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PAPER

Optimal transformations leading to normal distributions of positron emission tomography standardized uptake values

Matthew Scarpelli¹, Jens Eickhoff², Enrique Cuna³, Scott Perlman⁴ and Robert Jeraj^{1,5}¹ Department of Medical Physics, University of Wisconsin, 1111 Highland Ave, Room 1005, Madison, WI 53792, United States of America² Department of Biostatistics and Medical Informatics, University of Wisconsin, 600 Highland Ave, Madison, WI 53792, United States of America³ Centro Uruguayo De Imagenología Molecular (CUDIM), Av. Dr. Américo Ricaldoni 2010, 11600 Montevideo, Uruguay⁴ Department of Radiology, University of Wisconsin, 600 Highland Ave, Madison, WI 53792, United States of America⁵ University of Wisconsin Carbone Cancer Center, 600 Highland Ave, Madison, WI 53792, United States of AmericaE-mail: mscarpelli@wisc.edu**Keywords:** FDG PET, FLT PET, SUV, tumors, normal distribution**Abstract**

The statistical analysis of positron emission tomography (PET) standardized uptake value (SUV) measurements is challenging due to the skewed nature of SUV distributions. This limits utilization of powerful parametric statistical models for analyzing SUV measurements. An ad-hoc approach, which is frequently used in practice, is to blindly use a log transformation, which may or may not result in normal SUV distributions. This study sought to identify optimal transformations leading to normally distributed PET SUVs extracted from tumors and assess the effects of therapy on the optimal transformations. *Methods.* The optimal transformation for producing normal distributions of tumor SUVs was identified by iterating the Box–Cox transformation parameter (λ) and selecting the parameter that maximized the Shapiro–Wilk P -value. Optimal transformations were identified for tumor SUV_{max} distributions at both pre and post treatment. This study included 57 patients that underwent ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET scans (publicly available dataset). In addition, to test the generality of our transformation methodology, we included analysis of 27 patients that underwent ¹⁸F-Fluorothymidine (¹⁸F-FLT) PET scans at our institution. *Results.* After applying the optimal Box–Cox transformations, neither the pre nor the post treatment ¹⁸F-FDG SUV distributions deviated significantly from normality ($P > 0.10$). Similar results were found for ¹⁸F-FLT PET SUV distributions ($P > 0.10$). For both ¹⁸F-FDG and ¹⁸F-FLT SUV distributions, the skewness and kurtosis increased from pre to post treatment, leading to a decrease in the optimal Box–Cox transformation parameter from pre to post treatment. There were types of distributions encountered for both ¹⁸F-FDG and ¹⁸F-FLT where a log transformation was not optimal for providing normal SUV distributions. *Conclusion.* Optimization of the Box–Cox transformation, offers a solution for identifying normal SUV transformations for when the log transformation is insufficient. The log transformation is not always the appropriate transformation for producing normally distributed PET SUVs.

Introduction

The relative simplicity and quantitative nature of positron emission tomography (PET) standardized uptake values (SUVs) make them readily utilized in various oncologic applications of PET imaging (Thie 2004). Often analysis involves SUV measurements with some inherent correlation (tumor measurements derived from patients with multiple tumors, longitudinal measurements on a given patient/tumor, etc). Not accounting for these correlations can lead to incorrect conclusions. To circumvent analysis of correlated measurements, investigators often calculate a summary statistic to represent the correlated measurement. For example, when analyzing patients with multiple tumors, investigators may summarize SUVs for each patient (Wahl *et al* 2009, Liu *et al* 2011). Although this approach gives SUVs without intra-patient correlations, it discards information

(i.e. SUVs for each tumor are reduced to single SUV for each patient by taking the average, sum, or maximum SUV across all tumors within a patients) and consequently reduces statistical power.

