Am J Nucl Med Mol Imaging 2018;8(6):407-414
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0087865

Original Article

Pre-treatment partial-volume-corrected TLG is the best predictor of overall survival in patients with relapsing/refractory non-hodgkin lymphoma following radioimmunotherapy

Raheleh Taghvaei[1], Mahdi Zirakchian Zadeh[1,2], Reza Sirous[3], Sara Pourhassan Shamchi[1], William Y Raynor[1,4], Siavash Mehdizadeh Seraj[1], Mateen Moghbel[5], Shiyu Wang[6], Thomas J Werner[1], Hongming Zhuang[2], Abass Alavi[1]

[1]Department of Radiology, Hospital of The University of Pennsylvania, PA, USA; [2]Department of Radiology, Children's Hospital of Philadelphia, PA, USA; [3]University of Maryland Medical Center, Baltimore, MD, USA; [4]Drexel University College of Medicine, Philadelphia, PA, USA; [5]Department of Radiology, Stanford University Medical Center, Stanford, CA, USA; [6]Department of Dermatology, Hospital of The University of Pennsylvania, PA, USA

Received October 9, 2018; Accepted November 19, 2018; Epub December 20, 2018; Published December 30, 2018

Abstract: The role of fluorodeoxyglucose-positron emission tomography (FDG-PET) has been well established in assessment of lymphoma, including non-Hodgkin lymphoma (NHL). The aim of this study was to compare changes and survival predictive values of various quantification parameters of FDG-PET/CT in patients with relapsing/refractory lymphoma before and after radioimmunotherapy (RIT). Data from 17 patients with relapsing/refractory NHL, treated with targeted RIT after chemotherapy/radiotherapy, were retrospectively collected. FDG-PET/CT scans were performed approximately three months before and six months after RIT. An adaptive contrast-oriented thresholding algorithm was used to segment lesions on the FDG-PET images. Wilcoxon signed-rank tests were used to assess changes in SUVmax, SUVmean, partial volume-corrected SUVmean (pvcSUVmean), total lesion glycolysis (TLG), and pvcTLG before and after treatment. The patients were followed up after completing RIT for up to 10 years. Kaplan-Meier and Cox regression analyses evaluated the association between the quantification parameters and survival data. In the survived group, the decrease in mean percentage of change for TLG and pvcTLG was greater than SUVmax, SUVmean and pvcSUVmean [TLG: 253.9 to 106.9, -81.4%; $P = 0.052$ and pvcTLG: 368.9 to 153.3, -58.4%; $P = 0.04$]. In addition, overall survival (OS) was shorter in patients with pre-RIT pvcTLG more than 644 compared to those below this value (log-rank $P < 0.01$). In univariate Cox regression for OS, a higher baseline pvcTLG was a significant prognostic factor (HR: 6.8, $P = 0.02$). Our results showed that pre-treatment pvcTLG was the best predictor of OS in patients with relapsing/refractory NHL following RIT.

Keywords: Positron emission tomography, FDG, radioimmunotherapy, relapsing/refractory non-hodgkin lymphoma, global disease assessment, partial volume correction

Introduction

Non-Hodgkin lymphomas (NHL) account for approximately 90% of lymphomas, from which 85-90% arise from B lymphocytes [1]. The treatment for NHLs has undergone significant changes in recent years since Rituximab (monoclonal antibody against protein CD20) was approved by the US Food and Drug Administration (FDA) for the treatment of relapsing/refractory follicular NHL [2]. During the past 2 decades, two radioimmunotherapy (RIT) drugs have been employed for this purpose, Bexxar (monoclonal antibody linked with radioactive iodine-131) and Zevalin (^{90}Y-radiolabeled murine antibody) [3]. Both of these medications target and attach to the CD20 receptors on the surface of lymphocytes [3].

