Journal of Medical Imaging

MedicalImaging.SPIEDigitalLibrary.org

Assessment of patient selection criteria for quantitative imaging with respiratory-gated positron emission tomography

Stephen R. Bowen
Larry A. Pierce
Adam M. Alessio
Chi Liu
Scott D. Wollenweber
Charles W. Stearns
Paul E. Kinahan

Assessment of patient selection criteria for quantitative imaging with respiratory-gated positron emission tomography

Stephen R. Bowen,^{a,b,*} Larry A. Pierce,^b Adam M. Alessio,^b Chi Liu,^c Scott D. Wollenweber,^d Charles W. Stearns,^d and Paul E. Kinahan^b

^aUniversity of Washington School of Medicine, Department of Radiation Oncology, 1959 NE Pacific St, Seattle, Washington 98195, United States

^bUniversity of Washington School of Medicine, Department of Radiology, 1959 NE Pacific St, Seattle, Washington 98195, United States

^cYale University School of Medicine, Department of Diagnostic Radiology, New Haven, Connecticut 06510, United States

^dGE Healthcare, Waukesha, Wisconsin 53188, United States

Abstract. The objective of this investigation was to propose techniques for determining which patients are likely to benefit from quantitative respiratory-gated imaging by correlating respiratory patterns to changes in positron emission tomography (PET) metrics. Twenty-six lung and liver cancer patients underwent PET/computed tomography exams with recorded chest/abdominal displacements. Static and adaptive amplitude-gated [¹⁸F]fluoro-D-glucose (FDG) PET images were generated from list-mode acquisitions. Patients were grouped by respiratory pattern, lesion location, or degree of lesion attachment to anatomical structures. Respiratory pattern metrics were calculated during time intervals corresponding to PET field of views over lesions of interest. FDG PET images were quantified by lesion maximum standardized uptake value (SUV_{max}). Relative changes in SUV_{max} between static and gated PET images were tested for association to respiratory pattern metrics. Lower lung lesions and liver lesions had significantly higher changes in SUV_{max} than upper lung lesions (14 versus 3%, $p < 0.0001$). Correlation was highest (0.42 ± 0.10 , $r^2 = 0.59$, $p < 0.003$) between changes in SUV_{max} and non-standard respiratory pattern metrics. Lesion location had a significant impact on changes in PET quantification due to respiratory gating. Respiratory pattern metrics were correlated to changes in SUV_{max}, though sample size limited statistical power. Validation in larger cohorts may enable selection of patients prior to acquisition who would benefit from respiratory-gated PET imaging. © 2014 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.1.2.026001]

Keywords: positron emission tomography/computed tomography; 2-deoxy-2-[¹⁸F]fluoro-D-glucose; respiratory gating; patient selection.

Paper 14067RR received May 27, 2014; revised manuscript received Sep. 3, 2014; accepted for publication Sep. 3, 2014; published online Sep. 24, 2014.

1 Introduction

Positron emission tomography (PET) and computed tomography (CT) multimodality imaging have emerged as powerful tools for detection and staging of abdominothoracic cancer patients due to their high diagnostic and prognostic value.^{1,2} However, the expansion of PET/CT into quantitative applications for defining therapeutic target volumes^{3–5} and assessing therapeutic response⁶ has been limited in these disease sites due, in part, to uncertainties from respiratory-induced tumor motion.⁷ Static motion-blurred PET/CT images can artificially reduce apparent lesion uptake, increase apparent tracer-avid lesion volumes, and produce artifacts from mismatched CT-based attenuation correction.⁸ Respiratory gating in PET/CT is a technological advance with the potential of reducing this source of quantitative uncertainty through the compensation of respiratory-induced tumor motion.^{9,10}

Despite the potential for improvements in quantitative accuracy from respiratory-gated PET/CT,^{11–13} particularly for the definition of biological target volumes,¹⁴ its clinical utility varies tremendously due, in part, to patient-specific factors relating to the magnitude and variation in respiratory motion. While respiratory-gated PET/CT may increase contrast between tracer-avid

lesions and background, in some patients it may only lead to increased image noise levels with no contrast improvement.⁸ Patients who are poor candidates for single-bin or multibin respiratory gating under free-breathing conditions due to irregular respiratory patterns may instead benefit from static imaging with invasive motion suppression devices that apply abdominal compression or force a breath hold.^{15,16} A decision between free-breathing respiratory-gated and motion-suppressed static image acquisition would ideally be made *a priori* in order to avoid unnecessary scans and promote recent initiatives to image wisely. Therefore, a key question is which patients are likely to benefit from free-breathing respiratory-gated PET/CT imaging? Some form of patient classification is needed to decide between various motion compensation and motion suppression strategies to enable personalized PET/CT acquisition of abdominothoracic cancers.¹⁷