Parametric statistics techniques such as linear mixed effects models or model-based factor analysis can be used to analyze correlated data but the skewed nature of SUV distributions prevents these types of analysis (Burton *et al* 1998). Furthermore, skewed distributions limit use of other parametric statistical tests such as t-tests, linear regression, and analysis of variance (Altman and Bland 2009). If the normal assumptions of these statistical tests are violated, resulting parameter estimates and conclusions may not be reliable. This motivates data transformations that result in normal distributions and allow utilization of parametric statistics techniques (Bland and Altman 1996, Thie *et al* 2000, Trigonis *et al* 2014). Statistical power may be increased through use of these parametric techniques, potentially reducing the number of patients and expenses required for clinical studies.

^{18}F -fluorodeoxyglucose (^{18}F -FDG) is a widely used PET radiotracer for quantifying glucose utilization in tumors (Wahl *et al* 2009, Schwartz *et al* 2015). ^{18}F -FDG SUVs extracted from tumors have been shown to be positively skewed and a log transformation has been shown to provide normal SUV distributions in some cases (Thie *et al* 2000). ^{18}F -Fluorothymidine (^{18}F -FLT) is another commonly used PET tracer in oncology and provides a quantitative measure of cell proliferation; no study to our knowledge has assessed the normality of ^{18}F -FLT PET SUV distributions (Chalkidou *et al* 2012). We hypothesize that data transformations may be utilized to find transformations leading to normal distributions of PET SUVs. To test our hypothesis we investigated use of Box–Cox transformations for identifying optimal transformations leading to normal SUV distributions for ^{18}F -FDG and ^{18}F -FLT, including an assessment of the effect of therapy on the optimal transformation. Further, we investigated the lognormal behavior of these SUV distributions and compared optimally transformed and log transformed SUV distributions.

Methods

Identification of optimal transformations

To identify optimal transformations, we apply one parameter Box–Cox transformations to SUV distributions (equation (1)) (Box and Cox 1964).

$$T = \begin{cases} \frac{S^\lambda - 1}{\lambda} & \text{if } \lambda \neq 0 \\ \ln(S) & \text{if } \lambda = 0. \end{cases} \quad (1)$$

S is the untransformed SUV measurement, λ is the Box–Cox transformation parameter, and T is the resulting transformed SUV measurement. An optimal transformation is identified by conducting a grid search in order to ascertain the distribution of transformed values which most closely resembles a normal distribution. The transformation parameter is varied in increments of 0.01 within the range of -3 to $+3$. The optimal transformation parameter is selected as that which produces a transformed SUV distribution with the maximum Shapiro–Wilk P -value (Shapiro and Wilk 1965). Ninety-five percent confidence intervals (95% CI) for the optimal transformation parameter are calculated with non-parametric bootstrapping using the bias corrected and accelerated bootstrap implemented using the boot function in R version 3.4 (Efron 1987). The resampling for the bootstrap is performed on a patient-level with 10 000 iterations. Identification of an optimal transformation parameter is repeated separately for each imaging cohort. To characterize the resulting distributions, we calculate the distribution mean, skewness (equation (2)) and excess kurtosis (equation (3)).

$$\gamma_1 = \frac{\frac{1}{N} \sum_i^N (S_i - \bar{S})^3}{\left(\frac{1}{N} \sum_i^N (S_i - \bar{S})^2 \right)^{\frac{3}{2}}} \quad (2)$$

$$\gamma_2 = \frac{\frac{1}{N} \sum_i^N (S_i - \bar{S})^4}{\left(\frac{1}{N} \sum_i^N (S_i - \bar{S})^2 \right)^2} - 2. \quad (3)$$

N is the number of tumors in the SUV distribution, S_i is the SUV for the i th tumor, and $\bar{S}$ is the mean of the tumor SUV distribution. Quantile–Quantile plots (Q – Q plots) were also generated to characterize resulting distributions and their deviations from normality (Wilk and Gnanadesikan 1968, Filliben 1975).

Imaging cohorts

The transformation methodology is applied to two imaging cohorts. The first cohort is a publicly available dataset (Radiation Therapy Oncology Group 0522 from the Cancer Imaging Archive) that consists of patients with head and neck squamous cell carcinoma that underwent ^{18}F -FDG PET scans at baseline and eight weeks after radiation therapy (table 1) (Schwartz *et al* 2015). Since there are no publically available ^{18}F -FLT PET

Table 1. Summary of the patient cohorts utilized in this study.