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) can provide precious functional information based on the augmented uptake of glucose and metabolism in cancerous cells and shows cellular abnormalities

Table 1. Patients' characteristics and type of RIT

Patient	Age	Gender	Diagnosis	Type of RIT
RIT01	59	F	Follicular lymphoma transformed to DLBL	I-131 Tositumomab (Bexxar)
RIT02	66	F	Follicular lymphoma	In-111 Ibritumomab Tiuxetan (dx)/Y-90 Zevalin (tx)
RIT03	49	F	Follicular lymphoma	I-131 Tositumomab (Bexxar)
RIT04	55	F	Follicular lymphoma	I-131 Tositumomab (Bexxar)
RIT05	48	M	Follicular lymphoma	I-131 Tositumomab (Bexxar)
RIT06	52	M	Rituxan-refractory follicular lymphoma	I-131 Tositumomab (Bexxar)
RIT07	53	M	Rituximab-refractory follicular lymphoma	I-131 Tositumomab (Bexxar)
RIT08	43	M	Follicular lymphoma	I-131 Tositumomab (Bexxar)
RIT09	75	F	Follicular lymphoma transformed to DLBL	In-111 Ibritumomab Tiuxetan (dx)/Y-90 Zevalin (rx)
RIT10	67	M	Follicular lymphoma transformed to DLBL	I-131 Tositumomab (Bexxar)
RIT11	58	M	Primary mediastinal B-cell lymphoma	I-131 Tositumomab (Bexxar)
RIT12	65	F	Follicular lymphoma transformed to DLBL	I-131 Tositumomab (Bexxar)
RIT13	62	M	Rituxan-refractory follicular lymphoma	I-131 Tositumomab (Bexxar)
RIT14	59	F	Follicular lymphoma	I-131 Tositumomab (Bexxar)
RIT15	66	F	Follicular lymphoma	I-131 Tositumomab (Bexxar)
RIT16	58	M	Follicular large cell lymphoma	In-111 Ibritumomab Tiuxetan (dx)/Y-90 Zevalin (rx)
RIT17	54	M	Follicular lymphoma	In-111 Ibritumomab Tiuxetan (dx)/Y-90 Zevalin (rx)

Abbreviation. RIT: radioimmunotherapy.

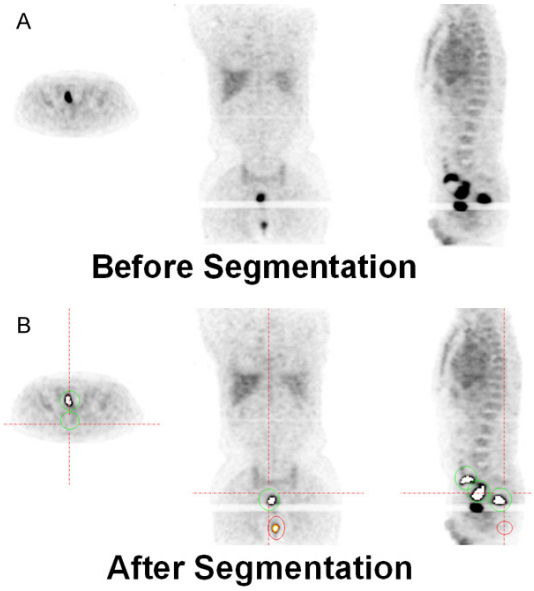

Figure 1. FDG-PET images of a 53-year-old male patient with relapsed follicular lymphoma. A. Pre-treatment FDG-PET images in the axial, coronal, sagittal planes illustrate abnormal increased FDG uptake in the pelvic area. B. The same PET images after segmentation of FDG avid lesions using iterative reconstruction algorithm discussed in the methods section. FDG-PET: ^{18}F-fluorodeoxyglucose positron emission tomography.

before structural alternations are visualized by conventional imaging modalities [4]. FDG-PET combined with computed tomography (CT) has been shown to be a powerful imaging modality in cancer imaging and is being routinely used for evaluation of patients with NHL [5]. The main benefit of PET over conventional imaging modalities is its more sensitive and accurate quantification of disease activity at different stages of the disease [6]. Thus, efforts to determine the impact of global measurement of disease activity in patients with cancer for improving the role of PET studies in medicine have become essential for both diagnostic and therapeutic purposes [6, 7].

