Published in final edited form as:

Clin Imaging. 2018 ; 49: 121–127. doi:10.1016/j.clinimag.2017.12.015.

Inter-operator variability in compartmental kinetic analysis of ¹⁸F-fluoromisonidazole dynamic PET

Sadek A. Nehmeh^{a,*}, Jazmin Schwartz^b, Milan Grkovski^b, Ivan Yeung^c, Charles M. Laymon^d, Mark Muzi^e, and John L. Humm^b

^aWeill Cornell Medical College, New York, NY, United States

^bDepartment of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY, United States

^cDepartment of Medical Physics, Princess Margaret Cancer Center, Toronto, Ontario, Canada

^dDepartments of Radiology and Bioengineering, University of Pittsburgh, Pittsburgh, PA, United States

^eDepartment of Radiology, University of Washington, Seattle, WA, United States

Abstract

Purpose: To assess the inter-operator variability in compartment analysis (CA) of dynamic-FMISO (dyn-FMISO) PET.

Methods: Study-I: Five investigators conducted CA for 23 NSCLC dyn-FMISO tumor time-activity-curves. Study-II: Four operators performed CA for four NSCLC dyn-FMISO datasets. Repeatability of Kinetic-Rate-Constants (KRCs) was assessed.

Results: Study-I: Strong correlation (ICC > 0.9) and interchangeable results among operators existed for all KRCs. Study-II: Up to 103% variability in tumor segmentation, and weaker ICC in KRCs (ICC- V_B = 0.53; ICC- K_1 = 0.91; ICC- K_1/k_2 = 0.25; ICC- k_3 = 0.32; ICC- K_i = 0.54) existed. All KRCs were repeatable among the different operators.

Conclusions: Inter-operator variability in CA of dyn-FMISO was shown to be within statistical errors.

Keywords

Variability; Kinetic analysis; Dynamic PET

1. Introduction

Assessing tumor response is key component in clinical trials, especially when these are carried out across multiple institutions. In order for results to be reliable, it is indispensable that the image analysis be reproducible both within and across the different test sites.

*Corresponding author at: Weill Cornell Medical College, 515 East 71st St, New York, NY 10021, United States. san28@med.cornell.edu (S.A. Nehmeh).

Conflict of Interest: None

Tumor hypoxia has been shown to be an independent prognostic marker in several malignancies, including Non-Small Cell Lung Cancer (NSCLC) [1]. Hypoxic tumors, in general, express more aggressive phenotype, are radio-resistant, and have thus an increased likelihood of loco-regional recurrence, distant metastasis, poor overall outcome [2–5]. Potential treatment strategies for overcoming tumor hypoxia and improving local control rates include the use of radio-sensitizing drugs and biological image-guided dose escalation to hypoxic tumor sub-regions [6–10]. Rational application of such strategies would require that hypoxia can be shown accurately in the clinical setting, that its extent and severity can be quantified accurately, and that these parameters indeed correlate with poor patient outcome when current standard treatment regimens are applied. ^{18}F -Fluoromisonidazole (18F-FMISO) PET has been recognized as a non-invasive method for detecting tumor hypoxia in several solid tumors, including NSCLC [2]. Rajendran et al. showed that 18F-FMISO uptake was directly related to tissue hypoxia [11]. However, the application of 18F-FMISO for assessment of the hypoxic fraction in NSCLC is yet to be defined. Different Tumor/Blood (T/B), Tumor/Muscle (T/Mu), and tumor/Mediastinum (T/Me) threshold ratios have been proposed as semi-quantitative criteria for delineating hypoxic tumor volumes [2, 11–13]; for example, Eschmann et al. showed that a T/Me > 2 was a predictive factor for local recurrence in lung cancer. However, Thorwarth et al. demonstrated that no single threshold in the late 18F-FMISO images may be adequate and sufficient to represent the spatial distribution of hypoxia within tumors [2, 14]. Instead, they suggested that kinetic analysis of dynamic 18F-FMISO PET images should be used to extract local hypoxia and perfusion characteristics of tumor tissue [8]. In a separate study, Wang and co-workers argued that the physiologic clearance of 18F-FMISO from highly perfused normal tissue may result in T/B comparable to that in a tumor at the time of patient imaging [15]. Eschmann et al. demonstrated that qualitative analysis of time-activity curves can reveal 3 curve types (associated with rapid washout, intermediate or delayed washout, and accumulation), and that these curves have correlated with treatment outcome after radiotherapy [2]. In particular, an accumulation-type curve, a high 18F-FMISO SUV, and a high T/Me at 4 h after injection were highly suggestive of an incomplete response to treatment [2]. Following a more quantitative approach, Wang and co-workers showed the usefulness of identifying tumor hypoxia based on a scatter plot of the T/B vs 18F-FMISO influx rate, Ki [15].