Cohort	Tracer	Disease	Therapy	Timepoints	Number of patients	Number of tumors
1	^{18}F -FDG	Head and neck primary and nodal tumors	Radiation therapy	Pre, post	52	126
2	^{18}F -FLT	Various metastatic solid tumors	VEGFR-TKI	Pre, post	27	70

datasets, the second cohort consists of ^{18}F -FLT PET imaging data from our institution (University of Wisconsin Carbone Cancer Center). This includes patients with metastatic cancers that underwent ^{18}F -FLT PET scanning at baseline and after two weeks of vascular endothelial growth factor receptor tyrosine kinase inhibition (Bruce *et al* 2015, Scarpelli *et al* 2016). For both cohorts, the SUV is calculated as the ratio of the activity concentration in a voxel to the total injected activity divided by patient weight. The maximum SUV of voxels within a tumor (SUV_{max}) is extracted from each tumor and the resulting distributions of tumor SUV_{max} are analyzed using our transformation methodology.

Results

The effect of the Box–Cox transformation on SUVs is shown figure 1. When the transformation parameter is less than one, the Box–Cox transform reduces positive skewness by shifting higher SUVs closer to lower SUVs. The amount of shift is determined by the transformation parameter, with lower values of the transformation parameter leading to greater shift in SUVs.

Untransformed SUV distributions from both cohorts deviated significantly from normality, demonstrating relatively high coefficients of variation as well as high values of skewness and excess kurtosis (table 2). The Box–Cox optimization for the ^{18}F -FDG distributions led to identification of a maximum in the Shapiro–Wilk P -value at the pre (figure 2(a)) and post (figure 2(b)) treatment time points, indicating optimal transformations for producing normal SUV distributions. The optimal transformation parameter at pre treatment was $\lambda = 0.42$ (95% CI: 0.17 to 0.67) and at post treatment was $\lambda = -0.01$ (95% CI: -0.58 to 0.41).

Figure 3 shows Q–Q plots for the untransformed, log transformed, and optimally transformed ^{18}F -FDG SUV distributions. The untransformed SUV distributions had quantiles greater than expected for normal distributions, indicating non-normal behavior (figures 3(a) and (d)). After a log transformation, the SUV distributions exhibited more normal behavior (figures 3(b) and (e)); however, some quantiles fall below what is expected for a normal distribution (figure 3(b)). The quantiles for the optimally transformed distributions demonstrated good agreement with expected normal quantiles (figures 3(c) and (f)).

The optimal Box–Cox transformation parameters for both patient cohorts are shown in figure 4. The optimal SUV transform for tumors imaged with ^{18}F -FLT PET at our institution were $\lambda = -0.02$ (95% CI: -0.34 to 0.30) and $\lambda = -0.37$ (95% CI: -0.77 to -0.03) at pre and post treatment, respectively. For both ^{18}F -FDG and ^{18}F -FLT, therapy resulted in increased skewness and kurtosis in SUV distributions, leading to a decrease in the optimal transformation parameter from pre to post treatment. After applying the optimal transformations, all SUV distributions had reduced skewness and excess kurtosis and none of the distributions deviated significantly from normality. A log transformation also resulted in reduced skewness and excess kurtosis but the pre treatment ^{18}F -FDG SUV distribution remained significantly non-normal (table 2).

Discussion

It is often assumed that a log transformation is adequate for providing normally distributed PET SUVs extracted from tumors; however, this study presented cases where the log transformation was not optimal for producing normal SUV distributions. Through optimization of the Box–Cox transformation, we identified transformations leading to normally distributed SUVs, even in cases where the log transformation failed to provide normal distributions. Importantly, the results showed that therapy can alter the optimal transformation leading to normally distributed SUVs. This indicates that although a transformation (e.g. log) may provide sufficiently normal SUV distributions at one timepoint (prior to therapy) it may not do so at another timepoint (post therapy).