The conventional approaches of PET quantification suffer from many deficiencies and could therefore be misleading in the management of NHL patients. These deficiencies include limited sampling of the disease sites by confining measurements to specific locations, which may not reflect the overall disease activity. Furthermore, a standard size region of interest samples only a segment of the affected area, which is subject to partial volume effect (PVE) and can thus significantly underestimate the true degree of disease activity in the lesions [8]. Therefore, there is a need to overcome the abovementioned shortcomings by adopting techniques that allow accurate estimation of the total burden of disease. In this study, we aimed to compare the changes and survival predictive values of different quantification parameters of FDG-PET/CT imaging in patients

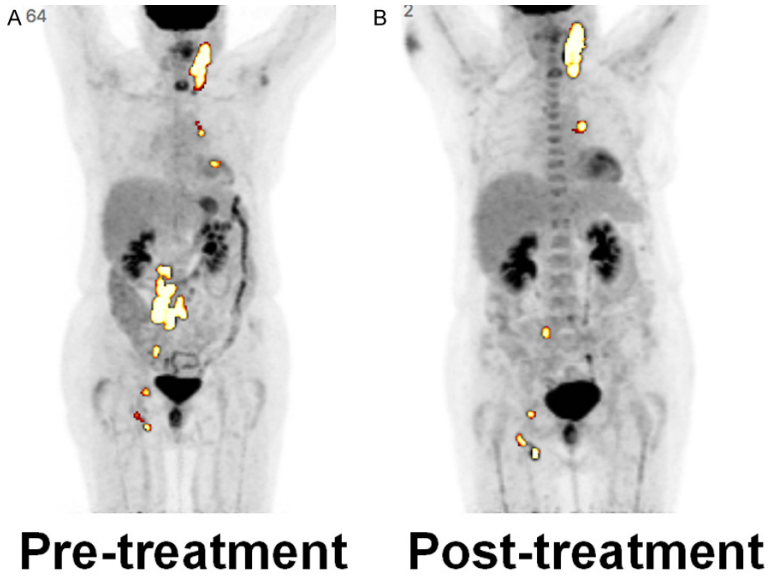

Figure 2. FDG-PET images of a 65-year-old female patient with diffuse large B-cell lymphoma. A. FDG-PET scan before treatment demonstrates cervical, abdominal and inguinal lymph nodes involvement. B. FDG-PET scan of the same patient after treatment illustrates partial response to treatment. TLG and pvcTLG decreased from 623.4 and 1045.8 to 43.5 and 48.1 after the treatment, respectively. FDG-PET: fluorodeoxyglucose positron emission tomography; pvc: partial volume corrected; TLG: total lesion glycolysis.

with relapsing/refractory NHL before and after RIT.

Methods

Patients

Institutional Review Board (IRB) approval for data collection and image analysis as well as a Health Insurance Portability and Accountability Act (HIPAA) waiver were secured to conduct this research study. In this retrospective evaluation, we studied 17 patients with relapsing/refractory NHL (8 females and 9 males) aged 43-75 years (mean = 58.2 ± 8.1 years) (**Table 1**). The patients were treated with targeted-RIT (^{131}I-tositumomabor or ^{90}Y-Zevalin) following chemotherapy/radiotherapy. FDG-PET scans were performed approximately three months before and six months after RIT. Over a period of up to ten years of follow up, ten patients survived, comprising the survived group, and seven patients died, comprising the deceased group.

Image acquisition

FDG-PET/CT scans of patients were performed on integrated PET/CT (Gemini TF; Philips Healthcare, The Netherlands). Blood glucose was first measured and approximately 555 MBq (15 mCi) of FDG was administered after at least 8 hours of fasting if the levels were below 200 (mg/dl). Images were acquired 60 minutes after intravenous injection of FDG. Attenuation correction was performed on the PET image with low-dose unenhanced CT images.

