

ORIGINAL ARTICLE

Comparison of end-expiratory respiratory gating methods for PET/CT

MARKUS HARTEELA^{1,*}, HEIDI HIRVI^{1,*}, ANNA MÄKIPÄÄ^{1,*}, JARMO TEUHO^{2,*}, TUOMAS KOIVUMÄKI^{3,4}, MARKO M. MÄKELÄ¹ & MIKA TERÄS²

¹Department of Mathematics and Statistics, University of Turku, Turku, Finland, ²Turku PET Centre, Turku University Hospital, Turku, Finland, ³Department of Applied Physics, University of Eastern Finland, Kuopio, Finland and ⁴Diagnostic Imaging Centre, Kuopio University Hospital, Kuopio, Finland

ABSTRACT

Background. Respiratory motion in positron emission tomography/computed tomography (PET/CT) causes underestimation of standardized uptake value (SUV) and variation of lesion volume, while PET and CT attenuation correction (CTAC) mismatch may introduce artefacts. The aim was to compare end-expiratory gating methods of PET and CTAC.

Material and methods. Three methods named the minimum-constant, slope-based and amplitude-median were developed and evaluated on gating efficiency. Method evaluation and optimization was performed on 23 simulated and 23 recorded signals from a mixed patient group. The optimized methods were applied in PET/CT imaging of seven patients, consisting of non-gated CTAC, whole-body PET and four-dimensional (4D) PET/CT. Gating efficiency was evaluated by preservation of the respiratory signal, PET-CTAC alignment, image noise and measurement of lesion SUV maximum (SUV_{max}), SUV mean (SUV_{mean}) and volume. The methods were evaluated with non-gated PET and end-expiratory phase of five-bin phase-gated PET. End-expiratory gated 4D-CTAC and averaged CTAC were compared for attenuation correction of end-expiratory gated PET.

Results. Mean fraction of data preserved was larger (23–34%) with end-expiratory gating compared to phase-gated PET. End-expiratory gating showed increased SUV_{max} (8.2–8.4 g/ml), SUV_{mean} (5.7–5.8 g/ml) and decreased lesion volume (-11.3–16.8%) compared to non-gated PET (SUV_{max} 6.2 g/ml, SUV_{mean} 4.7 g/ml) and phase-gated PET (SUV_{max} 8.0 g/ml, SUV_{mean} 5.6 g/ml). Using averaged CTAC and end-expiratory 4D-CTAC produced similar results concerning SUV_{max}, with less than 5% difference. Additionally, CTAC-PET-mismatch was minimal when end-expiratory 4D-CTAC was used.

Conclusion. End-expiratory gating in PET/CT results in SUV_{max} and SUV_{mean} increase and reduced lesion volume compared to non-gated PET and phase-gated PET. End-expiratory 4D-CTAC or averaged CTAC will offer similar accuracy for attenuation correction of end-expiratory gated PET.

Respiratory motion is a well-known problem in positron emission tomography/computed tomography (PET/CT). Motion blurring causes increased partial volume effects (PVE), underestimation of maximal standardized uptake value (SUV_{max}) and average standardized uptake value (SUV_{mean}) and variation of lesion volume [1–4]. Additionally, small targets may be troublesome to differentiate as the lesion target-to-background ratio is reduced [1–4]. Finally, a respiratory-induced spatial mismatch between

positron emission tomography (PET) and computed tomography attenuation correction (CTAC) may introduce AC artefacts, especially in borders of two tissues with large density differences [1–4].

To reduce the effect of motion, numerous respiratory gating methods have been introduced [5,6]. The most common method used in the clinical practice is phase-gated PET/CT [7]. In phase-gated PET/CT, the PET list-mode data and phase-matched four-dimensional CT (4D CT) images are divided to

* These authors contributed equally.