Several studies have reported on the inter-observer reproducibility of tumor SUV [16–18]. Yet, to our knowledge, the inter-operator reproducibility of CA has not been previously reported. Quantitating the inter-operator variability in kinetic analysis becomes particularly critical in multi-center trials that involve multiple investigators performing the analysis. In this retrospective study, we assess the interoperator variability in CA in a cohort of NSCLC patients who underwent dynamic FMISO PET imaging. The study focuses on two aspects; (1) the variability of CA due to differences in mathematical modeling as carried out by different operators in a pre-defined set of time-activity-curves (TACs) (both input and output functions); and (2) the variability in CA when operators perform the entire analysis pipeline, from tumor segmentation through full kinetic analyses.

2. Methods and materials

2.1. FDG PET

Four NSCLC patients were included in this study. Each patient underwent a baseline FDG PET/CT study. Patients were injected intravenously with 461 ± 6 MBq of FDG (range, 455–466 MBq) following a fasting period of at least 6 h. Whole-body PET scans were acquired for 3 min per bed position at an average of 60 min post-injection. Data were acquired on a Discovery STE PET/CT scanner (GE Healthcare Inc.), with a resolution of ~ 5.5 mm FWHM at the center of the FOV. In each case, 4D-CT images were acquired and, subsequently, an average CT (CT_{avg}) was generated and used to correct for attenuation of the PET images, which were acquired in free-breathing. PET emission data were corrected for attenuation, scatter, and random events, and then iteratively reconstructed into $128 \times 128 \times 47$ matrices (voxel dimensions, $5.47 \times 5.47 \times 3.27$ mm) using the ordered subset expectation maximization (OSEM) algorithm provided by the manufacturer (2 iterations, 20 subsets, and post-processing Gaussian filter with 6.0 mm FWHM).

2.2. FMISO dynamic PET

All patients underwent a baseline FMISO dynamic PET scan within one week following the FDG study. FMISO scans were performed on a Discovery STE PET/CT scanner. PET acquisition was initiated simultaneously with the bolus injection 399 ± 9 MBq of 18F-fluoromisonidazole (range, 388–407 MBq). FMISO data were acquired in dynamic mode over one bed position centered at the lesion for 45 min (6×30 s, 7×60 s, and 7×300 s frames). Two additional 10-min static image sets were acquired at 96 ± 4 min (range, 90–103 min) and 163 ± 17 (range, 150–186 min) post-injection. For each of the three FMISO sessions, a 4D-CT was acquired, and the corresponding CT_{avg} was used to correct for PET attenuation correction. All FMISO PET images were reconstructed using the same parameters as for the FDG study.

2.3. Study-I

This study served as a quality assurance test to ensure the interoperator reproducibility of CA in the absence of operator-specific preprocessing analysis (e.g. tumor segmentation, image registration, decay correction, ...). This task seems obvious, especially in the case where all operators use the same software and kinetic model. Yet, variation in the resulting fitting parameters, KRC in this case, would be expected due to differences in data weighing, starting seeds, fitting algorithm, number of iterations before reaching convergence... during the data fitting process. The inter-operator variability in the FMISO-PET KRCs due to discrepancies in such parameters among different operators was therefore assessed. Five operators from five institutions were included in this study. Each one defined the image-derived (a) input function for each of 4 patients using the aorta and (b) tumor TACs for each lesion and patient observed in dynamic FMISO studies. Together, the 5 operators derived a total of 23 TACs for the 4 patients studied (in one case, a small lesion was present in the field of view; only three out of the five operators reported it). These 23 TACs were de-identified by the senior operator and then re-shared with the other four investigators for independent analysis. The variability in CA among the operators was therefore due to mathematical modeling only.

2.4. Study-II

Four operators each carried out full CA only for the TACs each identified for each of the four dynamic FMISO PET datasets of Study-I. The variabilities in the corresponding target volumes, input functions, output functions, and KRCs (V_b , K_1 , K_1/k_2 , and k_3) were assessed.