Image analysis

An expert assessed both the pre-RIT and post-RIT scans blinded to patients' outcome. To measure FDG uptake in lesions quantitatively, an adaptive contrast-oriented thresholding algorithm (ROVER software, ABX, Radeberg, Germany) was employed to examine all focal active lesions. This technique delineated the boundaries of lesions based on PET images and combined background correction and local adaptive thresholding in an iterative algorithm model [9-12] (**Figure 1**). Standardized uptake values (SUVs) including SUVmax, SUVmean, partial volume-corrected SUVmean (pvcSUVmean), and tumor metabolic volume (TMV) were measured. The SUVs are considered as conventional parameters for quantification of PET images. In order to perform a global assessment of disease burden, novel quantification parameters including total lesion glycolysis (TLG) and the partial volume-corrected TLG (pvcTLG) were calculated with the formulas shown below:

$$TLG = TMV \times SUVmean$$

$$pvcTLG = TMV \times pvcSUVmean$$

The changes in different parameters were evaluated before and after treatment (**Figure 2**).

Study analysis

Statistical analyses were performed using IBM SPSS statics version 25. Wilcoxon signed-rank tests were performed to compare the pre- and post-RIT FDG uptake values in the survived and

Table 2. Changes in conventional and novel parameters for measuring FDG before and after RIT in the survived group (Number of Subjects: 17)

Parameters	Before RIT (mean ± SD)	After RIT (mean ± SD)	Percentage of Change	*P*
SUVmax	9.8 ± 7.3	5.9 ± 9.7	-38.9%	0.2
SUVmean	4.9 ± 3.8	2.4 ± 3.6	-50.2%	0.1
pvcSUVmean	7.7 ± 6.2	3.9 ± 5.8	-48.8%	0.1
TLG	253.9 ± 299.3	106.9 ± 186.6	-81.4%	0.052
pvcTLG	368.9 ± 433.5	153.3 ± 258.7	-58.4%	0.04*

Abbreviations. pvc: partial volume corrected; SUV: standardized uptake values; TLG: total lesion glycolysis. *Statistically significant.

Table 3. Changes in conventional and novel parameters for measuring FDG before and after RIT in the deceased group (Number of Subjects: 17)

Parameters	Before RIT (mean ± SD)	After RIT (mean ± SD)	Percentage of Change	*P*
SUVmax	12.4 ± 12.1	9.9 ± 12.5	-19.6%	0.5
SUVmean	3.4 ± 2.0	4.6 ± 6.0	35.7%	0.6
pvcSUVmean	5.3 ± 3.7	8.1 ± 11.1	53.1%	0.5
TLG	365 ± 269.7	375.4 ± 520.5	2.8%	0.9
pvcTLG	531.0 ± 387.7	657.9 ± 950.5	23.9%	0.8

Abbreviations. pvc: partial volume corrected; SUV: standardized uptake values; TLG: total lesion glycolysis.

deceased groups. Receiver operation characteristic (ROC) curve analysis was used to define the cutoff values for the categorization of low and high SUVmax, SUVmean, pvcSUVmean, TLG and pvcTLG (not shown). Kaplan-Meier plots were used to show survival according to before and after treatment measurements and the log-rank test demonstrated whether the difference was significant [13, 14]. Progression-free survival (PFS) and overall survival (OS) was calculated using Kaplan-Meier analysis and Cox regression was used to calculate hazard ratio (HR) for survival analysis.

Results

Changes in FDG uptake before and after RIT

Tables 2 and **3** show the changes in conventional and novel parameters for measuring FDG uptake before and after RIT in survived and deceased groups, respectively. The pvcSUVmean and pvcTLG were corrected for the partial volume effect. In the survived group, the respective average SUVmax, SUVmean, and pvcSUVmean were 9.8, 4.9 and 7.7 before treatment, which then decreased by 38.9%, 50.2% and 48.8% following RIT but the changes were not statistically significant. Similarly, changes in the deceased group in SUVmax, SUVmean, and pvcSUVmean before and after RIT were not statistically significant (12.4, 3.4, and 5.3 pre-RIT, and 9.9, 4.6, and 8.1 post-RIT, respectively).

In global assessment analysis, TLG did not show a significant decrease after the treatment (from 253.9 to 106.9; P = 0.052), but pvcTLG significantly decreased from 368.9 to 153.3 in the survived group (P = 0.04) (**Table 2**). In contrast, the TLG and pvcTLG were insignificantly increased in deceased group from 365 to 375.3 (P = 0.9) and from 531.0 to 657.9 (P = 0.8), respectively (**Table 3**).