Several patient classification strategies for respiratory-gated PET/CT are conceivable. Prior investigations on signal processing of respiratory traces revealed that patients may be grouped into three broad categories: 60% of patients can be classified as periodic breathers with reproducible end-expiration displacement (type 1), 20% as periodic breathers with normal (Gaussian)

*Address all correspondence to: Stephen R. Bowen, E-mail: srbowen@uw.edu

distributions of end-expiration displacement (type 2), and 20% as chaotic breathers (type 3).⁸ Further evidence suggests that respiratory-induced tumor motion may be a strong function of location within the lung or proximity to the diaphragm.¹⁸ However, it is still unknown whether classification schemes would impact quantitative differences in PET images.

The purpose of this study is to propose preliminary quantitative and reproducible selection methods with the potential to determine which patients are likely to benefit from respiratory motion compensation during PET/CT acquisition. To that end, patients were first grouped according to classifiers related to respiratory pattern and CT-based lesion factors. These subpopulations were subsequently analyzed for correlations between respiratory pattern features and quantitative improvements in respiratory-gated PET/CT images relative to static PET/CT.

2 Materials and Methods

Twenty-six lung and liver cancer patients with confirmed lesions based on prior diagnostic exam reports underwent PET/CT examinations, during which time-dependent traces of abdominal displacement as a surrogate for respiratory motion were recorded with the Real-time Position Management™ (RPM, Varian Inc., Santa Clara, California, USA) infrared camera and reflective marker block system.¹⁶ Prior CT images were also reviewed for potential patient classification parameters. Retrospective patient data review and analysis was conducted under approval from the local Institutional Review Board and complied with the Health Insurance Portability and Accountability Act.

2.1 Patient Respiratory Traces

Respiratory traces were analyzed over time courses corresponding to the PET acquisition that contained each lesion of interest, shown for an example patient in Fig. 1. This technique ensured that the extraneous portion of the respiratory signal [Fig. 1(a), blue curve] not contributing to changes in image quantification was omitted from the analysis, leaving a reduced time interval at a single PET bed position [Fig. 1(a), green curve]. This was achieved by matching time intervals from the Varian RPM

trace, sampled at 30 Hz, to those in the list-mode PET data during the lesion-containing axial field of view. Patients were grouped using a classification scheme⁸ into type 1 breathers with regular end-expiration displacements [Fig. 1(c)] and type 2 or 3 breathers with irregular distributed displacement [Fig. 1(b)].

2.2 PET Image Acquisition and Reconstruction

Patients were injected with 370 MBq (nominal) of 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) and scanned on a Discovery STE™ PET/CT scanner (GE Healthcare, Waukesha, Wisconsin, USA).¹⁹ The majority of patient scans ($n = 24$) were acquired with whole-body two-dimensional (2-D) PET list-mode data at 60 min postinjection for 7 min per bed position. Two additional patient scans were acquired with three-dimensional (3-D) PET list-mode data at 95 min postinjection for 5 min per bed position, which were included to augment the number of studies. Static sinograms were generated via conventional rebinning of list-mode data. Gated sinograms were generated retrospectively by sorting the same list-mode data for each patient scan according to the cycle-based quiescent period gating (QPG) method.²⁰ Cycle QPG was designed to optimize the tradeoff between noise and motion blurring by collecting PET list-mode data that corresponded to the lowest 20% of the cycle-to-cycle amplitude range. For most patients, the resulting images include approximately half of the PET coincidence events (minimal noise increase) and 20% of the relative motion events (minimal motion blurring).²⁰ All static and gated images were attenuation-corrected with helical CT or phase-averaged cine CT,²¹ reconstructed with ordered subset expectation-maximization over 2 iterations and 28 subsets,²² filtered with a 6-mm-wide Gaussian postreconstruction filter, and sampled onto a 70-cm transverse field-of-view grid of 3.65 mm × 3.65 mm × 3.27 mm voxels. Sample images are shown in Fig. 2.

2.3 Statistical Analysis

The metric used to assess quantitative improvement in respiratory-gated PET images was the following:

Fig. 1 Respiratory trace analysis on specific positron emission tomography (PET) bed positions of interest. For the same patient, analysis over the duration of the whole-body PET scan [(a), blue trace] results in significant baseline signal drift and an irregular breathing pattern (b). However, restricting analysis over the duration of the PET axial field of view that contains the lesion of interest reduces baseline signal drift [(a), green trace section] and produces a regular displacement histogram (c). Such variations in respiratory pattern are patient-specific. Solid red lines denote mean displacement and dashed red lines denote standard deviation.