Correspondence: J. Teuvo, Turku PET Centre, Turku University Hospital, Kiinamylynkatu 4-8, 20520 Turku, Finland. E-mail: jarmo.teuvo@tyks.fi

(Received 22 April 2014; accepted 14 May 2014)

equivalent-size segments temporally [7]. To improve the temporal match between PET and CTAC, methods based on average CT have been deemed effective [8–10]. While numerous amplitude-based gating methods have been introduced [11], they have not yet gained a wide adoption clinically although commercial solutions exist [12]. Additionally, several methods based on breath hold performed PET/CT have been introduced [13,14]. The benefit of these methods is improved spatial match between PET and CTAC and an improved signal-to-noise ratio (SNR) [13,14].

Methodologically, phase-gating does not take into account neither the baseline drift in the respiratory signal nor the variation of the cycle amplitudes [15]. Furthermore, both effects have been reported to exist in a considerable proportion of patients. As gating bins have equivalent magnitude, using more than five bins conserves less than 20% of acquisition statistics, resulting to noise increase unless acquisition time is increased accordingly. Additionally, increased noise levels have been reported to cause variation in SUVmax measurements [15].

Therefore, extracting a long-duration, stable respiratory period would be beneficial for respiratory gating as proposed by Liu et al. [15]. The respiratory period would need to be: 1) inherently stable for maximal motion reduction; 2) have a long duration to conserve count statistics; and 3) be easily extractable from the signal. Therefore, both the SNR and SUVmax should improve if the lesion trajectory follows the quiescent period of respiration [15]. Additionally, as Liu et al. applied end-expiratory gating only to PET, they concluded that end-expiratory gated CT would potentially improve the quantitative accuracy of the gated images and encouraged further studies [15].

The aim of this study was to apply and compare end-expiratory gating methods to both PET and CT. Based on these requirements, three end-expiratory respiratory gating methods were developed. The methods were validated and optimized with simulation studies and analysis of patient respiratory signals. The optimized methods were then applied to an oncologic PET/CT study and were evaluated concurrently with phase-based respiratory gating.

Material and methods

Three end-expiratory methods to form gated PET/CT images from the respiratory signal recorded with a Varian Real-Time Position Management (RPM) (Varian Medical Systems, Palo Alto, CA, USA) were developed and evaluated. The development was based on two principles: the end-expiratory periods

should be extracted and at least 20% of the respiratory data should be saved. The methods were named as: minimum-constant, slope-based and amplitude-median method and were designed to be optimal to a particular type of respiratory curve. The inherent properties of the developed gating methods are summarized in Supplementary Table I available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.926028>.

Each method has a set of parameters which can be used for patient-specific optimization. However, in this study the parameters were optimized empirically with analysis of simulated and previously acquired signals, after which a set of fixed parameters was used. After optimization, the parameters were fixed with values of 1.0% and 30% for the minimum-constant method, 1.0 and 1.0 for the slope-based method and with values of 26% for the amplitude threshold and 65% for the median of selected points for the amplitude-median method.

Minimum-constant method

The minimum-constant method finds the minimum amplitude in the RPM signal for every respiratory cycle and evaluates the found minima based on their median absolute deviation (Supplementary Figure 1, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.926028>). The median absolute deviation can be multiplied by a factor of 0.8–2.0, where a larger value results in larger preservation of signal. A constant value is computed as a product of the median amplitude and the parameterized percent amplitude threshold, where a preferable value is 20%–40%. For every selected respiratory cycle, the amplitude threshold is specified as a sum of the minimum of the respiratory cycle and the constant value. The end-expiratory period is defined as an area which falls within the specified amplitude threshold. Finally, extracted periods which have a median deviation of five times larger than the deviation in the entire signal from the median respiratory cycle length are discarded.

Slope-based method

The slope-based method finds the minima and maxima of cycle amplitudes and evaluates two values for every cycle: the left and the right slope thresholds, which are the slopes of the lines between the minimum and the maxima of each cycle. Size of the period can be adjusted with parameterized threshold coefficients, where the preferable range is 0.8–1.2 (Supplementary Figure 2, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.926028>). The method discards periods on the

following principles: 1) the median deviation of duration is three times larger than the deviation in the entire signal; 2) the difference between the first and the last point of the period is farther than 90% from the median of other differences; and 3) the value of the first point is farther than 90% from the mean of the first points of the other periods.

