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Original Article

Variant allele fraction of genomic alterations in circulating tumor DNA (%ctDNA) correlates with SUV_{max} in PET scan

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Abstract: The relationship between higher variant allele fraction (VAF) of genomic alterations in circulating tumor DNA (%ctDNA), an indicator of poor outcome, and maximum standardized uptake value (SUV_{max}), the most commonly used semi-quantitative parameter in ^{18}F-FDG PET/CT, has not been studied. Overall, 433 cancer patients had blood-based next generation sequencing. Maximum and sum of %ctDNA alterations (%$ctDNA_{max}$ and %$ctDNA_{sum}$, respectively) represent the maximum and sum of VAF, reported as a percentage. The subset of 46 eligible patients had treatment-naïve metastatic disease and PET/CT imaging, with median 13 days prior to ctDNA testing. We found a linear correlation between the maximum VAF (%$ctDNA_{max}$) (as well as the sum of the VAFs (%$ctDNA_{sum}$)) and SUV_{max} of the most ^{18}F-FDG-avid lesion (r=0.43, P=0.003; r=0.43, P=0.002; respectively). Our data suggest that SUV_{max} may be a non-invasive and readily available surrogate indicator for %ctDNA, a prognostic factor for patient survival. Since higher %ctDNA has been previously correlated with worse outcome, the relationship between SUV_{max}, %ctDNA and survival warrants further study.

Keywords: Genomic alterations, circulating tumor DNA (ctDNA), Variant allele fraction of genomic alterations in circulating tumor DNA (%ctDNA), SUV_{max}, cancer, PET/CT

Introduction

PET/CT with ^{18}F-FDG is commonly performed in the initial staging and subsequent evaluation of patients with cancer. With recent advances in genomic data acquisition, exploring correlations between imaging and genomic alterations is of interest, as there is the possibility that imaging can ultimately serve as a non-invasive and readily available surrogate for molecular features [1, 2].

Genomic alterations are the hallmark of cancer and can be used to predict survival by acting as prognostic or predictive biomarkers [3, 4]. Genomic abnormalities can be deduced from interrogation of either tissue biopsy or the so-called liquid biopsy. A liquid biopsy is obtained from fluids such as blood plasma that contains circulating tumor cells (CTCs) or circulating cell-free DNA fragments, designated as circulating tumor DNA (ctDNA), as well as exosomes (EXOs), namely membrane-encapsulated subcellular structures containing proteins and nucleic acids shed from tumor cells into the bloodstream [5, 6]. Liquid biopsies are increasingly being leveraged in the clinical setting because, compared to tissue biopsy, they are non-invasive, faster, and associated with less technical difficulty and morbidity [7]. If there is a contraindication to an invasive tissue biopsy or the tissue sample is inadequate, liquid biopsies may be the only choice for genomic evaluation [8]. It was recently shown that higher variant allele fractions (VAFs) (also known as percent circulating tumor DNA (%ctDNA)) for genomic alterations in liquid biopsies correlate with shorter patient survival [9-11]. Higher total number of alterations in ctDNA may also be an indicator of

more aggressive tumor biology and poorer survival [12].

Maximum standardized uptake value (SUV_{max}) is the most commonly used semiquantitative measurement, for the semi-quantification of FDG PET in a region of interest. It is the most robust, reliable, accurate and reproducible value for assessment of treatment response in cancer patients [13]. We recently demonstrated that SUV_{max} is related to the tumor mutational burden (TMB) and total number of oncogenic anomalies in the tissue biopsy [14, 15]. In this study, we sought to evaluate the relationship between SUV_{max} and the %ctDNA of genomic alterations in liquid biopsies.

Materials and methods

Patient selection

We interrogated our database of 433 consecutive eligible patients with cancer, at University of California San Diego Moores Center for Personalized Cancer Therapy, for whom NGS (ctDNA and tissue DNA) had been performed (June 2014 to Sept 2017). Eligibility implied patients meeting UCSD IRB guidelines for waiver or consent. This study was conducted in accordance with the UCSD internal review board (IRB)-approved protocol (NCT02478931) [16]. Among these patients, we found 46 individuals with advanced cancers who had undergone ^{18}F-FDG PET/CT within 64 days prior to the blood draw (to ensure acceptable temporal correlation between imaging and genomic evaluation) and had no history of prior systemic treatment. Data were abstracted from the electronic medical record.