Survival analysis

The optimal cutoffs of 296 and 644 were determined by ROC analysis for TLG and pvcTLG (area under the curve (AUC): 0.6, sensitivity: 0.7, specificity: 0.6 and AUC: 0.7, sensitivity: 0.7, specificity: 0.8, respectively) (**Figure 3A** and **3C**). Apart from pvcTLG, Kaplan-Meier analysis did not reveal significant differences in OS for other FDG uptake parameters, including pre-treatment TLG (**Figure 3B**). The Kaplan-Meier survival analysis for pvcTLG at baseline showed that a pvcTLG higher than 644 was associated with shorter OS compared to those with a pvcTLG below that threshold (average survival: 46.7 vs. 119.8 months; log rank test < 0.01) (**Figure 3D**). There was no significant correlation between PFS and either conventional or novel methods of quantification. Univariate Cox regression analysis for OS showed that a higher baseline pvcTLG was a significant prognostic factor (HR: 6.9, 95% CI: 1.3-36.7, P = 0.02) (**Table 4**). We did not observe any significant *p*-values for the post-treatment parameters in survival analysis.

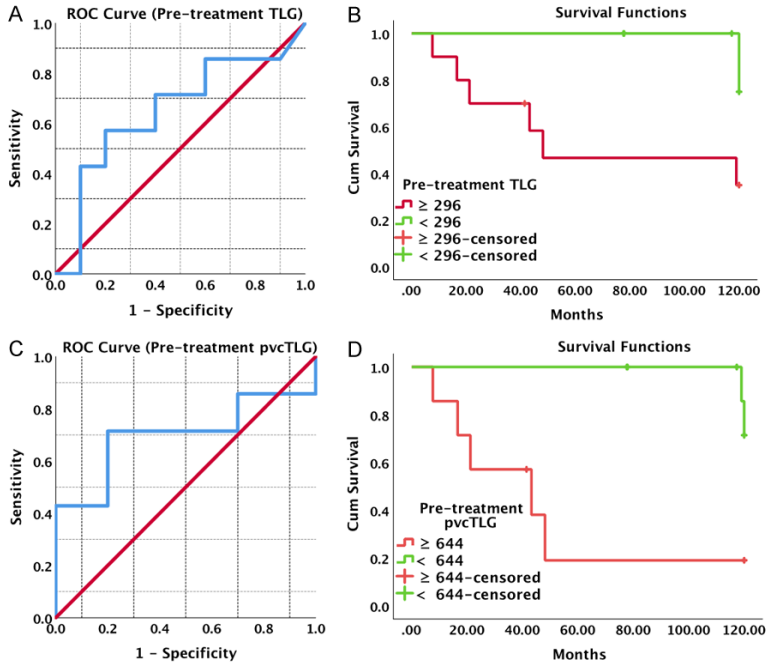

Figure 3. ROC and cumulative survival curves for pre-treatment TLG and pvcTLG. A. Optimal cutoff of 296 (AUC: 0.6, sensitivity: 0.7, specificity: 0.6) was determined for pre-treatment TLG. B. A statically significant difference was not observed in OS Kaplan-Meier analysis for TLG. C. Optimal cutoff of 644 was determined for pre-treatment pvcTLG (AUC: 0.7, sensitivity: 0.7, specificity: 0.8). D. OS was shorter in patients with pre-RIT pvcTLG more than 644 compared to those below this value (log-rank $P < 0.01$). AUC: area under the curve; OS: overall survival; pvc: partial volume corrected; RIT: radioimmunotherapy; ROC: receiver operating characteristic; TLG: total lesion glycolysis.

Table 4. Univariate analysis for OS of global assessment measurements using Cox proportional hazard model

Parameters	HR	95% CI	*P*
Baseline TLG	3.4	0.6-17.7	0.1
Follow-up TLG	2.8	0.5-14.7	0.2
Baseline pvcTLG	6.9	1.3-36.7	0.02*
Follow-up pvcTLG	2.4	0.5-10.6	0.2

Abbreviations. CI: confidence interval; HR: hazard ration; OS: overall survival; pvc: partial volume corrected; TLG: total lesion glycolysis. *Statistically significant.