Amplitude-median method

Liu et al. introduced [15] a cycle-based quiescent period gating (QPG) method. The cycle-based method extracts RPM data below a certain percent threshold of the amplitude in each cycle [15]. The amplitude-median method is partly based on a similar idea: the method selects the end-expiratory periods based on a percent amplitude threshold (Supplementary Figure 3, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.926028>). The percent amplitude threshold and the threshold value related to the median of the selected points are parameterized, where the preferable values for the percent amplitude threshold is between 20% and 30% and the median of the selected points is 60–80%.

Computer simulation

The methods were tested and validated with 23 simulated RPM signals. The simulated signals were created based on sine curve, where random variation was introduced on duration of the cycles, baseline drift and respiratory amplitude (Supplementary Figure 4, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.926028>). In addition, the cycle bases were made less sharp in order to imitate more of the end-expiratory periods. In general, the simulated and RPM signals are similar in appearance, although the simulated signals appear much smoother as they do not contain amplitude fluctuations or noise typical to RPM signals (Supplementary Figure 5, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.926028>).

Method evaluation was based on efficiency of extracting the end-expiratory period. To derive an estimate of the SNR, the fraction of the respiratory signal preserved was calculated. The analysis was performed on simulated RPM signals and repeated for RPM signals from 23 clinical studies. The RPM signals were gathered from patients with suspected oncologic, cardiac sarcoidosis or coronary plaque pathology during PET/CT imaging. The parameters specific for each method were optimized, after which a set of fixed parameters was created and used for rest of the study.

Patient study

Patient study consisted of seven oncologic patients with altogether nine quantifiable lesions. Written informed consent was obtained from all patients and the study was conducted according to the guidelines of the declaration of Helsinki. The study was approved by the ethical committee of Kuopio University Hospital. Patient data was acquired with the Discovery 690 (D690) PET/CT scanner (General Electric Medical Systems, Waukesha, WI, USA) [16].

Imaging protocol consisted of a non-gated CTAC and a whole-body PET scan followed by 4D PET/CT of one bed position. 4D PET was collected for 10 minutes, while the whole-body scan was acquired for two minutes per bed position. 4D CT was collected immediately after 4D PET acquisition to exclude any potential respiratory changes. The imaging time of each bed position in 4D CT was the average breathing period observed during the 4D PET acquisition added with one second.

Non-gated CTAC and 4D CT were acquired with the standard protocol. Non-gated CTAC was a helical low-dose CT at 120 kV with a current of 10–80 mA. The current was adjusted by dose adaptation software according to the noise level and patient anatomy. 4D CT was acquired at 80 kV and 30 mA. Respiratory data was collected with the RPM Respiratory Gating System, which tracks the respiratory signal by following the vertical displacement of a plastic marker block [6]. The RPM allows respiratory triggers to be recorded to the PET list-mode data and collection of 4D CT for retrospective gating of CT. Additionally, the respiratory signals can be exported for off-line processing.

All PET image reconstructions were performed off-line with the GE research gating tool (RGT) software package. For non-gated PET, a non-gated CTAC was used for attenuation correction of PET images. For respiratory-gated PET, both end-expiratory gated 4D-CTAC and averaged CTAC from 4D CT acquisition were used in attenuation correction of PET images. All necessary quantitative corrections were performed. Images were reconstructed by using a 700 mm field-of-view (FOV), $256 \times 256 \times 47$ image matrix size and 6 mm Gaussian post-filtering. The image reconstruction algorithm was a 3D ordered-subset-expectation-maximum 3D-OSEM with two iterations and 24 subsets. No resolution modeling (PSF) was applied in image reconstruction.

Method comparison

Gating efficiency was evaluated visually and quantitatively. The methods were compared against non-gated PET and five-bin phase-gated PET, where bin

number 3 was selected for comparison with the end-expiratory gating methods. PET-CT alignment and image quality in regard to image noise increase were evaluated. Liver SUV standard deviation as an approximation of image noise was measured with a spherical VOI with a size of 7.90 cm³ placed on a homogenous part of the liver. As an alternative measure of the SNR, fraction of counts preserved in each end-expiratory gate was used similarly to Liu et al. [15].