The motivation for identifying normal SUV transformations is utilization of statistically powerful parametric models for analyzing correlated measures (Burton *et al* 1998). Accounting for these correlations becomes even more important when the degree of correlation increases or the number of correlated measurements increases. For example, patients with metastatic bone disease can have tens of metastatic tumors so analyses must account for intra-patient correlation of tumor SUVs to ensure reliable parameter estimates (Lin *et al* 2016, Rowe *et al* 2016).

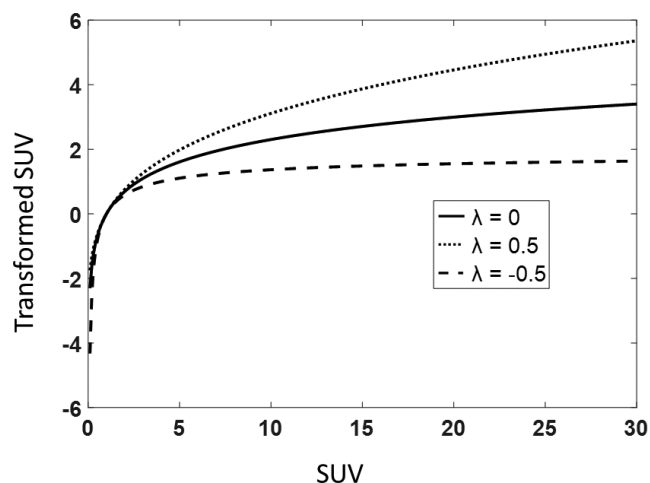


Figure 1. For a given transformation parameter λ , the Box–Cox transform reduces positive skew by shifting high SUVs closer to low SUVs. Various values of the transformation parameter are shown by different curves.

Table 2. Summary of the untransformed, optimally transformed, and log transformed SUV distributions.

Cohort	Time	No transform					Optimally transformed					Log transformed ($\lambda = 0$)				
		Mean	CV ^a	γ_1^b	γ_2^c	P-value ^d	Mean	CV ^a	γ_1	γ_2	P-value	Mean	CV ^a	γ_1	γ_2	P-value
1 FDG	Pre	12.3	0.59	0.9	2.4	<0.01	4.2	0.41	0.0	0.5	0.12	2.3	0.29	−0.5	0.6	<0.01
	Post	3.2	0.53	1.7	5.2	<0.01	1.0	0.47	0.1	1.6	0.21	1.0	0.47	0.1	1.6	0.21
2 FLT	Pre	6.0	0.61	1.3	2.2	<0.01	1.9	0.36	0.0	0.5	0.49	1.6	0.36	0.0	0.5	0.49
	Post	4.6	0.73	1.6	3.0	<0.01	1.0	0.39	0.0	0.2	0.30	1.3	0.49	0.4	0.4	0.05

^a Coefficient of variation.

^b Skewness.

^c Excess kurtosis.

^d Shapiro–Wilk P-value for assessing distribution normality.

