

QQ quantification analysis of DCE-MRI for Osteosarcoma

Junyu Guo¹ and Wilburn E Reddick¹

¹St Jude Children's Research Hospital, Memphis, TN, United States

INTRODUCTION: DCE-MRI has been investigated as a potential predictive biomarker for histologic response and as a prognostic biomarker for the clinical outcome [1-2]. In these studies, statistical analysis of a longitudinal DCE-MRI study is usually performed based on the mean values for each osteosarcoma (OS) tumor, which is one of the most common malignant bone tumors in children in the United States. However, each bone tumor could contain tens of thousands of voxels, which form a histogram with rich information. Analysis using a single mean value for each tumor discards a substantial amount of information contained in the histogram. In this study, we present a quantile-quantile (QQ) plot quantification method to measure the changes between the baseline and the following DCE-MRI examinations on a single phase II trial for pediatric OS patients.

METHOD: Simulations were performed to demonstrate changes of QQ plots of X and Y measures for the different distribution. To generate QQ plots, X and Y were first normalized by the median value of X. The changes of QQ plots were simulated in several cases: a. the same Gaussian distributions, b. Y shifting to the left relative to X, c. Y expanding relative to X, d. two Gaussian peaks in Y, e. Y following a Rician distribution. The histogram and the corresponding QQ plots are shown in Fig 1. We can see that, assuming the same type of distribution of X and Y, the change of the median value corresponds a shift relative to the identity line; shifting up or down of the QQ curve relative to the identity line correspond to an increase or decrease of the median value of Y. The change of the standard deviation (std) caused a rotation of the QQ curve; a larger slope (>1) of the QQ curve indicates a std of Y larger than X; and a smaller slope (<1) indicates a smaller std of Y. The different distribution with two Gaussian peaks and the Rician distribution made more complicated combinations of shift and rotation in a local range to generate different shapes of the QQ curve.

In this study, the changes of Y relative to X in the QQ plot were quantified based on the different quartiles and the shape of the QQ curve. First, we compute the four areas, which represent the difference between the QQ curve and the identity line in three ranges as shown in Fig. 2a, and the reference area in the 2nd and 3rd quartiles under the identity line in Fig. 2b. A_{Q1} , A_{Q23} , and A_{Q4} are negative under the identity line, and positive above the identity line; A_{QR} is a positive area. The 0.5% of the QQ curve at each end is excluded to compute A_{Q1} and A_{Q4} for the stability of quantification. X_{Q1} , X_{Q3} , Y_{Q1} , and Y_{Q3} are the normalized quartile 1 and 3 for X and Y in Fig. 2a. Five QQ parameters can be computed from those variables using the following equations:

$$R_{Q1} = \frac{A_{Q1}}{A_{QR}}, R_{Q23} = \frac{A_{Q23}}{A_{QR}}, R_{Q4} = \frac{A_{Q4}}{A_{QR}}, K_0 = \frac{Y_{Q3} - Y_{Q1}}{X_{Q3} - X_{Q1}}, dK = \overline{|K(X) - K_0|}$$

Where R_{Q1} , R_{Q23} , and R_{Q4} are the ratios of three areas of difference in different quartiles to the reference

area; K_0 is the slope of the QQ curve computed from cut points: quartile 1 and 3 in X and Y, which is equal to the ratio of std of Y over X if both X and Y have a Gaussian distribution; dK is the average of absolute difference between the slope of the QQ curve at each points and K_0 , which indicates the difference of the distribution between X and Y.

The QQ quantification was used to analyze the DCE-MRI pharmacokinetic parameters from 31 OS patients at six serial time points (the baseline, Day-2, Day1, Day5, week5, week10). First, 16 slices of 3D DCE-MRI data were acquired and analyzed to generate pharmacokinetic parameters for each voxel using a two-compartment pharmacokinetic model [3]. Conventionally, the mean value within tumor ROI drawn by a radiologist was calculated for each tumor for further statistical analysis. In the QQ quantification, five QQ parameters were computed from the whole tumor in each examination except the baseline. In addition, the skewness and kurtosis in each examination were computed for comparison. The nonparametric Wilcoxon rank-sum test was performed to explore the difference between responder and non-responder and between event free survival (EFS) and non-EFS group.

RESULTS: The mean values of K^{trans} were only significantly different at week10 ($p=0.038$) between EFS and non-EFS group, but not at other time points for EFS and response analysis. R_{Q4} was significantly different on Day-2 between responder and non-responder groups in Fig 3a.; dK was significantly different on Day1 between EFS and non-EFS groups in Fig 3b. We didn't find any significant difference for the skewness and kurtosis of K^{trans} at any time points for either response or EFS analysis.

CONCLUSION: We present the QQ quantification method, which could generate five QQ parameters to describe the different characteristics of the change of tumor histograms due to the treatment. We have shown that the results of in vivo DCE-MRI data analysis using the QQ quantification and found that the QQ quantification could potentially provide very early biomarkers for histologic response and EFS, which the mean values did not provide in this study. The QQ quantification could have broadly applications in the similar longitudinal studies. Our findings in OS patients warrant further investigation in larger cohorts of patients.

REFERENCE:

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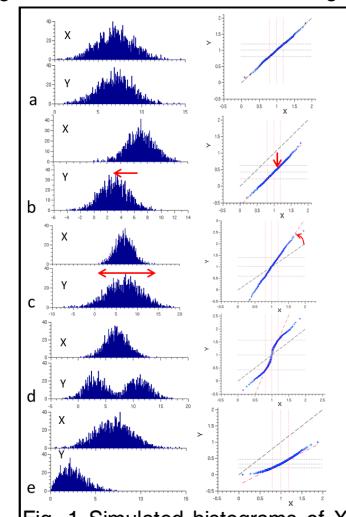


Fig. 1 Simulated histograms of X and Y, and their QQ plots on the right. (a.-e.) Changes of Y histogram relative to X histogram in five cases.

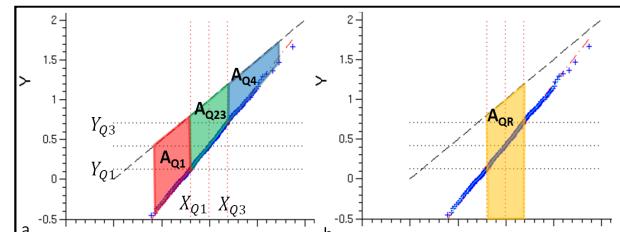


Fig. 2 Diagram of quantification in QQ plot. (a) Three areas of difference between the QQ curve and the identity line. (b.) the reference area in the 2nd and 3rd quartiles under the identity line.

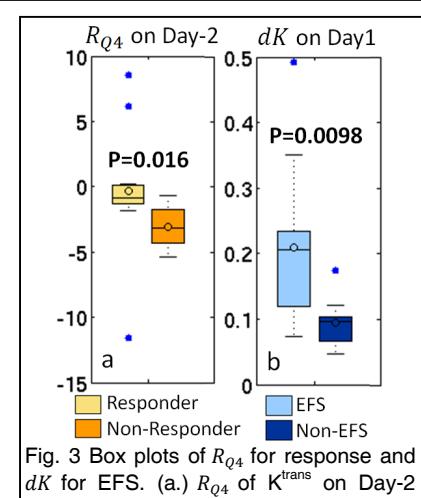


Fig. 3 Box plots of R_{Q4} for response and dK for EFS. (a.) R_{Q4} of K^{trans} on Day-2 between responder and non-responder; (b.) dK of K^{trans} on Day1 between EFS and non-EFS patients.