In the quantitative evaluation, lesion SUV_{max}, SUV_{mean} and volume were measured. SUV and volume measurements were performed on an AW Workstation 4.5 (GE Medical Systems, Milwaukee, WI, USA) utilizing contour-based definition of volume of interest (VOI). SUV_{max} was determined as the maximum uptake value of a voxel while SUV_{mean} was determined as the mean uptake in the VOI. Tumor volume was measured as a percentage threshold from SUV_{max}, where 50% threshold was applied to five patients and 60% threshold was applied to two patients.

The accuracy of CT gating was evaluated between end-expiratory gated 4D-CTAC and averaged CTAC by comparing lesion SUV_{max}, SUV_{mean} and volume. End-expiratory gated 4D-CTAC was derived by applying the gating methods to CT RPM signal and CT images collected during 4D CT. Averaged CTAC was implemented as a weighted average of all respiratory phases collected during 4D CT.

Results

The fraction of saved respiratory signal in the end-expiratory bin had a good agreement between the simulated signals and patient signals. Mean fraction of signal preserved was $23 \pm 2\%$ for minimum-constant, $25 \pm 5\%$ for slope-based, $30 \pm 1\%$ for amplitude-median in simulations and $23 \pm 5\%$ for minimum-constant, $32 \pm 6\%$ for slope-based, $33 \pm 4\%$ for amplitude-median in patient signals. The processing time for each method was similar to standard phase-gating, requiring only few seconds to derive the gating information. Based on signal analysis of 23 patients, the slope-based method was able to preserve the required 20% of the respiratory signal with least amount of required acquisition time in 14 patients while the amplitude-median was the fastest method in nine patients.

The noise level in end-expiratory gated PET images was improved over phase-gated PET as a larger fraction of counts was preserved. Similarly, the measured standard deviation of SUV in a homogenous VOI in liver was 0.157 for non-gated, 0.314 for phase-gated and 0.243 for amplitude-median, 0.257 slope-based and 0.286 for minimum-constant

method on average. Non-gated images had the least amount of image noise, as expected. Finally, the methods were able to save a large fraction of emission data similarly to the simulation and patient signals when applied to the oncologic study (Figure 1).

While averaged CTAC improved the PET-CT alignment in all cases, the CT-mismatch was evaluated minimal when end-expiratory gated 4D-CTAC was used, which is supported by the quantitative results. Additionally, in a single patient, a CT- to PET mismatch was detected in phase-gated PET which obscured a location of a lesion detectable in other methodologies. The mismatch was due to a respiratory change, which occurred during the collection of the PET data. All of the developed methods were insensitive to this respiratory change and were able to delineate the lesion successfully. Individual patients experienced fairly large increases in SUV_{max} and SUV_{mean} (Figure 2).

In the quantitative evaluation, all methods proved to be superior to non-gated PET and improved quantitative accuracy by average increase in SUV_{max} and SUV_{mean} compared to phase-gated PET (Table I, Supplementary Figures 6 and 7, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.926028>). Largest increase in SUV_{max} and SUV_{mean} compared to non-gated PET and phase-gated PET was measured when both PET and CT were gated to the end-expiratory phase (Table I). By using any of the end-expiratory gating methods for PET with averaged CTAC offered similar increase in SUV_{max} and SUV_{mean} compared to end-expiratory gated 4D-CTAC (Table I).

Lesion volume reduction was larger in end-expiratory gating methods than in non-gated PET or