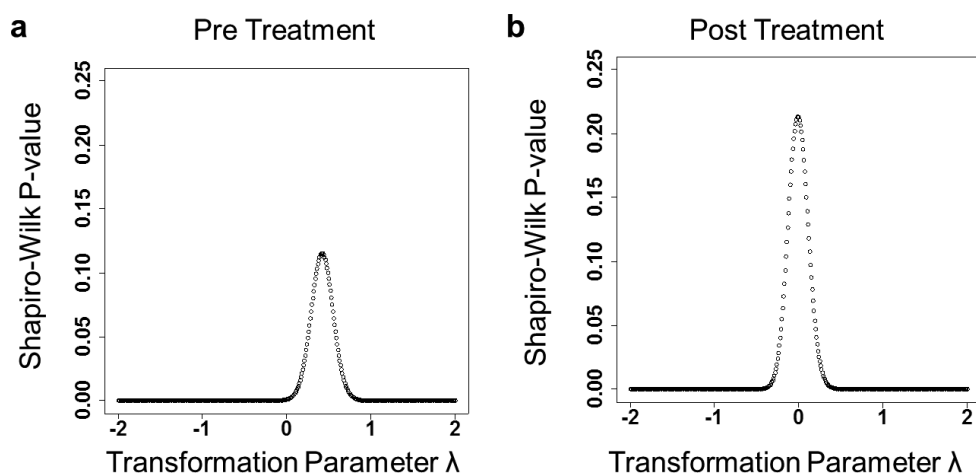
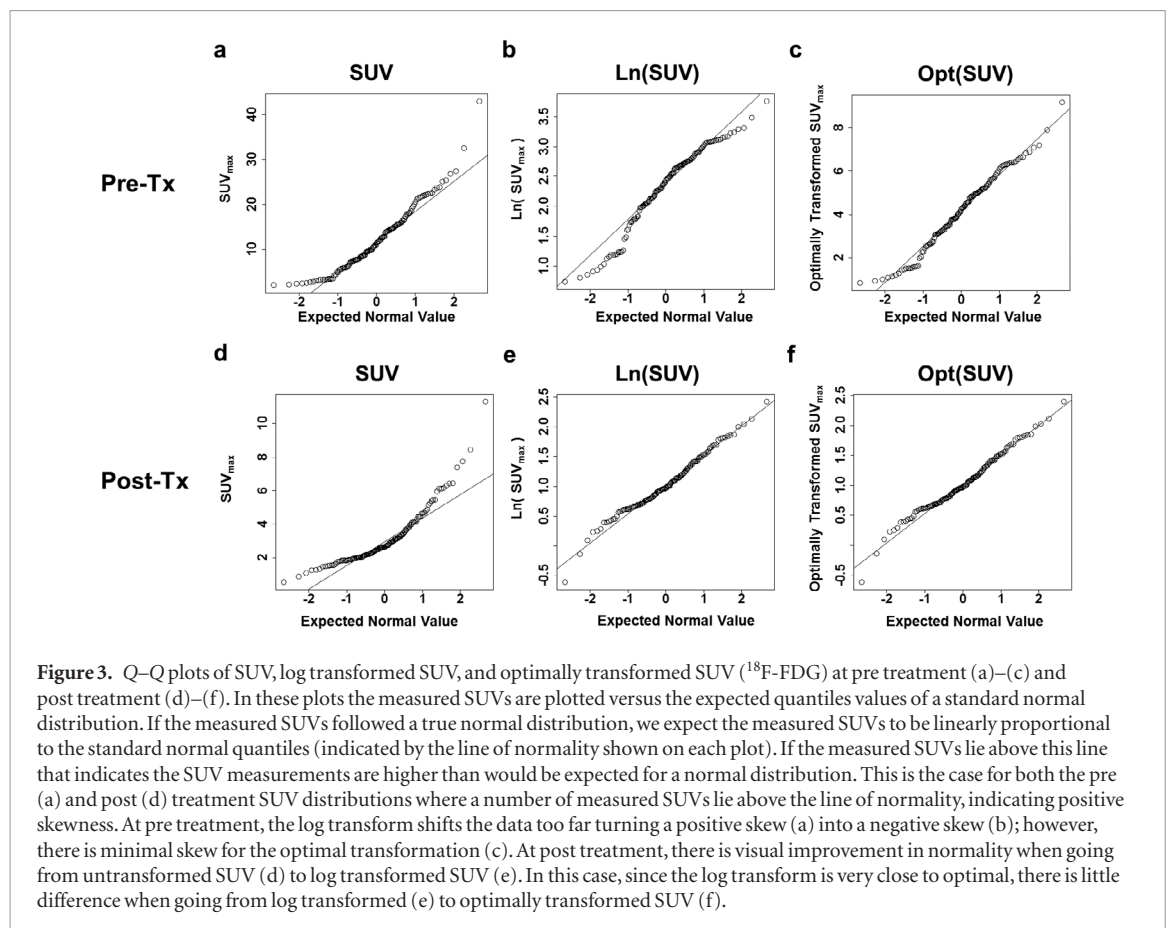


Figure 2. Optimization for ^{18}F -FDG tumor SUV distributions at pre treatment (a) and post treatment (b). The transformation parameter producing the SUV distribution with the highest Shapiro–Wilk P-value was deemed optimal.