2.5. Compartmental kinetic analysis

The two late FMISO image sets were first decay corrected to the time of injection, and then registered to those of the first dynamic FMISO session by means of the corresponding CT images. The input functions and tumor TACs were then defined using the full dynamic FMISO image set. Except for one operator, the target volume was segmented on the FDG PET images after registering those to the first dynamic FMISO images. The corresponding volume of interest (VOI) was copied to the FMISO dynamic dataset. The remaining operator created a mean FMISO image by averaging together the last five time frames of the dynamic FMISO. Subsequently, this operator defined the FMISO avid tumor volume using a threshold value equal to 50% of SUV_{max} on this average image set. No partial volume correction was applied by any of the investigators. After defining the tumor VOI, each operator extracted the relevant tumor TAC from the full dynamic dataset.

All operators performed CA using an irreversible 3-compartment model with 2 tissue compartments and one compartment for the blood input function. A summary of the methodologies and parameters used by each of the operators is shown in table1.

3. Statistical analysis

The intraclass correlation coefficient (ICC) was used to determine the global reproducibility of target volumes and kinetic results across the different operators. Subsequently, the reproducibility of KRCs was re-assessed as follows: (1) every possible operator pair-combination was determined and then (2) all values compared for every operator pair using a hierarchical approach [19]. The hierarchical approach involves a two-step analysis process. First, Pearson's correlation coefficient, r , was calculated. Secondly, if the correlation is strong ($r > 0.75$), then Passing-Bablok non-parametric regression [20] analysis is performed to determine the interchangeability of the measurements among the operators. The cumulative sum test for linearity proposed by Passing and Bablok [20] was used to assure the validity of the approach (Passing-Bablok can be applied only if a linear relationship exists between the two variables being investigated [20]). Finally, the corresponding limits of agreements (LoA) were calculated by means of Bland-Altman analysis [21] after insuring that the differences between two sets of results (i.e. those corresponding to each pair of operators, operator (i) and operator (j)) are normally distributed according to the Kolmogorov-Smirnov test.

4. Results

For Study-I, the ICC's for testing the consistency of KRCs among the five operators were as follows; $ICC-V_B = 0.90$; $ICC-K_1 = 0.96$; $ICC-K_1/k_2 = 0.95$; $ICC-k_3 = 0.99$; $ICC-ki = 0.99$. Besides, a strong Pearson correlation, $r > 0.75$ was observed for the pair-wise permutation among the operators for each of the KRCs deduced from the kinetic analysis of the 23 TACs.

For the same data set, i.e. the 23 TACs, Passing-Bablok analysis showed the results to be inter-changeable for V_b , K_1 , and K_1/k_2 among the four operators with no systematic or proportional bias. A slight proportional bias (Passing-Bablok analysis showed the 95% CI to not include the value of “1”, but may not be statistically significant) was observed for both k_3 and K_i . The non-parametric regression analysis results with the corresponding 95% confidence intervals (CI), and the LoA's, as determined by Bland-Altman analysis are summarized in Table 2.

Special interest is in K_1 (surrogate for tumor blood flow) and k_3 (surrogate for hypoxia); the corresponding Passing-Bablok and Bland-Altman plots for K_1 , k_3 , and K_i respectively are also displayed in Fig. 1.

Coronal images for patient #1 and patient #4 are shown in Fig. 2. The corresponding target volumes (depicted by different colors) as they were contoured by the four operators are also displayed.

The segmentation methods used by the four operators are listed in Table 1. The ICC for the segmented target volumes was 0.36, and the corresponding coefficients of variability (defined as the standard deviation divided by the average tumor volumes as measured by the four operators) were 30.2%, 92.8%, 52.2%, and 103.3% respectively. A summary of the tumor volumes as segmented by the four operators is presented in Table 3.

The input and output functions for the two extreme lesions, i.e. for patient #1 and patient #4, are presented in Fig. 3.

Frame-by-frame correlation of the input functions using the pairwise permutation among the operators showed strong Pearson correlations in all cases ($R > 0.97$). Apart from patient #4 ($r = 0.74$), high Pearson correlations ($r > 0.91$) were observed in the case of output functions as well. The distribution of the Pearson correlation R 's among pair-operators for the input and output functions respectively is shown in Fig. 4.

Passing-Bablok analysis showed the KRCs to be inter-changeable among the four operators with no systematic or proportional biases. The corresponding Passing-Bablok and Bland-Altman plots for K_1 , k_3 , and K_i respectively are also displayed in Fig. 5. The non-parametric regression analysis results with the corresponding 95% CI and the LoA's, as determined by Bland-Altman analysis, are summarized in Table 4.