Fig. 2 Example static and cycle quiescent period gating (QPG) PET patient coronal maximum intensity projection images with color bar in units of standardized uptake value (SUV). A patient with liver lesions displays significant increase in maximum SUV and lesion contrast recovery through motion blurring reduction between static ($SUV_{\max} = 9.5$) (a) and cycle QPG ($SUV_{\max} = 15.3$, 60% increase) (b) PET images (arrows). A patient with a mediastinal lung lesion shows insignificant changes quantitatively between static (c) and cycle QPG (d) PET images. High interpatient variability in efficacy of respiratory-gated PET motivates the need for patient selection methods and guidelines.

$$\text{Relative change in } SUV_{\max} \equiv \frac{SUV_{\max}^{\text{gated}} - SUV_{\max}^{\text{static}}}{SUV_{\max}^{\text{static}}}. \quad (1)$$

A key strength of this metric is that relative changes between static and respiratory-gated SUV metrics were calculated on a per-patient basis from identical list-mode data and CT attenuation correction, which builds in a patient-specific control. Several patient classifiers were tested for subpopulation mean differences using an independent two-sample and two-sided t test: respiratory trace type ($n = 17$ type 1 regular breathers versus $n = 9$ type 2 or 3 irregular breathers), CT-defined location of lesions ($n = 15$ lower lung lesions and liver lesions versus $n = 11$ upper lung lesions), and CT-defined detached lesions ($n = 15$ detached lesions versus $n = 11$ attached lesions). Lesion location was assigned to the lower lung lesions and liver group if the center of mass on CT resided inferior to the axial plane that bisects the lung (i.e., distance from lung apex to lesion centroid $>$ half distance from lung apex to diaphragm dome). Lesions were considered detached if no visible soft tissue connected the mediastinum or chest wall to the lesion on a lung window CT.

Tests of statistical correlation between respiratory parameters and relative changes in $SUV_{\max}$ were conducted using univariate and multivariate linear regressions. The following parameters were included in the regression models: mean respiratory trace amplitude, amplitude:diameter ratio, motion reduction, and the geometric mean of motion reduction and data fraction. The amplitude:diameter ratio was defined as the mean respiratory trace amplitude divided by the lesion longest axis on CT. Motion reduction was defined as the relative change in sample standard deviation between the total RPM-defined respiratory displacement distribution (s_T) and the cycle QPG bin respiratory displacement distribution (s_Q)

$$\text{Motion reduction} \equiv \frac{s_T - s_Q}{s_T}. \quad (2)$$

This is illustrated in Fig. 3 for two patients, showing their total displacement histograms (green) and cycle QPG

displacement histograms (blue) calibrated to the centimeter of marker motion. The patient in Fig. 3(a) has a narrower cycle QPG displacement histogram relative to the total displacement histogram, resulting in a high motion reduction of 80%. On the other hand, the patient in Fig. 3(b) has a lower integral cycle QPG displacement histogram but a similar width relative to the total displacement, resulting in a low motion reduction of 14%. Higher motion reduction was hypothesized to result in greater change in gated PET image $SUV_{\max}$ relative to the static PET. The last respiratory parameter was defined as the geometric mean of the motion reduction and cycle QPG time bin fraction of the total trace time.

Motion reduction and data fraction

$$\equiv \sqrt{\text{Motion reduction} \times \frac{\text{Cycle QPG time bin}}{\text{Total trace time}}}. \quad (3)$$

The geometric mean renormalizes the combined motion reduction and data fraction metrics onto a common scale where each percentage point increase in the macroparameter is equivalent to a percentage point increase in the individual parameters. This combined metric penalizes respiratory traces where the time spent in the cycle QPG bin represents a small fraction of the total trace time. While the average cycle QPG time bin represented half of the total trace time on average, the patient in Fig. 3(b) has significantly fewer total counts in the cycle QPG displacement histogram, indicating low data fraction retained. A higher geometric mean of motion reduction and data fraction was hypothesized to correspond to greater changes in gated PET quantification.

Finally, respiratory parameter threshold sensitivity and specificity for predicting relative changes in $SUV_{\max}$ cutoffs were calculated as an alternative to continuous linear associations. This was achieved by fixing the change in $SUV_{\max}$ for the patient population and varying each respiratory parameter value to maximize its accuracy in separating patient groups above and below the $SUV_{\max}$ change cutoff.

Fig. 3 Motion reduction metric for two example patients, calculated as the relative change in deviation between the total Real-Time Position Management™ trace displacement distribution (green histogram) and the cycle QPG bin displacement distribution (blue histogram). The liver lesion patient had high motion reduction of 80% between displacement distributions (a), whereas the mediastinal lung lesion patient has low motion reduction of 14% (b).