^{18}F -FDG is the most commonly used PET radiotracer in clinical oncology; thus, we sought to identify normal transformations for ^{18}F -FDG PET SUVs. After applying optimal Box–Cox transformations, both pre and post treatment ^{18}F -FDG SUV distributions were normally distributed. After applying a log transformation to the pre treatment ^{18}F -FDG SUV distribution, it deviated significantly from normality. Interestingly, after applying a log transformation to the post treatment ^{18}F -FDG SUV distribution, it did not deviate significantly from normality.

^{18}F -FLT PET SUVs provide a measure of cell proliferation and are becoming increasingly utilized in oncologic research (Liu *et al* 2011, Trigonis *et al* 2014, Bruce *et al* 2015, Scarpelli *et al* 2016). After applying optimal



Box–Cox transformations, both pre and post treatment ^{18}F -FLT SUV distributions were normally distributed, providing further validation of the Box–Cox transformation methodology. After log transforming the ^{18}F -FLT SUVs, the pre treatment distribution was normally distributed but the post treatment distribution deviated significantly from normality. Just as with ^{18}F -FDG SUVs, these results indicate therapy can alter the lognormal behavior of ^{18}F -FLT SUVs. This underlies the importance of assessing whether transformed SUV distributions are sufficiently normal before performing statistical tests that require distribution normality.

The relatively high coefficients of variation for the tumor SUV distributions that have a lower bound of zero, suggests non-normal behavior; this is further supported by relatively high values of skewness and excess kurtosis. Some have speculated that tumor SUV distributions deviate from normality since the morphologic features of tumor vasculature follow lognormal distributions (Thie *et al* 2000). Given the deviation from normal and log-normal behavior found in this study for both PET tracers it seems likely additional physiologic factors in addition to vascular morphology are influencing the behavior of tumor SUV distributions. For example, the distribution of cell densities across different tumors and or the distribution of tracer phosphorylation rates across different tumors could impact the behavior of tumor SUV distributions. Furthermore, SUV data that is compiled from multiple institutions will be influenced by differences in PET scanners and imaging protocols across institutions that could alter the behavior of underlying SUV distributions (Fahey *et al* 2010, Binns *et al* 2011).

For both ^{18}F -FDG and ^{18}F -FLT SUV distributions, the skewness and kurtosis increased during therapy. An increase in kurtosis implies a greater number of outliers; this accompanied by an increase in skewness indicates an increase in the number of outliers that are greater than the mean. Thus, for both patient cohorts in this study, therapy led to an increase in the number of SUV outliers that were greater than the mean (this increase is evident in figures 3(a) and (d)). The increase in positive outliers from pre to post therapy may represent resistant tumors that are more refractory to therapy relative to the rest of the tumor population. This effect led to a decrease in the optimal Box–Cox transformation parameter from pre to post treatment for both patient cohorts. This result indicates selection of the optimal normal transformation will likely change depending on whether analysis is performed on SUVs extracted before, during, or after therapy. However, this does not rule out the possibility that a single transform may be adequate for providing normal distributions at pre and post treatment. If one desired to analyze multiple timepoints with the same transform, the Box–Cox optimization could be modified to take into account the distributions from all timepoints simultaneously. For example one could identify the transformation parameter that maximizes the minimum Shapiro–Wilk P -value resulting from the transformed distributions.