5. Discussion

Pharmacokinetic analysis of dynamic PET images can provide more detailed information about tumor biology than static imaging by unveiling information about the tracer kinetics. When used as a means to assess prognosis and predict response, kinetic parameters may provide more relevant metrics that improve the correlation with outcome compared to static SUV measurements [22]. For example, in a study using FDG imaging of NSCLC patients, the authors showed that fractional changes in SUV between pre- and post-therapy are different than those deduced from CA. The authors implied that the use of SUV to assess treatment response may under- or over-estimate the results compared to CA [23]. Changes in

radiotracer delivery (K_1) and flux (K_i) predicted both disease-free-survival and overall survival whereas static SUV predicted overall survival only [22]. Likewise, in a study that included 75 locally-advanced breast cancer patients treated with neoadjuvant chemotherapy, kinetic measures were shown to be more robust predictors of pathologic response than SUV ($AUC = 0.97$ vs $AUC = 0.84$) [22]. Conducting compartmental kinetic analysis in multicenter trials can be a challenge due to the many sources of variability and errors, e.g. tumor volume delineation, input function volume of interest delineation, image registration (in long dynamic studies that involve multiple sessions, differences in kinetic analysis software tool and model fitting algorithm, etc.).

In this study, we focused on assessing the intra-operator variability in kinetic analysis of dynamic FMISO PET images. In the first study described here, we sought to estimate the CA rate constant variability arising either from using different software with diverse model fitting algorithms or from alternative parameter definitions. In order to do this, the investigators carried out kinetic analysis using the same set of TACs and corresponding input functions provided to them (Study-I). The results showed a very strong reproducibility of the KRCs among all investigators ($ICC > 0.9$ for all KRCs). k_3 and K_i showed a slight proportional bias (95% CI for the slope in the Passing-Bablok analysis was 1.0008 to 1.0329 and 0.9781 to 0.9948 for k_3 and K_i respectively, thus missing the unity slope) which may be statistically insignificant.

Larger variability among operators was observed when each carried out the full analysis (Study-II) pipeline for each patient independently (i.e. delineated the lesion, derived input and output functions, and carried out kinetic analysis). The variation in methods of tumor delineation significantly contributed to the differences observed in each kinetic parameter across operators; a coefficient of variability among the investigators ranging between 32% and 103% for the four patients was observed. Thus, the resulting variability in the KRCs in study-II versus study-I was larger, and is reflected in the correspondingly weak ICC's. However, using a pair-wise permutation approach among investigators, Passing-Bablok analysis showed the kinetic analysis results to be interchangeable for all parameters.

One of the limitations of this study is the small number of operators and patients. Nevertheless, from these results, it may be postulated that, in a larger statistical sample, kinetic analysis may be reproducible among multiple investigators. Even so, in multi-center trials, consistency in the outcome of such analysis may be improved by establishing a well-defined strategy across the different institutions for (1) tumor segmentation (e.g. 50% threshold of SUV_{max}) and (2) for determining the relevant input function volume of interest.

6. Conclusion

This study included the analysis of 5 kinetic PET data sets by 5 different institutions and was conducted as part of a quantitative imaging network (QIN) challenge. The study findings support the contention that compartmental kinetic analysis can be made robust across multi-center trials provided a reproducible methodology for delineating the tumor volume and defining the input function volume of interest can be established.

Acknowledgment

This study was supported by NIH grants U01CA157442-01A1, U01 CA140230, R50CA211270, and P30 CA047904.

