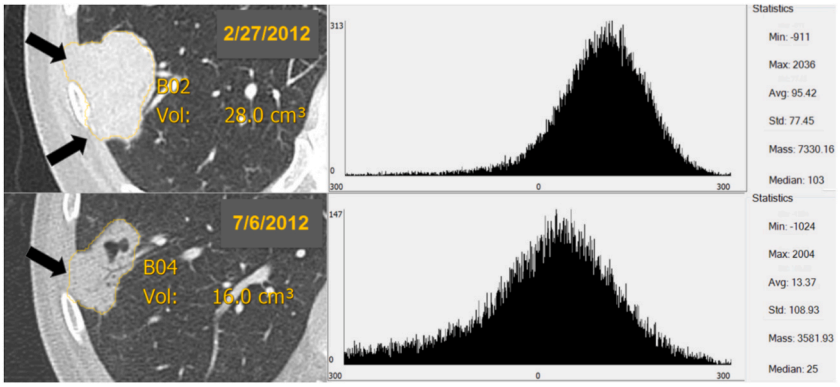

Fig. 4. Viable Tumor Volume (VTV) of a Lung Lesion Air Bronchogram
VTV (Viable Tumor Volume) compared to RECIST v 1.1 criteria. Top left- Axial CT (computerized tomography) of segmented lung lesion on baseline exam with corresponding histogram (top right). Bottom figure - Axial CT of the same lesion showing cavitary components; including air bronchogram with a dramatic histogram shift to the left, 5 months after initiation of therapy. This lesion also became smaller in volume (from 28.0 to 17.2 cm^3) whereas the sum of longest diameters (RECIST 1.1) went from 4.5 to 4.2 cm. The threshold parameters were changed to −350 to plus 300 (not used in the analysis in this study) to highlight this lung lesion density shift that contained many more negative HU due to cavitary degradations. HU average was 93.3 at baseline and 2.2 after treatment. Note also the increased number of lower densities in the follow-up exam (5 months post treatment).

RECIST was designed as a criteria to assess RR from cytotoxic chemotherapeutic agents in rapidly growing tumors. Of note, "stable disease" requires comparison to a baseline study, and radiologists should avoid this terminology in the impression, unless the calculation is done on a verified target lesion and compared to a known baseline exam (Lisovoski F, B. D., Papo T., & Goasguen J, 1987).

In this pilot study, we showed that several tumors had a decrease in volume and density from baseline to best response, despite being labeled as SD by RECIST. A quantitative volumetric and density criterion for partial response has not been established, however, one could argue that a percentage decrease of 15–20% could be viewed as a potential start number to be validated in the future as a PR. In this small sample of patients, 2 patients' target lesions had such a decrease in volume and 6 patients' target lesions had such a decrease in density.

Our pilot study also showed significant variation between three observers, a fact that should be considered before applying volumetric criteria using semi-automatic segmentation. Semi-automated segmentation, if had been proven consistent, would have been easier to generalize as not every site has automated capabilities; but as seen in our study, using semi-automated segmentation carried a high variability rate (16.1% overall and 14.1% in lung lesions). A higher variability was seen in the liver lesions due to differences in margin location decisions made during manual segmentation by three different raters. This reinforces the need for an automated segmentation method, especially when the lesion margins are ill-defined. Some inter-observer differences with our volumetric analysis may have been compounded by rounding volumes to a tenth of a cm^3, where the modality of our PACS carries as far as 100th of a centimeter.

We acknowledge the limitations of this study. We analyzed a small sample size, as ACC is a rare tumor and we also did not have access to all the scans of the patients treated on the phase 2 study [5]. Scans that were acquired from other centers than that of the authors were of variable quality and slice thickness, more often thicker than 2 mm. Ideally, each author that was segmenting lesions across the same patients should have done so on the same slice for consistent measures, however; because the lesions were identified by different radiologists at the two centers, there was variability in CT acquisition. Slice thickness and soft, hard algorithm differences may have caused slight variability among volume and density measurements. Lastly, despite several advances in semi-automated volumetric segmentation, the process remains time-consuming and reserved for imaging centers with core lab capabilities [10]. Additionally, the authors realize the lack of clear correlation between volumetric and density changes, RECIST, and outcomes, however, we believe this pilot study may provide guidance in future prospective studies that can better compare response criteria.

Future studies are planned in patients with ACC evaluating VTV as potential response criteria. In order to validate such criteria in ACC, we advocate that studies would need to incorporate other metrics, including patient-reported outcomes of clinical benefit, change in tumor growth curve, and ultimately, improvement in tumor-specific survival. More so, a definition of a tumor "response" to a drug should be a composite of all the previously mentioned metrics, not only a mere description of reduction in the size of tumor. This current study was not designed to establish such volumetric or density criteria, but it can be viewed as a pilot, "thought-provoking" report. We did not have in the phase 2 study of vorinostat, quality of life questionnaires that could have helped in instances where an objective improvement in symptoms accompanied a decrease in volume and density without a PR by RECIST [5]. From a technical point of view, future studies should also compare volumetric tumor densities by having researchers segment (on) the same slice. Ideally, one single modality of imaging (CT or MRI) should be used to standardize the criteria, however, this approach limits flexibility, for example on patients with metallic implants that cannot undergo MRI.

7. Conclusions

This pilot study demonstrates that two-dimensional criteria such as RECIST may not be optimal to assess response to therapy, especially with evolving tools within PACS that can assess volumetric size, density, and texture. Though several tumors decreased in volumetric size and tumor density from baseline to best response in patients categorized SD by RECIST, we can only speculate treatment related necrosis effects based on established criteria such as [11]. Automated segmentation is preferred to manual or semi-automatic due to the inter-observer variability described herein. Holistically, volumetric analysis to include size and density shows promise as a more comprehensive approach to measure tumor changes in ACC over two diameter criteria such as RECIST. Caution to inter-observer variation should be taken into consideration, especially when lesion margins are ill-defined, as we demonstrated.

Author contribution statement

Malarkey ME - Performed the experiments, Contributed reagents, materials, analysis tools or data, Wrote the paper.
Toscano AP - Performed the experiments, Contributed reagents, materials, analysis tools or data, Wrote the paper.
Solomon J - Performed the experiments, Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data, Wrote the paper.
Machado LB - Conceived and designed the experiments, Performed the experiments, Contributed reagents, materials, analysis tools or data, Wrote the paper.
Bagheri M – Performed the experiments, Contributed reagents, materials, analysis tools or data.
Chen, A - Contributed reagents, materials, analysis tools or data.
LoRusso P - Contributed reagents, materials, analysis tools or data.
Folio LR - Conceived and designed the experiments, Contributed reagents, materials, analysis tools or data, Wrote the paper.
Goncalves PH - Conceived and designed the experiments, Contributed reagents, materials, analysis tools or data, Wrote the paper.

Disclaimer

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Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

The clinical trial described in this paper was registered at ClinicalTrials.gov under the registration number Identifier: NCT01175980.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Les Folio has a research agreement with the PACS mentioned in this paper (Philips, Netherlands). Laura Machado was part of a research agreement with the PACS mentioned in this paper. The following authors have no conflicts of interest: Molly Malarkey, Alexandra Toscano, Mohammad Hadi Bagheri, Jeffrey Solomon, Patricia LoRusso, Alice Chen, and Priscila Goncalves.

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