Discussion

One of the earliest indications for clinical assessment of disease activity by FDG-PET imaging was the evaluation of treatment response in patients with lymphoma [15-18]. However, most PET studies have used SUVmax as an index of tumor metabolism in lymphoma [19-21], which does not accurately reflect the overall disease burden. In our study, conventional parameters such as SUVmax and SUVmean failed to show a significant change in either the surviving or the deceased group following RIT. Also, the pvcSUVmean did not demonstrate a significant change in these patients following RIT.

Inefficiency of conventional methods of FDG-PET quantification is concerning [22]. Differences in the image acquisition parameters such as scanner, attenuation and scatter correction result in differences in SUV measurements acquired at different centers [23]. Moreover, measuring focal SUV without partial volume correction (PVC) and global disease assessment cannot provide the physician with precise information following treatment. To overcome these shortcomings, we assessed metabolic and volumetric characteristics of lesions with global parameters including TLG and pvcTLG.

TLG is indicative of the global metabolic burden of disease, as it combines tumor volumetric values with metabolic data to create a unique index. The usefulness of TLG in the assessment of lymphoma has also been shown in several studies [24, 25]. In a study conducted by Berkowitz et al., whole-body metabolic burden (WBMB) was introduced as a novel quantification technique for the assessment of tumor activity in NHL, and it was shown that WBMB is a superior approach compared to conventional techniques [26]. WBMB was calculated as the sum of the individual metabolic burdens of all the lesions identified [27]. Cazaentre et al. showed that baseline TLG could be used as a predictor for response to RIT in patients with NHL, while conventional prognostic parameters could not predict response following RIT [28]. In this study, the decrease in TLG in the survived group following treatment was higher than conventional methods of quantification, but statically insignificant [253.9 to 106.9, -81.4%; P = 0.052]. In addition, Kaplan-Meier and Cox regression analysis failed to show any statical-

ly significant association between TLG and OS or PFS.

The application of PVC improved the accuracy of TLG for predicting survival in this study. Our results showed that higher pre-RIT pvcTLG correlated with shorter OS. Moreover, the survived group had a statically significant decrease in pvcTLG following RIT. PVE, is a significant factor, reducing quality of the PET images and can lead to a bias by underestimating actual metabolic activity of the tumor [29]. In spite of significant advances in PET instrumentation over the years, PET images are of relatively poor quality due to limited spatial resolution of this modality, causing smaller objects to appear larger [30]. PVC has been shown to increase the accuracy of the quantification of PET images in cancers [31-33]. Several methods have been suggested for correcting PVE. The iterative thresholding algorithm used in this study (ROVER software) allows for automatic model-free correction of uptake values.

There are some limitations to our study. First, in this retrospective study we evaluated only 17 patients. A larger sample of patients in a prospective study would improve the power of the study regarding the association of global quantification parameters with OS and PFS in patients with NHL. Secondly, this study lacks inter and intra observer reliability tests to demonstrate the reproducibility of these results.

Conclusion

To our knowledge, this is the first study that investigated the role of global parameters compared to conventional measurements for analyzing FDG-PET images of patients with relapsing/refractory NHL following RIT. In this study, conventional methods of FDG-PET quantification failed to show a statically significant association with OS and PFS. The application of PVC enhanced the accuracy of TLG for predicting survival in patients with NHL following RIT.

Disclosure of conflict of interest

None.

Address correspondence to: Abass Alavi, Department of Radiology, Hospital of The University of Pennsylvania, 3400 Spruce St, Philadelphia PA 19104, USA. Tel: 215-662-3069; Fax: 215-573-4107; E-mail: abass.alavi@uphs.upenn.edu

References

[1] Shankland KR, Armitage JO and Hancock BW. Non-hodgkin lymphoma. Lancet 2012; 380: 848-857.

[2] McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, Heyman MR, Bence-Bruckler I, White CA and Cabanillas F. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998; 16: 2825-2833.