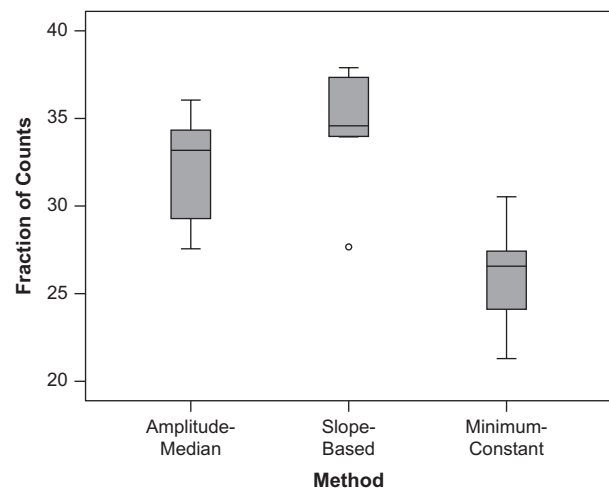


Figure 1. Box-plot of the fraction of counts saved in the PET/CT patient study by each method. Whiskers define the maximum and minimum value of the counts saved, while the horizontal line defines the median of the counts saved.

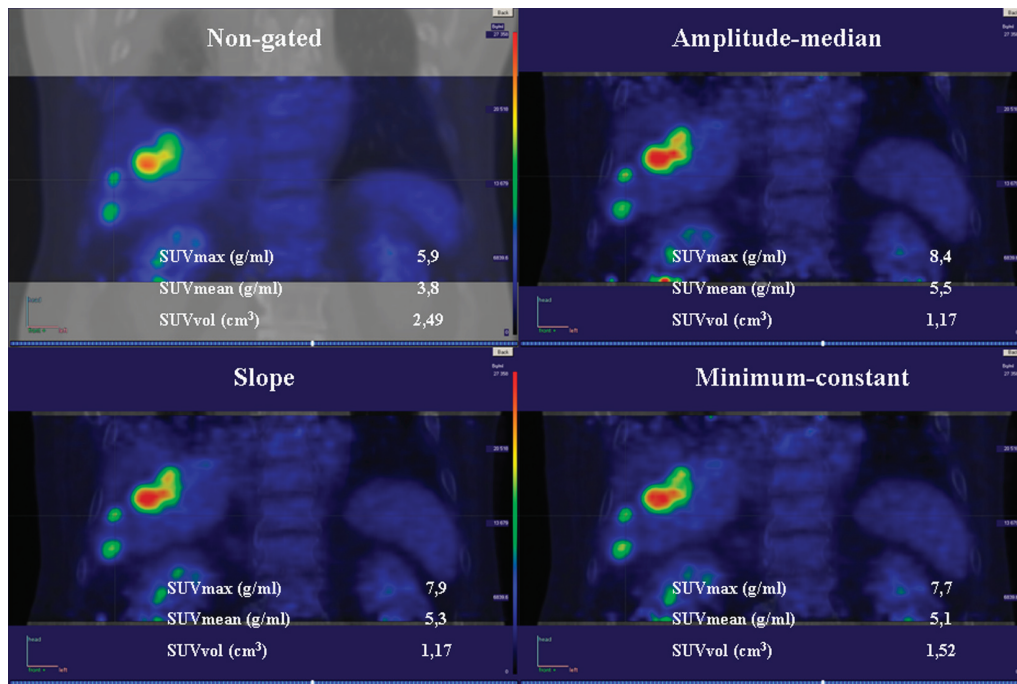


Figure 2. Example case of a patient, showing a clear increase in SUVmax and SUV mean with reduction of lesion volume.

phase-gated PET (Table I). Even after an unquantifiable lesion on phase-gated PET measurement was dismissed from volume measurement, the end-expiratory gating methods displayed a larger lesion volume reduction on average. Concerning individual patients, at least one of the gating methods was superior to phase-gated PET in each measurement, exhibiting a larger SUVmax, SUVmean and smaller lesion volume than phase-gated PET (Table I, Supplementary Figures 6 and 7 available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.926028>). All methods had a considerably larger SUVmax, SUVmean and smaller lesion volume compared to non-gated PET (Table I).

Discussion

In five-bin phase-gating the fraction of counts in a bin is 20%, if no cycles are discarded and if the gates

are divided equally. Increasing the number of gates will increase motion compensation but will also result to lower SNR, which will hinder visual interpretation and might cause variability in SUV measurements [17]. Each of the developed gating methods was able to preserve at least the required 20% in both the simulated and recorded respiratory signals and also in the patient study. Furthermore, in majority of cases the fraction of counts saved was 30% or more, allowing a reasonable trade-off between SNR and motion compensation. The liver SUV standard deviation measurements are also consistent with the fractions of counts saved in the patient signals.