^{18}F-FDG PET-CT imaging

Patients had ^{18}F-FDG PET-CT imaging as needed routinely, for their disease assessment, and follow-up. Fasting for at least six hours prior to the scan,was a standard part of the imaging protocol. Immediately before the ^{18}F-FDG injection, blood glucose levels were measured and no patient had a blood glucose level >160 mg/dl, to avoid inaccurate semiquantitative SUV_{max} and need for glucose correction [17]. Within 10 seconds, patients were injected with 370-740 MBq ^{18}F-FDG, intravenously. Multi-station 3-dimensional (3D) whole body PET acquisition with CT was performed for ~60 min, using the same GE Discovery VCT scanner (Waukesha, WI) for all the patients, following an uptake period of one hour in a quiet room at rest. Whole-body CT was performed from the region of the head to the mid-thigh or toes. PET imaging was performed, in the 3D acquisition mode, at a rate of 2 minutes/bed position, after the CT scan. CT images were reconstructed onto a 512×512 matrix. With a standard whole-body 3D iterative reconstruction, PET images were reconstructed using: 2 iterations; 28 subsets onto a 128×128 matrix with decay correction, attenuation correction, and scatter correction. The photon energy window was standard at 425-650 keV. The reconstruction diameter was 70 cm, the slice thickness was 3.27 mm, the pixel size was 5.47 mm×5.47 mm, and the spatial resolution was 5 mm.

Image analysis

PET images were interpreted by a nuclear medicine physician and verified by a second nuclear medicine physician, on the pictures archiving and communication system (PACS), (AGFA Impax 6.3, Mortsel Belgium). SUV of the most ^{18}F-FDG-avid lesion, larger than 1 cm, was obtained by manually placing a circular region of interest (ROI) at the site of the maximum ^{18}F-FDG uptake and the maximal activity (SUV_{max}) was recorded. We calculated SUV as decay-corrected activity of tissue volume (kBq/mL)/injected ^{18}F-FDG activity per body mass (kBq/g). For 2 patients without elevated focal ^{18}F-FDG uptake on PET, a rounded SUV_{max} of 0 was recorded.

Sequencing

Guardant Health, Inc. (Redwood City, CA), a Clinical Laboratory Improvement Amendment (CLIA)-certified and College of American Pathologists (CAP)-accredited clinical laboratory, performed digital Sequencing of ctDNA. The analytical and clinical validation of Guardant 360 was conducted in conformance with standards established by Evaluation of Genomic Applications in Practice and Prevention (EGAPP), the Standards for Reporting of Diagnostic Accuracy (STARD), REporting of tumor MARKer Studies (REMARK), and the recent Next-generation Sequencing: Standardization of Clinical Testing (Nex-StoCT) biomarker guidelines [18]. We isolated 5-30 ng of ctDNA from plasma, using two 10 mL Streck tubes drawn

Table 1. Patient characteristics

SUV_{max} (Mean ± SD)	6.97±4.56
Median (range)	6 (0-23)
Days between PET & blood draw (Mean ± SD)	18.2±16.7
Median (range)	13 (1-64)
$\%ctDNA_{sum}$ (Mean ± SD)	7.25±12.1
Median (range)	1.15 (0-43.5)
$\%ctDNA_{max}$ (Mean ± SD)	
(Mean ± SD)	5.16±9.28
Median (range)	0.85 (0-43.5)
Age at time of biopsy (years) (Mean ± SD)	58.3±12.5
Median (range)	59.5 (34-81)
Women (N (%))	30 (65.2%)
Men (N (%))	16 (34.7%)
Lung cancer (N (%))	19 (41%)
Gastrointestinal cancer (N (%))	8 (17%)
Breast cancer (N (%))	6 (13%)
Brain cancer (N (%))	5 (10%)
Head and neck cancer (N (%))	5 (10%)
Other cancers (N (%))	3 (6%)

Abbreviations: ctDNA = circulating tumor DNA; SD = standard deviation.

from each patient. Sequencing libraries were made with custom in-line barcode molecular tagging, and 15,000× read depth complete sequencing. The current panel uses hybrid capture and subsequent NGS of critical exons in a panel of 70 genes. It reports all four major types of genomic alterations (indels, point mutations, fusions, and copy-number amplifications). To remove false positive results, post-sequencing bioinformatics matches the complementary strands of each barcoded DNA fragment [18]. VAF represents %ctDNA alteration reported as percentage and computed as the number of mutated DNA molecules divided by the total number (mutated plus wild-type) of DNA fragments at that allele. Most of the cell-free DNA is wild-type (germline); therefore, the median VAF of somatic alterations is <0.5%. $ctDNA_{sum}$ was defined as sum of individual alterations in the ctDNA, not including variants of unknown significance (VUS). $ctDNA_{max}$ was defined as maximum individual alteration in the ctDNA, not including VUS.