The effectiveness of patient classifiers was determined from statistical separation between subpopulation group means. These classifiers were used to define a subpopulation of patients on which to conduct linear univariate and multivariate regression analysis between respiratory parameters and PET parameters. Furthermore, rudimentary thresholds in respiratory parameters were sought out to refine patient selection guidelines.

3 Results

3.1 Patient Class Statistical Separation

Statistical distributions of relative change in SUV_{max} are shown for patient groups when classified by trace type, lesion location, and lesion degree of attachment (Fig. 4). Type 1 regular breathers had higher relative changes in SUV_{max} compared to type 2 or 3 irregular breathers (11 versus 7%), and detached lesions had higher relative changes in SUV_{max} compared to attached lesions (12 versus 6%), but these differences did not reach statistical significance in an independent two-sample t test ($p > 0.08$). Lower lung lesions and liver lesions, on average, had higher relative changes in SUV_{max} than upper lung lesions (14 versus 3%, $p < 0.0001$). Note that for the cohort of lower lung lesions and liver lesion patients, the interpatient variability in SUV_{max} change is large (interquartile range = 17%, range = 27%).

3.2 Linear Regression of Relative SUV_{max} Changes Versus Respiratory Parameters

Once patients were grouped using lesion location, linear associations between the variance in respiratory parameters and variance in SUV_{max} change were computed. The fitted parameters are reported in Fig. 5 for lower lung lesions and liver sites (blue markers and trend lines) and upper lung sites (red markers and trend lines). Each marker represents a patient lesion relative change in SUV_{max} versus trace amplitude [Fig. 5(a)], relative change in SUV_{max} versus motion reduction [Fig. 5(b)], relative change in SUV_{max} versus amplitude:diameter ratio [Fig. 5(c)], and relative change in SUV_{max} versus the geometric mean of motion reduction and data fraction [Fig. 5(d)]. For visual reference, markers contain labels of respiratory pattern (type 1 to 3). Type 1 regular breathers with lower lung or liver lesions primarily occupy the upper right quadrant of Fig. 5(d) that is characterized by high the relative change in SUV_{max} and high geometric mean of motion reduction and data fraction. Type 2 or 3 irregular breathers with lower lung or liver lesions occupy the lower left quadrant of Fig. 5(d) that is characterized by the low relative change in SUV_{max} and low geometric mean of motion reduction and data fraction. Due to missing or spurious signals from the RPM camera, the motion reduction and data fraction metrics could not be accurately calculated for three patients, who were censored from the remaining analysis.

Fig. 4 Comparison of patient subpopulation relative changes in SUV_{max} grouped by respiratory trace type (a), lesion location (b), and lesion translational freedom (c). Distribution means (markers), medians (middle lines), lower/upper quartiles (boxes), and ranges (whiskers) are denoted for every patient subpopulation. Only lesion location separated patient changes in SUV_{max} with statistical significance ($p < 0.0001$). N.S., not significant at 0.05 level.

Fig. 5 Linear associations between respiratory trace parameters and relative changes in SUV_{max} . Linear regression coefficients and standard errors were calculated for lower lung lesions and liver lesions (blue markers and lines) and upper lung lesions (red markers and lines). Trace type (1 to 3) is denoted by marker labels as an additional visual reference. Both the motion reduction metric ($r^2 = 0.33$, $p < 0.03$) and geometric mean of motion reduction and data fraction metric ($r^2 = 0.59$, $p < 0.003$) show significant linear association to $\% \Delta SUV_{max}$ in lower lung lesions and liver lesions, making them potential predictive parameters for respiratory-gated PET patient selection. *N.S.*, not significant at 0.05 level.

Neither the amplitude nor amplitude:diameter ratio was found to correlate to changes in SUV_{max} . Both the motion reduction metric ($r^2 = 0.33$, $p < 0.03$) and geometric mean of motion reduction and data fraction metric ($r^2 = 0.59$, $p < 0.003$) were correlated to relative changes in SUV_{max} for lower lung lesions and liver lesions. In particular, for every 10% increase in the geometric mean of motion reduction and data fraction, there was a 4.2% increase in the relative SUV_{max} changes. Note that the variance in all respiratory parameters for upper lung lesion patients was independent of relative changes in SUV_{max} , with regression coefficients not significantly different from zero.

3.3 Multivariate Regression of Relative SUV_{max} Changes Versus Respiratory Parameters

Four pairings of respiratory parameters were tested for association to relative changes in SUV_{max} using multivariate regression models: (1) amplitude with motion reduction, (2) amplitude with motion reduction and data fraction, (3) amplitude:diameter ratio with motion reduction, and (4) amplitude:diameter ratio with motion reduction and data fraction. Only (4), shown in Table 1, increased the coefficient of determination relative to the univariate regression of Fig. 5 ($r^2_{multi} = 0.68$ versus $r^2_{uni} = 0.59$), but this increase in explained variance resulted in a slightly reduced statistical significance compared to the geometric mean of motion reduction and data fraction alone ($p < 0.005$ versus $p < 0.003$). Standard errors in multivariate

Table 1 Multivariate regression model of the percent increase in maximum standardized uptake value versus respiratory parameters ($r^2 = 0.68$, $p < 0.005$).