References

- [1]. Sura S, Intensity-modulated radiation therapy (IMRT) for inoperable nonsmall cell lung cancer: the Memorial Sloan-Kettering Cancer Center (MSKCC) experience. *Radiother Oncol* 2008;87(1):17–23.18343515
- [2]. Eschmann SM, Prognostic impact of hypoxia imaging with 18F-misonidazole PET in non-small cell lung cancer and head and neck cancer before radiotherapy. *J Nucl Med* 2005;46(2):253–60.15695784
- [3]. Hockel M, Intratumoral pO₂ predicts survival in advanced cancer of the uterine cervix. *Radiother Oncol* 1993;26(1):45–50.8438086
- [4]. Koukourakis MI, Hypoxia-inducible factor (HIF1A and HIF2A), angiogenesis, and chemoradiotherapy outcome of squamous cell head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2002;53(5):1192–202.12128120
- [5]. Le QT, An evaluation of tumor oxygenation and gene expression in patients with early stage non-small cell lung cancers. *Clin Cancer Res* 2006;12(5):1507–14.16533775
- [6]. Lee NY, Fluorine-18-labeled fluoromisonidazole positron emission and computed tomography-guided intensity-modulated radiotherapy for head and neck cancer: a feasibility study. *Int J Radiat Oncol Biol Phys* 2008;70(1):2–13.17869020
- [7]. Das SK, Feasibility of optimizing the dose distribution in lung tumors using fluorine-18-fluorodeoxyglucose positron emission tomography and single photon emission computed tomography guided dose prescriptions. *Med Phys* 2004;31 (6):1452–61.15259648
- [8]. van Lin EN, IMRT boost dose planning on dominant intraprostatic lesions: gold marker-based three-dimensional fusion of CT with dynamic contrast-enhanced and 1H-spectroscopic MRI. *Int J Radiat Oncol Biol Phys* 2006;65(1):291–303.16618584
- [9]. Madani I, Positron emission tomography-guided, focal-dose escalation using intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2007;68(1):126–35.17448871
- [10]. Vanderstraeten B, [18F]fluoro-deoxy-glucose positron emission tomography ([18F]FDG-PET) voxel intensity-based intensity-modulated radiation therapy (IMRT) for head and neck cancer. *Radiother Oncol* 2006;79(3):249–58.16564588
- [11]. Rajendran JG, [(18)F]FMISO and [(18)F]FDG PET imaging in soft tissue sarcomas: correlation of hypoxia, metabolism and VEGF expression. *Eur J Nucl Med Mol Imaging* 2003;30(5):695–704.12632200
- [12]. Rasey JS, Quantifying regional hypoxia in human tumors with positron emission tomography of [18F] fluoromisonidazole: a pretherapy study of 37 patients. *Int J Radiat Oncol Biol Phys* 1996;36(2):417–28.8892467
- [13]. Koh WJ, Evaluation of oxygenation status during fractionated radiotherapy in human nonsmall cell lung cancers using [F-18]fluoromisonidazole positron emission tomography. *Int J Radiat Oncol Biol Phys* 1995;33(2):391–8.7673026
- [14]. Thorwarth D, A kinetic model for dynamic [18F]-Fmiso PET data to analyse tumour hypoxia. *Phys Med Biol* 2005;50(10):2209–24.15876662
- [15]. Wang W, Evaluation of a compartmental model for estimating tumor hypoxia via FMISO dynamic PET imaging. *Phys Med Biol* 2009;54(10):3083–99.19420418
- [16]. Minn H, Lung cancer: reproducibility of quantitative measurements for evaluating 2-[F-18]-fluoro-2-deoxy-D-glucose uptake at PET. *Radiology* 1995;196(1):167–73.7784562
- [17]. Marom EM, Interobserver and intraobserver variability of standardized uptake value measurements in non-small-cell lung cancer. *J Thorac Imaging* 2006;21(3):205–12.16915065
- [18]. Nahmias C, Wahl LM. Reproducibility of standardized uptake value measurements determined by 18F-FDG PET in malignant tumors. *J Nucl Med* 2008;49(11):1804–8.18927325

- [19]. Grkovski M, Feasibility of ¹⁸F-fluoromisonidazole kinetic modeling in head and neck cancer using shortened acquisition times. *J Nucl Med* 2016;57(3):334–41.26609178
- [20]. Passing H, Bablok. A new biometrical procedure for testing the equality of measurements from two different analytical methods. Application of linear regression procedures for method comparison studies in clinical chemistry, Part I. *J Clin Chem Clin Biochem* 1983;21(11):709–20.6655447
- [21]. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1(8476):307–10.2868172
- [22]. Dunnwald LK, PET tumor metabolism in locally advanced breast cancer patients undergoing neoadjuvant chemotherapy: value of static versus kinetic measures of fluorodeoxyglucose uptake. *Clin Cancer Res* 2011;17(8):2400–9.21364034
- [23]. Cheebsumon P, Measuring response to therapy using FDG PET: semi-quantitative and full kinetic analysis. *Eur J Nucl Med Mol Imaging* 2011;38(5):832–42.21210109

Fig. 1.

Left column: Passing-Bablok results for K_1 (top), k_3 (middle), and K_i (bottom) deduced from the kinetic analysis of previously deduced 23 FMISO TACs (dotted line - unity line; solid line - best fit; dashed lines - 95% CI). The corresponding Bland-Altman plots are shown in the right column (solid line – mean value; dashed lines – 95% CI). Each data point corresponds to two investigators (i) and (j).