Several methods to gate PET emission data with multiple or single breath holds have proven to preserve even a larger fraction of the emission data [13,14]. However, these methods need considerable patient-technologist co-operation, which might increase the variability in SUV measurements

Table I. Measured SUVmax and SUVmean values with each gating method.

Method	SUVmax g/ml (mean \pm SD)	SUVmean g/ml (mean \pm SD)	SUVmax change (%)	SUVmean change (%)	Volume change (%)
Non-gated PET	6.2 \pm 2.1	4.7 \pm 1.5	–	–	–
Phase-gated PET	8.0 \pm 2.7	5.6 \pm 1.9	16.16	16.00	–3.1
Minimum-constant (Gated CT)	8.2 \pm 2.5	5.7 \pm 1.7	17.64	17.65	–9.6
Slope-based (Gated CT)	8.2 \pm 2.6	5.7 \pm 1.8	17.94	18.60	–11.3
Amplitude-median (Gated CT)	8.4 \pm 2.7	5.8 \pm 1.8	19.34	19.23	–13.1
Minimum-constant (Average CT)	8.2 \pm 2.2	5.7 \pm 1.5	17.61	17.97	–16.8
Slope-based (Average CT)	8.1 \pm 2.3	5.7 \pm 1.6	17.05	17.49	–12.1
Amplitude-median (Average CT)	8.3 \pm 2.4	5.7 \pm 1.5	18.38	18.29	–19.0

if breath hold instructions are not followed accordingly. Additionally, not all patients may be able to produce optimal breath holds due to old age or existing pathology. The benefit of the end-expiratory gating compared to breath hold methods is the ability to acquire the PET and CT data in free breathing. Additionally, the spatial match between PET and CT is also improved.

In their article, Liu et al. proposed that end-expiratory gating methods could be improved by creating a weighted average CTAC or 4D CT for attenuation correction and encouraged further studies [15]. Based on the results, using either averaged CTAC or end-expiratory gated 4D-CTAC will result in similar increase in SUV_{max}, SUV_{mean} and reduction of lesion volume. Rosario et al. found similarly only small differences between phase-matched and mid-ventilation averaged attenuation correction, with the largest differences in the tumor volume between averaged and phased attenuation correction [18]. The minimal differences between average CTAC and end-expiratory gated 4D-CTAC are therefore consistent with their findings (Table I).

Additionally, the PET-CT match is improved when using either of the methods, based on the visual analysis. However, with mobile tumors residing in the vicinity of large density differences, end-expiratory 4D-CTAC combined with end-expiratory PET should provide the most accurate estimate of the tumor SUV recovery [19]. With large, immobile tumors the average attenuation correction (average CTAC) should give the correct result as it is nearly the same as end-expiratory attenuation correction [19]. Therefore, average CTAC can be recommended as an alternative where 4D CT is not technically possible.

Gating of both PET and CT to the end-expiratory phase improved quantitative accuracy or offered similar accuracy compared to standard phase-gated PET in all tested cases except one, when the most appropriate method for gating the respiratory signal in question is selected. This is expected, since each method was specifically developed to be suitable for various types of respiratory signals commonly encountered in patients (Supplementary Table I available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.926028>). Additionally, the quantitative accuracy of each method could be improved by patient-specific tuning of the method-specific parameters. To ease the selection of the appropriate gating settings, the gating settings should be automatically determined for the respiratory signal in question.

However, in the evaluation of treatment response and especially when using 4D PET/CT for radiotherapy planning a set of standardized parameters

and methods are needed to minimize SUV and volume variations between sessions [20–22]. Theoretically, end-expiratory gating should produce more consistent results between imaging sessions. The quality and reproducibility of the respiratory signal recording and the reproducibility of the extracted respiratory period will have an effect on the SUV and lesion volume measurements between consecutive treatment and imaging sessions [20,21]. Ultimately, the most suitable method for end-expiratory gating will have the smallest variability between consecutive sessions.