Respiratory parameter	Regression coefficient	Standard error
Amplitude:Diameter ratio	-0.31	±0.15
Motion reduction and data fraction	0.58	±0.12

regression coefficients also increased relative to univariate coefficients. Note that the regression coefficient for the amplitude:diameter ratio parameter is negative in the multivariate linear model compared to a positive value in the univariate linear model [Fig. 5(c)]. This implies that the variance in SUV_{max} change is explained primarily by the motion reduction and data fraction macroparameter, while amplitude:diameter ratio is a secondary explanatory variable.

3.4 Respiratory Parameter Thresholds for Patient Selection

As with regression for linear associations, the lower lung lesions and liver patient subpopulation was also analyzed for respiratory

Fig. 6 Respiratory trace metric values indexed across lower lung lesions and liver lesion patients by increasing relative change in SUV_{max} . Patient images are sorted into small changes in SUV_{max} (red markers), intermediate changes in SUV_{max} (gray markers), and large changes in SUV_{max} (blue markers). Of all metrics, only the geometric mean of motion reduction and data fraction (D) show a possible threshold for separating patients with large changes in SUV_{max} from those with intermediate/small changes.

parameter thresholds that may further enhance patient selection criteria. Patients were indexed by increasing relative changes in SUV_{max} , and their respiratory parameter values are shown in Fig. 6. A fourth patient was censored from this threshold analysis due to an asymptotically high amplitude:diameter ratio driven by uncertainty in estimation of a small lesion diameter. Visually, no discernible thresholds in mean trace amplitude, motion reduction, or amplitude:diameter ratio were evident across patients. The geometric mean of motion reduction and data fraction metric revealed a possible threshold by sorting patients above and below a relative change in SUV_{max} of 20% [Fig. 6(d), blue markers versus gray/red markers]. Specifically, a threshold of 42% in geometric mean of motion reduction and data fraction could separate the two small groups of patients with 100% (4/4) sensitivity and 86% (6/7) specificity. Note that these results for a limited sample size may not be robust to the interpatient variation in a larger population, but could point to a testable hypothesis that a threshold exists.

4 Discussion

To determine which abdominothoracic cancer patients are likely to benefit from respiratory-gated PET/CT under free-breathing conditions, this investigation developed selection methods based on respiratory patterns for prediction of quantitative changes in cycle QPG PET relative to static PET. Of the subpopulations, patients grouped by lesion location had the highest statistical separation in relative SUV_{max} changes between gated and static images. Upper lung lesions had minimal quantitative changes in cycle QPG PET/CT, making this patient group less likely to benefit from this type of respiratory gating. This has been identified in analyses of respiratory patterns and internal tumor trajectories,²³ but, to the authors' knowledge, has not previously

been shown from statistical analysis of differences in PET quantification.

The variance in SUV_{max} changes for lower lung lesions and liver lesion patients could be explained as a linear correlation to a single macroparameter: the geometric mean of motion reduction and data fraction. Furthermore, the association indicated a possible threshold by which to sort the small patient cohort. Common errors introduced by couch motion or patient chest wall drift in position, which would otherwise add unwanted variance to the data, were reduced when processing respiratory traces over time courses that corresponded to PET axial field of views that contained lesions of interest. The unexplained variance was also lowered by *a priori* knowledge of lesion characteristics from CT that subdivided the patient population.

Several limitations of this investigation should be noted. First and foremost, the statistical power to both classify patient subpopulations and associate respiratory parameters to imaging parameters was decreased by sample size, which was most evident in the multivariate regression models. Despite additional free parameters, the statistical significance was reduced compared to univariate regression due to model overfitting. The trends revealed in the study require larger-scale testing in order to boost statistical power necessary for multivariate modeling. To statistically power our study at the 90% level, we have estimated the minimum patient sample sizes to detect a given effect size for various hypothesis tests. Our preliminary data have shown an effect size of ~10% difference between respiratory-gated and static ungated FDG PET/CT uptake, with a variance in the data of the same 10% magnitude. Table 2 summarizes the power analysis for conducting the quantitative imaging trial. Testing for differences between group means by the *t* test (two-sided) is sufficiently powered by our current study on 26 patients, which supports our result that patients with lower lung/liver lesion have significantly higher change in FDG PET/CT uptake than patients with upper lung lesions. Detection of differences between group variances by the *F* test (two-sided) would require nearly 40 patients, while detection of differences in linear proportionality would require collecting data from ~200 patients.