Statistical analysis

Statistical analysis was performed using R, version 3.5.2. The diagnostics from the statistical model indicated that SUV_{max} and %ctDNA alterations should be analyzed on the logarithmic scale. We found that if we log-transform only one variable or neither of the two variables, there were still outliers and strongly influential points that made the model a poor fit. However, in the log-scale, there was no evidence, based on the residual-vs.-leverage and residuals-vs.-fitted plots of the log-scale data analysis, that any point was exerting undue influence over the correlation, therefore no data point was removed as an outlier. Because there were multiple SUV_{max}, $\%ctDNA_{max}$, and $\%ctDNA_{sum}$ with rounded zero values, these values were first transformed to a shifted-log by adding 1 prior to applying a base 10 logarithm to the values. The Pearson's correlation was determined from the regression of the shifted-log SUV_{max} with the shifted-log $\%ctDNA_{max}$, and shifted-log $\%ctDNA_{sum}$.

Results

Patient characteristics

In our database of 433 patients with diverse cancers and tissue and blood ctDNA NGS, we found 46 patients with metastatic malignancies who had undergone ^{18}F-FDG PET/CT within 64 days prior to their blood draw and were treatment naïve in the metastatic setting. Patients' median age was 59.5 years (range: 34-81 years). There was a predominance of women over men [n=30 (65.2%): n=16 (34.7%)]. The primary organ for the primary cancer was lung (41%), followed by gastrointestinal (17%), breast (13%), brain and head and neck (10% each), and other (6%) (**Table 1**).

%ctDNA analysis

$\%ctDNA_{sum}$ and $\%ctDNA_{max}$ are the sum of the percentages of each deleterious ctDNA alteration and the maximum %ctDNA of any deleterious alteration, respectively; %ctDNA represents the VAF reported as a percentage. Median time between the PET/CT and blood draw was 13 days. Of the 46 patients evaluated, 34 (73.9%) had at least one ctDNA alteration. Mean ± standard deviation, median and range of $\%ctDNA_{sum}$ were 7.25±12.1, 1.15, and 0-43.5, respectively. Mean ± standard deviation, median and range of $\%ctDNA_{max}$ were 5.16±9.28, 0.85, and 0-43.5, respectively.

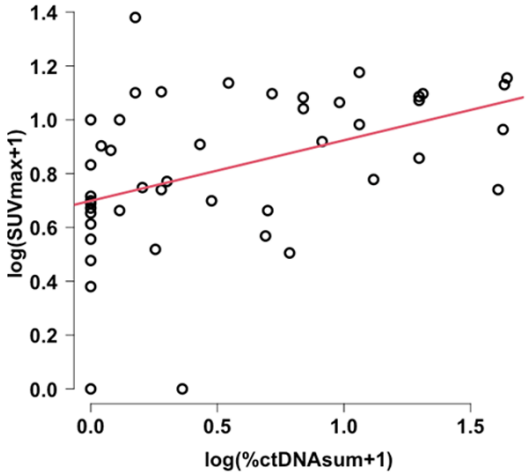

Figure 1. log(SUV_{max}+1) is linearly correlated with the log(%$ctDNA_{sum}$+1) (r=0.43, P=0.002) using Pearson's correlation. The graph represents the regression on the shifted-log scale. The circles represent individual data points, N=46. Only deleterious alterations (no VUSs) are included in %ctDNA calculations.

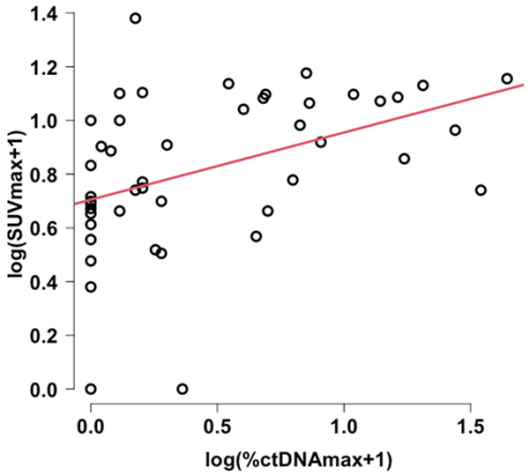

Figure 2. log(SUV_{max}+1) is linearly correlated with log(%$ctDNA_{max}$+1) (r=0.43, P=0.003) using Pearson's correlation. The graph represents the regression on the shifted-log scale. The circles represent individual data points, N=46. Only deleterious alterations (no VUSs) are included in %ctDNA calculations.