A limitation of the end-expiratory gating is similar as in methods using multiple or single breath holds [13,14]. In both, only a single PET bin is produced by the image reconstruction which does not allow quantifying tumor motion from PET. Therefore, tumor motion has to be quantified from the 4D CT series alone as motion information is commonly desired for radiotherapy planning [20–22]. This might eventually limit the applicability of end-expiratory gated PET in radiotherapy planning. Thus, studies on applicability of end-expiratory gated PET in radiotherapy planning are therefore highly encouraged.

It should be noted that the respiratory trace quality and the internal tumor motion also play a large role in efficiency of respiratory gating. Assuring a successful recording of a regular breathing pattern is essential [21]. In this study, it was clearly seen that each method performs slightly differently in individual subjects, although all methods were able to achieve a similar accuracy on average. This is expected, as each method was designed to be optimal for a certain type of respiratory trace.

Therefore, it is expected that not all patient cases will exhibit a large SUV increase due to imperfect external-internal motion correlation between the optical marker and tumor motion. The exact knowledge of tumor motion would have to be derived from raw PET data [23]. Methods which use this knowledge improving correlation of external gating signal should therefore be even more effective. Additionally, due to the small size of the patient group in this feasibility study, a larger clinical study of the applicability of end-expiratory gating for gated PET/CT is warranted.

In conclusion, three methods for end-expiratory respiratory gating in PET/CT were successfully developed and applied in a patient study. All methods were superior in quantitative accuracy when compared against non-gated PET. Quantitative accuracy and image quality over phase-gated PET is improved when the most suitable method for the respiratory signal in question is selected. Using either averaged CTAC or end-expiratory gated 4D-CTAC for PET

attenuation correction will result in increase of SUV_{max} and SUV_{mean} and reduction of lesion volume, while using end-expiratory gated 4D-CTAC will result in larger SUV_{max} and SUV_{mean} over averaged CTAC.