Second, the use of one-dimensional chest/abdominal displacement traces as correlates of 3-D internal tumor motion is commonplace but may not always yield accurate results.^{24–26} The strength of this correlation is patient-specific as well as time-dependent during and between PET/CT acquisitions, which can lead to residual uncompensated motion in the lateral and anterior-posterior dimensions.²⁷ Third, SUV_{max} is known to be sensitive to noise,²⁸ which will tend to bias its absolute value in gated images.⁸ The investigation mitigated this source of error by using a gating scheme to retain, on average, half of the counts relative to static acquisitions. A separate analysis was conducted

Table 2 Sample size estimation to detect the effect of respiratory pattern metrics on respiratory-gated positron emission tomography quantification at a desired statistical power.

Statistical test	Alpha	Power	Sample size
Two-sample <i>t</i> test	0.05	0.9	23
Two-sample <i>F</i> test	0.05	0.9	37
Two-sample proportionality	0.05	0.9	188

using SUV_{peak} ,²⁹ which is considered less sensitive to statistical noise than SUV_{max} . This analysis yielded results and trends similar to those using SUV_{max} (data not shown), indicating that the chosen gating scheme is not biased from excessive noise.

Another consideration is the appropriate choice of CT-based attenuation correction (CTAC) and its impact on modeling the quantitative changes of respiratory-gated PET. Ideally, static PET images should be corrected by a motion-averaged CTAC, while gated PET should be corrected by a phase- or amplitude-matched CTAC. This study included patients undergoing routine diagnostic PET scans in which low dose helical CTAC was indicated, while others were scanned with multibin respiratory-gated cine CTAC. By implementing a relative measure of change between static and gated SUV from the same list-mode data, along with an identical attenuation correction image, the investigation kept the magnitude of this error constant. In lung lesions surrounded by lower-density tissue, mismatches in CTAC reduce the apparent differences in image uptake between static and respiratory-gated PET scans, while in liver lesions, the effect is negligible due to more homogeneous attenuation through soft tissue. Nevertheless, statistical associations between respiratory pattern metrics and imaging metrics still emerged, indicating that absolute errors in attenuation correction might be mitigated by the use of relative quantitative changes. This also applies to differences in PET acquisition mode (2-D versus 3-D mode) that can affect absolute SUV quantification. Without ground truth measurements of SUV_{max} for different acquisition and CTAC modes under motionless conditions against which to compare, the reported relative changes between static and gated images do not represent improvements in absolute accuracy but rather patient-specific variations linked to respiratory motion. A future study to validate these methods would not mix different modes of acquisition and CTAC in the patient cohort, but instead would standardize them for static and respiratory-gated PET images.

Clinicians who depend on quantitatively accurate PET/CT images are often challenged by decisions on how best to manage respiratory motion during image acquisition. Erroneous changes of SUV due to respiratory motion may not affect diagnosis, but can confound quantitative longitudinal studies that monitor disease progression or assess response to therapy. Respiratory-gated PET corrected for attenuation by respiratory-gated cine CT provides higher potential accuracy in treatment response assessment than static motion-blurred PET/CT; the former is also burdened by increased complexity to minimize errors due to motion mismatch between PET and CT images. The tradeoff between accuracy and reproducibility of gated and static PET is also confounded by changes in patient respiratory patterns over the course of treatment, which may no longer blur a static PET image in the same manner as at baseline. Respiratory gating methods, such as cycle QPG, account for low-frequency drifts and gate PET images based on relative amplitude, making them more robust to intrascan and interscan variation in respiratory pattern for treatment response assessment.

The ability to identify patients with a predicted benefit in quantitative assessment from respiratory-gated PET/CT can streamline clinical workflows while personalizing patient care. Alternatively, patients whose respiratory-gated PET/CT is predicted to be ineffective due to irregular breathing patterns can be triaged to other forms of motion management. In clinical workflows that do not require a decision between free-breathing

respiratory-gated image acquisition and motion-suppressed image acquisition *a priori*, patient selection methods may be applied to the PET list-mode data *a posteriori* to estimate the utility of respiratory-gated image reconstruction relative to static image reconstruction. Rather than seek a single solution to motion compensation in PET/CT for all abdominal and thoracic cancer patients, physicians can increasingly rely on quantitative selection criteria that maximize the rate of clinical success.