[3] Iagaru A, Mittra ES, Ganjoo K, Knox SJ and Goris ML. 131 I-tositumomab (Bexxar®) vs. 90 Y-ibritumomab (Zevalin®) therapy of low-grade refractory/relapsed non-hodgkin lymphoma. Mol Imaging Biol 2010; 12: 198-203.

[4] Almuhaideb A, Papathanasiou N and Bomanji J. ^{18}F-FDG PET/CT imaging in oncology. Ann Saudi Med 2011; 31: 3-13.

[5] Ansell SM and Armitage JO. Positron emission tomographic scans in lymphoma: convention and controversy. Mayo Clin Proc 2012; 87: 571-580.

[6] Alavi A, Werner TJ, Hoilund-Carlsen PF and Zaidi H. Correction for partial volume effect is a must, not a luxury, to fully exploit the potential of quantitative PET imaging in clinical oncology. Mol Imaging Biol 2018; 20: 1-3.

[7] Alavi A, Newberg AB, Souder E and Berlin JA. Quantitative analysis of PET and MRI data in normal aging and Alzheimer's disease: atrophy weighted total brain metabolism and absolute whole brain metabolism as reliable discriminators. J Nucl Med 1993; 34: 1681-1687.

[8] Hess S, Blomberg BA, Rakheja R, Friedman K, Kwee TC, Høilund-Carlsen PF and Alavi A. A brief overview of novel approaches to FDG PET imaging and quantification. Clin Transl Imaging 2014; 2: 187-198.

[9] Hofheinz F, Langner J, Petr J, Beuthien-Baumann B, Oehme L, Steinbach J, Kotzerke J and van den Hoff J. A method for model-free partial volume correction in oncological PET. EJNMMI Res 2012; 2: 16.

[10] Hofheinz F, Dittrich S, Potzsch C and Hoff J. Effects of cold sphere walls in PET phantom measurements on the volume reproducing threshold. Phys Med Biol 2010; 55: 1099-1113.

[11] Hofheinz F, Potzsch C, Oehme L, Beuthien-Baumann B, Steinbach J, Kotzerke J and van den Hoff J. Automatic volume delineation in onco-