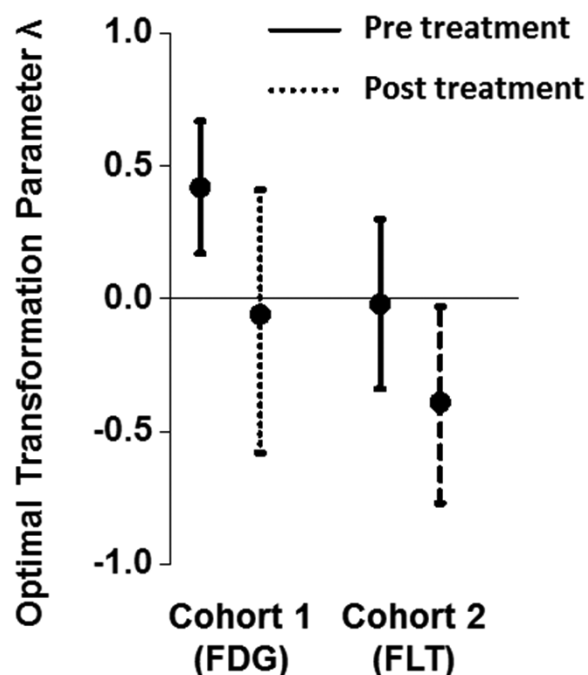


Figure 4. Optimal transformation parameters and 95% confidence intervals for both cohorts at pre and post treatment. There are cases where the optimal transform deviates significantly from $\lambda = 0$, indicating a log transformation is not likely to be optimal for producing normal SUV distributions.

Oftentimes changes in PET SUVs are used to characterize tumor responses to therapy (Wahl *et al* 2009, Liu *et al* 2011, Trigonis *et al* 2014, Bruce *et al* 2015, Scarpelli *et al* 2016). This may require analysis of negative values since tumor SUVs may decrease during treatment. One of the limitations of the one-parameter Box–Cox transformation is that it cannot be used to transform distributions with negative values. However, one could still assess changes in SUVs by performing the Box–Cox transformation prior to calculating changes i.e. perform a normal transformation on the SUVs and then calculate changes on the transformed scale. This would require that the same transformation be applied to both the pre and post timepoints. Since the optimal transformation parameter decreased for both ^{18}F -FDG and ^{18}F -FLT SUV distributions from pre to post treatment, assessing changes across timepoints may require the optimization be modified so that a single normal transformation is found for both the pre and post treatment SUV distributions simultaneously.

The methodology presented here could be applied to identify normal transformations for other SUV metrics and to distributions of imaging-based parameters derived from other imaging modalities such as magnetic resonance and computed tomography. Furthermore, although this analysis focused on normal transformations for tumor summarized SUV metrics (i.e. SUV_{max}) the methodology could be extended to voxel-based SUV distributions arising from tumors or organs. For example one may wish to normalize the voxel-based SUV distributions within healthy organs so that identification of outlier voxels indicative of pathology would become straightforward and intuitive (Hara *et al* 2015). This type of assessment would no longer be limited to characterizing therapeutic responses but could be applied more broadly to disease identification and or diagnosis. In fact normal transformations could be of great value for disease diagnosis, where knowing underlying biomarker distributions in healthy and diseased patients might aid in discriminating between the two (Fluss *et al* 2005, Schisterman and Perkins 2007). Regardless, analyses that require normally distributed data, should utilize an approach similar to what is presented here to identify normal transformations; otherwise, results from statistical tests may be inaccurate and lead to erroneous conclusions.

Conclusion

We demonstrate how Box–Cox transformations can be utilized to identify the optimal normal transformations for ^{18}F -FDG and ^{18}F -FLT SUV distributions extracted from tumors before and after treatment. Importantly, it was showed that SUV distributions can significantly change from pre to post treatment, indicating the optimal transformation leading to a normal distribution will likely change during the course of therapy. These normal SUV transformations enable powerful parametric statistical modelling for analyzing correlated measurements and enable use of other parametric statistical tests (*t*-tests, linear regression, analysis of variance, etc) when analyzing PET SUVs. In the future, we will utilize this work to incorporate parametric statistical modelling into

PET study designs to increase statistical power, potentially reducing the number of patients and expenses required to meet clinical endpoints. We will also be utilizing this work to generate reference normal distributions of SUVs in healthy patients so that when a prospective patient is scanned, regions of disease can be readily identified and characterized based on deviations from the reference normal distribution. The methods presented in this work need not be limited to analysis of medical images however and could be applied more broadly to any medical biomarker to improve understanding of distribution behavior. This would help to minimize errors in statistical testing and facilitate selection of appropriate tests to maximize statistical power.

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Conflicts of interest

The authors declare no conflicts of interest related to this work.

ORCID iDs

Matthew Scarpelli  <https://orcid.org/0000-0003-0735-1682>

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