The results point to a possible quantitative patient selection algorithm for cycle QPG PET/CT acquisitions, which would involve the (1) calculation of the lesion center-of-mass location on diagnostic CT to identify only lower lung or liver lesions, (2) collection of a sample respiratory pattern prior to PET/CT acquisition (~5 min) with the patient in the scanning position, (3) estimation of the geometric mean of motion reduction and data fraction metric for the pattern with baseline correction, if necessary, to overcome limited respiratory trace sampling, and (4) clinical decision to either perform a cycle QPG PET/CT scan under free-breathing conditions or to invasively suppress respiratory motion. In the event that a recent diagnostic CT is not available for lesion location determination, clinical practice may need to be altered to accommodate the interpretation of a diagnostic CT prior to the PET acquisition. The duration of the preliminary respiratory pattern and motion assessment can contribute to unintended consequences that must be considered for the image acquisition, such as patient discomfort and reduced scanning throughput.

While the methodology of this investigation is generalizable to other respiratory gating techniques, the fitted model parameters would likely vary between them to form unique patient selection models. For instance, equal count binning schemes that use a fixed percentage of data, as well as motion correction of all detected events via registration to a reference respiratory phase,³⁰⁻³² would not have variance in the data fraction metric, but would still be affected by the motion reduction metric. Such respiratory motion correction algorithms could be validated prospectively on a larger patient population as a part of a future investigation.

5 Conclusions

The observed statistical trends in this investigation support quantitative classification schemes over qualitative one-size-fits-all solutions for patients undergoing respiratory-gated PET/CT imaging. Regression modeling can be validated in a larger patient population and generalized for prediction of quantitative changes from different respiratory motion compensation approaches. Patient selection algorithms form the foundation for future motion-managed PET/CT protocols that increase the quantitative accuracy with which clinicians define biological targets and assess response to therapy.

Acknowledgments

This work was supported by a research contract from GE Healthcare (Waukesha, Wisconsin). The authors are grateful to Koji Iwata and Beilei Wang for insightful discussions.

References

1. J. F. Vansteenkiste et al., "Lymph node staging in non-small-cell lung cancer with FDG-PET scan: a prospective study on 690 lymph node stations from 68 patients," *J. Clin. Oncol.* **16**(6), 2142-2149 (1998).