SUV_{max} correlates with %$ctDNA_{sum}$ and %$ctDNA_{max}$

The Pearson correlation coefficient was r=0.43 (P=0.002) for the linear correlation between the shifted-log sum of VAFs of genomic alterations in circulating tumor DNA (%$ctDNA_{sum}$) and shifted-log SUV_{max} (**Figure 1**). The Pearson correlation coefficient was r=0.43 (P=0.003) for the linear correlation between the shifted-log maximum VAF of genomic alterations in circulating tumor DNA (%$ctDNA_{max}$) and shifted-log SUV_{max} (**Figure 2**).

Discussion

Here we present the PET imaging correlates of genomic alterations in patients with diverse metastatic cancers. Prior PET studies have investigated the relationship between glucose metabolic rate and tumor immune microenvironment and have shown an association between metabolic and immune profiles [19, 20]. ^{18}F-FDG PET imaging has been suggested as a method to estimate tumor immune status [21]. To our knowledge, this is the first report which investigates the relationship between SUV_{max} and %ctDNA of genomic alterations. We previously demonstrated a significant positive correlation between SUV_{max} and TMB, speculating metabolic reconfiguration and immune inflammatory response as potential causes [15]. Our hypothesis is that a higher burden of ctDNA genomic alterations, as reflected by %ctDNA, might correlate with higher SUV_{max} with a similar rationale.

From 433 evaluated pan-cancer patients with ctDNA data, only 46 passed stringent criteria to be included in the study: (i) ^{18}F-FDG PET/CT within 64 days prior to the ctDNA blood draw; (ii) no history of prior systemic treatment; and (iii) advanced metastatic disease. These criteria ensured that the relationship between imaging and genomic data is not confounded by long time lapse or treatment. Our study confirmed that higher sum VAF of genomic alterations in circulating tumor DNA, (%$ctDNA_{sum}$), and higher maximum VAF of genomic alterations in ctDNA (%$ctDNA_{max}$), were both correlated with higher SUV_{max}, with moderate correlation coefficient of r=0.43 (P=0.002 and 0.003, respectively). Consistent with these results, we have previously shown that higher SUV_{max} is found in tumors with higher number of characterized genomic alterations [22].

We hypothesize that a higher load of genomic alterations, evidenced by higher sum and maximum VAF of genomic alterations in circulating tumor DNA (%$ctDNA_{max}$, and %$ctDNA_{sum}$) promote metabolic reconfiguration. This results in increased glucose metabolism rate and a higher SUV_{max}. Although higher VAF could be due to

higher mutational burden, resulting in metabolic reconfiguration, there are other possibilities that require future study. For instance, higher VAF could be due to larger tumor mass or due to tumor shedding more ctDNA and/or being more metabolically active. Alternatively, it is conceivable that both SUV_{max} and %ctDNA reflect tumor burden. An innate immune response to tumors with higher VAFs, may be an alternative explanation for the correlation between ctDNA alterations and SUV_{max}. The higher SUV_{max} (increased glycolytic activity) may be due to an immune cell infiltrate from an inflammatory response. Therefore, the exact mechanism for the finding of correlation between higher SUV_{max} and increased %ctDNA is not understood.

There are several important limitations in our study. First, %ctDNA and SUV_{max} parameters are not fully synchronized due to the retrospective study design; therefore, prospective studies with same-day imaging and blood draw are needed to validate our findings. Second, this was a single-center study and only 46 patients passed our stringent inclusion criteria even though the full cohort include 433 patients; thus, the sample size and number of centers in the study need to be expanded. Third, the underlying biochemical mechanism underlying the relationship between %ctDNA alterations and SUV_{max} is unknown and further studies are needed to shed light on the mechanism. Fourth, although higher %ctDNA has been demonstrate to correlate with poor outcome in several studies [9-11], we speculate that higher SUV_{max} may also be associated with a worse outcome [23], but didn't directly evaluate the prognostic impact of SUV_{max}, which needs to be performed to understand potential confounders in the relationship between SUV_{max} and prognosis. Thus, future larger prospective investigations should address the aforementioned four limitations to understand the relationship between SUV_{max}, %ctDNA, and patient survival are warranted. An important next study might be to test SUV_{max} as an indicator of %ctDNA and vice versa, and also to evaluate how effective each of these parameters, are alone or in combination, as prognostic indicators, and whether or not one can be a proxy for the other. In conclusion, we found a linear relationship between SUV_{max} and %ctDNA of the genomic alterations in the blood, assessed by next generation sequencing (NGS) of liquid biopsies. The relationship between SUV_{max}, %ctDNA and survival warrants further study to test SUVmax as an indicator of %ctDNA and vice versa, both being potential prognostic indicators.

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Disclosure of conflict of interest

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