Acknowledgements

The study was conducted within the Finnish Center of Excellence in Molecular Imaging in Cardiovascular and Metabolic Research and strategic Japanese-Finnish research cooperative program on “Application of Medical ICT Devices” supported both by the Academy of Finland, University of Turku, Turku University Hospital and Åbo Akademi University. This work was partly funded by Kuopio University Hospital (EVO, project 5031345), Academy of Finland (International Doctoral Programme in Biomedical Engineering and Medical Physics), Oskar Öflunds Stiftelse and Instrumentarium Science Foundation. Finally, the authors thank GE Healthcare for providing the RGT software in our use.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- [1] Liu C, Pierce LA 2nd, Alessio AM, Kinahan PE. The impact of respiratory motion on tumor quantification and delineation in static PET/CT imaging. *Phys Med Biol* 2009;54:7345–62.
- [2] Park S-J, Ionascu D, Killoran J, Mamede M, Gerbaudo VH, Chin L, et al. Evaluation of the combined effects of target size, respiratory motion and background activity on 3D and 4D PET/CT images. *Phys Med Biol* 2008;53:3661–79.
- [3] Pevsner A, Nehmeh SA, Humm JL, Mageras GS, Erdi YE. Effect of motion on tracer activity determination in CT attenuation corrected PET images: A lung phantom study. *Med Phys* 2005;32:2358–62.
- [4] Teo B-K, Saboury B, Munbodh R, Scheuermann J, Torigian DA, Zaidi H, et al. The effect of breathing irregularities on quantitative accuracy of respiratory gated PET/CT. *Med Phys* 2012;39:7390–7.
- [5] Dawood M, Büther F, Lang N, Schober O, Schäfers KP. Respiratory gating in positron emission tomography: A quantitative comparison of different gating schemes. *Med Phys* 2007;34:3067–76.
- [6] Nehmeh SA, Erdi YE, Ling CC, Rosenzweig KE, Schoder H, Larson SM, et al. Effect of respiratory gating on quantifying PET images of lung cancer. *J Nucl Med* 2002;43:876–81.
- [7] Nehmeh SA, Erdi YE, Pan T, Pevsner A, Rosenzweig KE, Yorke E, et al. Four-dimensional (4D) PET/CT imaging of the thorax. *Med Phys* 2004;31:3179–86.
- [8] Pan T, Mawlawi O, Luo D, Liu HH, Chi P-CM, Mar MV, et al. Attenuation correction of PET cardiac data with low-dose average CT in PET/CT. *Med Phys* 2006;33:3931–8.
- [9] Pan T, Mawlawi O, Nehmeh SA, Erdi YE, Luo D, Liu HH, et al. Attenuation correction of PET images with respiration-averaged CT images in PET/CT. *J Nucl Med* 2005;46:1481–7.
- [10] Chi P-CM, Mawlawi O, Nehmeh SA, Erdi YE, Balter PA, Luo D, et al. Design of respiration averaged CT for attenuation correction of the PET data from PET/CT. *Med Phys* 2007;34:2039–47.
- [11] Abdelnour AF, Nehmeh SA, Pan T, Humm JL, Vernon P, Schöder H, et al. Phase and amplitude binning for 4D-CT imaging. *Phys Med Biol* 2007 21;52:3515–29.
- [12] Van Elmpt W, Hamill J, Jones J, De Ruyscher D, Lambin P, Ollers M. Optimal gating compared to 3D and 4D PET reconstruction for characterization of lung tumours. *Eur J Nucl Med Mol Imaging* 2011;38:843–55.
- [13] Kawano T, Ohtake E, Inoue T. Deep-inspiration breath-hold PET/CT of lung cancer: Maximum standardized uptake value analysis of 108 patients. *J Nucl Med* 2008;49:1223–31.
- [14] Nehmeh SA, Erdi YE, Meirelles GSP, Squire O, Larson SM, Humm JL, et al. Deep-inspiration breath-hold PET/CT of the thorax. *J Nucl Med* 2007;48:22–6.
- [15] Liu C, Alessio A, Pierce L, Thielemans K, Wollenweber S, Ganin A, et al. Quiescent period respiratory gating for PET/CT. *Med Phys* 2010;37:5037–43.
- [16] Bettinardi V, Presotto L, Rapisarda E, Picchio M, Gianolli L, Gilardi MC. Physical performance of the new hybrid PET/CT Discovery-690. *Med Phys* 2011;38:5394–411.
- [17] Lodge MA, Chaudhry MA, Wahl RL. Noise considerations for PET quantification using maximum and peak standardized uptake value. *J Nucl Med* 2012;53:1041–7.
- [18] Rosario T, Ollers MC, Bosmans G, De Ruyscher D, Lambin P, Dekker A. Phased versus midventilation attenuation-corrected respiration-correlated PET for patients with non-small cell lung cancer. *J Nucl Med Technol* 2009;37:208–14.
- [19] Hamill JJ, Bosmans G, Dekker A. Respiratory-gated CT as a tool for the simulation of breathing artifacts in PET and PET/CT. *Med Phys* 2008;35:576–85.
- [20] Aristophanous M, Berbeco RI, Killoran JH, Yap JT, Sher DJ, Allen AM, et al. Clinical utility of 4D FDG-PET/CT scans in radiation treatment planning. *Int J Rad Oncol Biol Phys* 2012;82:e99–105.
- [21] Bettinardi V, Picchio M, Di Muzio N, Gianolli L, Gilardi MC, Messa C. Detection and compensation of organ/lesion motion using 4D-PET/CT respiratory gated acquisition techniques. *Radiother Oncol* 2010;96:311–6.
- [22] Jacob V, Astner ST, Bundschuh RA, Busch R, Souvatzoglou M, Wendl C, et al. Evaluation of the SUV values calculation and 4D PET integration in the radiotherapy treatment planning system. *Radiother Oncol* 2011; 98:323–9.
- [23] Liu C, Alessio AM, Kinahan PE. Respiratory motion correction for quantitative PET/CT using all detected events with internal-external motion correlation. *Med Phys* 2011;38: 2715–23.

Supplementary material available online

Supplementary Figures 1–7 and Table I.