2. Y. Imamura et al., "Prognostic value of SUV_{max} measurements obtained by FDG-PET in patients with non-small cell lung cancer receiving chemotherapy," *Lung Cancer* **71**(1), 49–54 (2011).
3. C. B. Caldwell et al., "Observer variation in contouring gross tumor volume in patients with poorly defined non-small-cell lung tumors on CT: the impact of 18FDG-hybrid PET fusion," *Int. J. Radiat. Oncol. Biol. Phys.* **51**(4), 923–931 (2001).
4. S. Senan and D. De Ruysscher, "Critical review of PET-CT for radiotherapy planning in lung cancer," *Crit. Rev. Oncol. Hematol.* **56**(3), 345–351 (2005).
5. V. Bettinardi et al., "PET/CT for radiotherapy: image acquisition and data processing," *Q. J. Nucl. Med. Mol. Imaging* **54**(5), 455–475 (2010).
6. N. E. Avril and W. A. Weber, "Monitoring response to treatment in patients utilizing PET," *Radiol. Clin. North Am.* **43**(1), 189–204 (2005).
7. S. A. Nehmeh et al., "Effect of respiratory gating on quantifying PET images of lung cancer," *J. Nucl. Med.* **43**(7), 876–881 (2002).
8. C. Liu et al., "The impact of respiratory motion on tumor quantification and delineation in static PET/CT imaging," *Phys. Med. Biol.* **54**(24), 7345–7362 (2009).
9. S. A. Nehmeh et al., "Reduction of respiratory motion artifacts in PET imaging of lung cancer by respiratory correlated dynamic PET: methodology and comparison with respiratory gated PET," *J. Nucl. Med.* **44**(10), 1644–1648 (2003).
10. M. Aristophanous et al., "Clinical utility of 4D FDG-PET/CT scans in radiation treatment planning," *Int. J. Radiat. Oncol. Biol. Phys.* **82**(1), e99–105 (2012).
11. V. Bettinardi et al., "Detection and compensation of organ/lesion motion using 4D-PET/CT respiratory gated acquisition techniques," *Radiother. Oncol.* **96**(3), 311–316 (2010).
12. V. Bettinardi et al., "Motion management in positron emission tomography/computed tomography for radiation treatment planning," *Semin. Nucl. Med.* **42**(5), 289–307 (2012).
13. L. Guerra et al., "Respiratory gated PET/CT in a European multicentre retrospective study: added diagnostic value in detection and characterization of lung lesions," *Eur. J. Nucl. Med. Mol. Imaging* **39**(9), 1381–1390 (2012).
14. M. Aristophanous et al., "Four-dimensional positron emission tomography: implications for dose painting of high-uptake regions," *Int. J. Radiat. Oncol. Biol. Phys.* **80**(3), 900–908 (2011).
15. J. W. Wong et al., "The use of active breathing control (ABC) to reduce margin for breathing motion," *Int. J. Radiat. Oncol. Biol. Phys.* **44**(4), 911–919 (1999).
16. P. J. Keall et al., "The management of respiratory motion in radiation oncology report of AAPM Task Group 76," *Med. Phys.* **33**(10), 3874–3900 (2006).
17. S. R. Bowen et al., "Challenges and opportunities in patient-specific, motion-managed, and PET/CT-guided radiation therapy of lung cancer: review and perspective," *Clin. Transl. Med.* **1**, 18 (2012).
18. S. S. Vedam et al., "Quantifying the predictability of diaphragm motion during respiration with a noninvasive external marker," *Med. Phys.* **30**, 505–513 (2003).
19. M. Teras et al., "Performance of the new generation of whole-body PET/CT scanners: discovery STE and discovery VCT," *Eur. J. Nucl. Med. Mol. Imaging* **34**(10), 1683–1692 (2007).
20. C. Liu et al., "Quiescent period respiratory gating for PET/CT," *Med. Phys.* **37**(9), 5037–5043 (2010).
21. J. H. Killoran et al., "Motion artifacts occurring at the lung/diaphragm interface using 4D CT attenuation correction of 4D PET scans," *J. Appl. Clin. Med. Phys.* **12**(4), 3502 (2011).
22. R. Boellaard, A. van Lingen, and A. A. Lammertsma, "Experimental and clinical evaluation of iterative reconstruction (OSEM) in dynamic PET: quantitative characteristics and effects on kinetic modeling," *J. Nucl. Med.* **42**(5), 808–817 (2001).
23. H. Shirato et al., "Intrafractional tumor motion: lung and liver," *Semin. Radiat. Oncol.* **14**(1), 10–18 (2004).
24. D. P. Gierga et al., "The correlation between internal and external markers for abdominal tumors: implications for respiratory gating," *Int. J. Radiat. Oncol. Biol. Phys.* **61**(5), 1551–1558 (2005).
25. D. Ionascu et al., "Internal-external correlation investigations of respiratory induced motion of lung tumors," *Med. Phys.* **34**(10), 3893–3903 (2007).
26. F. Ernst et al., "Correlation between external and internal respiratory motion: a validation study," *Int. J. Comput. Assist. Radiol. Surg.* **7**(3), 483–492 (2012).
27. R. I. Berbeco et al., "Residual motion of lung tumours in gated radiotherapy with external respiratory surrogates," *Phys. Med. Biol.* **50**(16), 3655–3667 (2005).
28. R. K. Doot et al., "Instrumentation factors affecting variance and bias of quantifying tracer uptake with PET/CT," *Med. Phys.* **37**, 6035–6046 (2010).
29. R. L. Wahl et al., "From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors," *J. Nucl. Med.* **50**(Suppl. 1), 122S–150S (2009).
30. M. Dawood et al., "Lung motion correction on respiratory gated 3-D PET/CT images," *IEEE Trans. Med. Imaging* **25**(4), 476–485 (2006).
31. M. Dawood et al., "Respiratory motion correction in 3-D PET data with advanced optical flow algorithms," *IEEE Trans. Med. Imaging* **27**(8), 1164–1175 (2008).
32. C. Liu, A. M. Alessio, and P. E. Kinahan, "Respiratory motion correction for quantitative PET/CT using all detected events with internal-external motion correlation," *Med. Phys.* **38**, 2715–2723 (2011).

Stephen R. Bowen is an assistant professor of medical physics in the Departments of Radiation Oncology and Radiology at the University of Washington. He received his PhD in medical physics at the University of Wisconsin in 2011. His current research interests include quantitative molecular imaging to guide personalized radiation therapy through tumor dose escalation and functional tissue avoidance.

Adam M. Alessio, PhD, is a research associate professor of radiology and adjunct associate professor of bioengineering and mechanical engineering at the University of Washington. He is involved in numerous translational research projects for topics including cardiac perfusion imaging, radiation dose optimization for PET and CT, and tomographic imaging. He received his PhD in electrical engineering from the University of Notre Dame and has been at UW since 2003. Details on Dr. Alessio's background can be found at <http://faculty.washington.edu/aalessio/>.

Charles W. Stearns, PhD, is chief engineer–PET at GE Healthcare in Waukesha, Wisconsin. He received his PhD in medical engineering from the Massachusetts Institute of Technology in 1990.

Paul E. Kinahan, PhD, FIEEE is a professor of radiology, bioengineering, and physics at the University of Washington. His research is centered around quantitative medical imaging.

Biographies for the other authors are not available.