logical PET. Evaluation of a dedicated software tool and comparison with manual delineation in clinical data sets. Nuklearmedizin 2012; 51: 9-16.
[12] Marin-Oyaga VA, Salavati A, Houshmand S, Pasha AK, Gharavi M, Saboury B, Basu S, Torigian DA and Alavi A. Feasibility and performance of an adaptive contrast-oriented FDG PET/CT quantification technique for global disease assessment of malignant pleural mesothelioma and a brief review of the literature. Hell J Nucl Med 2015; 18: 11-18.
[13] Kaplan EL and Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457-481.
[14] Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J and Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. Br J Cancer 1977; 35: 1-39.
[15] Okada J, Yoshikawa K, Imazeki K, Minoshima S, Uno K, Itami J, Kuyama J, Maruno H and Arimizu N. The use of FDG-PET in the detection and management of malignant lymphoma: correlation of uptake with prognosis. J Nucl Med 1991; 32: 686-691.
[16] Newman JS, Francis IR, Kaminski MS and Wahl RL. Imaging of lymphoma with PET with 2-[F-18]-fluoro-2-deoxy-D-glucose: correlation with CT. Radiology 1994; 190: 111-116.
[17] Hutchings M, Loft A, Hansen M, Pedersen LM, Buhl T, Jurlander J, Buus S, Keiding S, D'Amore F, Boesen AM, Berthelsen AK and Specht L. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 2006; 107: 52-59.
[18] Mikhaeel NG, Hutchings M, Fields PA, O'Doherty MJ and Timothy AR. FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma. Ann Oncol 2005; 16: 1514-1523.
[19] Ngeow J, Quek R, Ng D, Hee S, Tao M, Lim L, Tan Y and Lim S. High SUV uptake on FDG-PET/CT predicts for an aggressive B-cell lymphoma in a prospective study of primary FDG-PET/CT staging in lymphoma. Ann Oncol 2009; 20: 1543-1547.
[20] Liang JH, Ding CY, Gale RP, Wang L, Xu J, Qu XY, Fan L, Li TL, Li JY and Xu W. Prognostic value of whole-body SUVmax of nodal and extra-nodal lesions detected by ^{18}F-FDG PET/CT in extranodal NK/T-cell lymphoma. Oncotarget 2017; 8: 1737-1743.
[21] Chandra P, Akinbobuyi O, Liao A, Arora J, Chen Z, Lechowicz MJ, Langston AA, Kowalsky J, Cohen JB, Flowers CR, Bernal-Mizrachi L. Suvmax in 18-fluorodeoxyglucose PET/CT potentially predict the estimation of a positive biopsy in cases of lymphoma. Blood 2015; 126: 5043.
[22] Svoboda J, Chong EA, Chong ER, Nasta SD, Torigian D, Alavi A, Schuster SJ. Maximum standard uptake value (SUVmax) on FDG-PET imaging predicts time to first treatment in patients with low grade follicular lymphoma. Blood 2011; 118: 4204.
[23] Rossi C, Kanoun S, Berriolo-Riedinger A, Dygai-Cochet I, Humbert O, Legouge C, Chrétien ML, Bastie JN, Brunotte F and Casasnovas RO. Interim ^{18}F-FDG PET SUVmax reduction is superior to visual analysis in predicting outcome early in Hodgkin lymphoma patients. J Nucl Med 2014; 55: 569-573.
[24] Basu S, Kwee TC, Torigian D, Saboury B and Alavi A. Suboptimal and inadequate quantification: an alarming crisis in medical applications of PET. Eur J Nucl Med Mol Imaging 2011; 38: 1381-1382.
[25] Barrington SF and Kluge R. FDG PET for therapy monitoring in Hodgkin and non-Hodgkin lymphomas. Eur J Nucl Med Mol Imaging 2017; 44: 97-110.
[26] Berkowitz A, Basu S, Srinivas S, Sankaran S, Schuster S and Alavi A. Determination of whole-body metabolic burden as a quantitative measure of disease activity in lymphoma: a novel approach with fluorodeoxyglucose-PET. Nucl Med Commun 2008; 29: 521-526.
[27] Basu S, Zaidi H, Salavati A, Hess S, Carlsen PF and Alavi A. FDG PET/CT methodology for evaluation of treatment response in lymphoma: from "graded visual analysis" and "semiquantitative SUVmax" to global disease burden assessment. Eur J Nucl Med Mol Imaging 2014; 41: 2158-2160.
[28] Cazaentre T, Morschhauser F, Vermandel M, Betrouni N, Prangere T, Steinling M and Huglo D. Pre-therapy ^{18}F-FDG PET quantitative parameters help in predicting the response to radioimmunotherapy in non-Hodgkin lymphoma. Eur J Nucl Med Mol Imaging 2010; 37: 494-504.
[29] Weber WA. Use of PET for monitoring cancer therapy and for predicting outcome. J Nucl Med 2005; 46: 983-995.
[30] Rousset O, Rahmim A, Alavi A and Zaidi H. Partial volume correction strategies in PET. PET Clin 2007; 2: 235-249.
[31] Hickeson M, Yun M, Matthies A, Zhuang H, Adam LE, Lacorte L and Alavi A. Use of a corrected standardized uptake value based on the lesion size on CT permits accurate characterization of lung nodules on FDG-PET. Eur J Nucl Med Mol Imaging 2002; 29: 1639-1647.

[32] Cysouw MCF, Kramer GM, Hoekstra OS, Frings V, de Langen AJ, Smit EF, van den Eertwegh AJ, Oprea-Lager DE, Boellaard R. Accuracy and precision of partial-volume correction in oncological PET/CT studies. J Nucl Med 2016; 57: 1642-1649.

[33] Hoetjes NJ, van Velden FH, Hoekstra OS, Hoekstra CJ, Krak NC, Lammertsma AA, Boellaard R. Partial volume correction strategies for quantitative FDG PET in oncology. Eur J Nucl Med Mol Imaging 2010; 37: 1679-1687.