Fig. 2.
Coronal slices of patient #1 (left) and patient #4 (right). The target volumes as segmented by four Investigators are depicted by the different contours colors. (For Interpretation of the references to color In this figure legend, the reader Is referred to the web version of this article.)

Fig. 3.

Input (top row) and output (bottom row) functions for patient #1 (left column) and patient #4 (right column) respectively as deduced from the analysis carried out by the four Investigators (depicted by the different colors). The small panels in figures (a) and (c) correspond to the first 2 min and from 30 min to last time frame post-injection respectively. (For Interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 4.
Pair-wise Pearson correlation R's for the input (top) and output (bottom) functions.

Fig. 5.

Left column: Passing-Bablok results for K_1 (top), k_3 (middle), and K_i (bottom) deduced from the full kinetic analysis of four FMISO dynamic datasets (dotted line - unity line; solid line - best fit; dashed lines - 95% CI). The corresponding Bland-Altman plots are shown in the right column (solid line - mean value; dashed lines - 95% CI). Each data point corresponds to two Investigators (i) and (j).

Table 1

Summary of methodologies used by the different operators for kinetic analysis. Investigator #5 took part of study-I only

Operator #	Tumor segmentation method	Input function segmentation method	Kinetic analysis tool
1	50% threshold on FDG images	Hottest 90% in the aorta, in hottest frame	PMOD v3.5
2	Region Growing (GE AW v4.4) on FDG images	Hottest 25 voxels in the aorta, in the hottest frame	PMOD v3.5
3	Region growing (PMOD v3.6) on FDG images	Region going within the hottest region in the aorta	PMOD v3.6
4	50% threshold on average of last 5 time frame of dynamic FMISO	values 90% or greater of the maximum pixel value over 4 hot slices in the first minute	PMOD v3.5
5	–	–	PMOD v3.5

Table 2

Passing-Bablok and Bland-Altman analysis for the KRCs results from study-I.

KRC	Passing-Bablok		Bland-Altman	
	Slope (95% CI)	Intercept (95% CI)	Mean difference	95% limits of agreement (lower, upper)
Vb	1.0200 (0.9801 to 1.0683)	-0.0038 (-0.0021 to 0.0079)	-0.0011	(-0.0859 to 0.0632)
K1	0.9846 (0.9545 to 1.0069)	-0.0015 (-0.0054 to 0.0036)	0.0156	(-0.0727 to 0.1039)
K1/k2	1.0200 (0.9982 to 1.0591)	-0.0288 (-0.0674 to -0.0081)	0.0518	(-0.1093 to 0.2130)
k3	1.0159 (1.0008 to 1.0329)	0.0000 (0.0000 to 0.0001)	-0.0002	(-0.0014 to 0.0087)
Ki	0.9869 (0.9781 to 0.9948)	0.0000 (-0.0000 to 0.0000)	-0.0000	(-0.0007 to 0.0006)

Table 3

Summary of target volumes as segmented by four investigators

Investigator	Lesions volumes			
	Lesion1 (cc)	Lesion2 (cc)	Lesion3 (cc)	Lesion4 (cc)
1	36.48	9.00	15.06	29.00
2	26.11	6.75	16.72	36.75
3	45.08	24.55	45.38	535.79
4	23.57	1.92	33.84	380.12
avg	32.81	10.55	27.75	245.41
std	9.91	9.79	14.50	253.54

Table 4

Passing-Bablok and Bland-Altman analysis for the KRCs results from study-II.

KRC	Passing-Bablok		Bland-Altman	
	Slope (95% CI)	Intercept (95% CI)	Mean difference	95% limits of agreement (lower, upper)
Vb	1.3424 (0.8297 to 1.9854)	-0.0219 (-0.0845 to 0.0245)	-0.0074	(-0.2192 to 0.2045)
K1	0.9260 (0.7268 to 1.1727)	0.0011 (-0.0476 to 0.0367)	-0.0158	(-0.0731 to 0.1047)
K1/k2	0.8331 (0.4415 to 2.0952)	0.0516 (-1.0277 to 0.3936)	0.1126	(-0.3569 to 0.5820)
k3	1.2500 (0.6963 to 2.0000)	-0.0003 (-0.0016 to 0.0009)	-0.0007	(-0.0063 to 0.0049)
Ki	1.1600 (0.7333 to 1.8000)	0.0003 (-0.0015 to 0.0005)	-0.0002	(-0.0038 to 0.0035)