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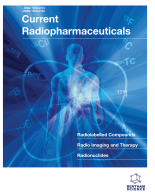
REVIEW ARTICLE

Respiratory Gating and the Performance of PET/CT in Pulmonary Lesions



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Abstract: ***Background:*** Motion artifacts related to the patient's breathing can be the cause of underestimation of the lesion uptake and can lead to missing of small lung lesions. The respiratory gating (RG) technology has demonstrated a significant increase in image quality.

Objective*:* The aim of this paper was to evaluate the advantages of RG technique on PET/CT performance in lung lesions. The impact of 4D-PET/CT on diagnosis (metabolic characterization), staging and re-staging lung cancer was also assessed, including its application for radiotherapy planning. Finally, new technologies for respiratory motion management were also discussed.

Methods*:* A comprehensive electronic search of the literature was performed by using Medline database (PubMed) searching "PET/CT", "gated" and "lung". Original articles, review articles, and editorials published in the last 10 years were selected, included and critically reviewed in order to select relevant articles.

Results: Many papers compared Standardized Uptake Value (SUV) in gated and ungated PET studies showing an increase in SUV of gated images, particularly for the small lesions located in medium and lower lung. In addition, other features as Metabolic Tumor Volume (MTV), Total Lesion Glycolysis (TLG) and textural-features presented differences when obtained from gated and ungated PET acquisitions. Besides the increase in quantification, gating techniques can determine an increase in the diagnostic accuracy of PET/CT. Gated PET/CT was evaluated for lung cancer staging, therapy response assessment and for radiation therapy planning.

Conclusion: New technologies able to track the motion of organs lesion directly from raw PET data, can reduce or definitively solve problems (*i.e.*: extended acquisition time, radiation exposure) currently limiting the use of gated PET/CT in clinical routine.

Keywords: PET/CT, respiratory gating, 4D-PET/TC, pulmonary lesions, lung cancer, radiomics.

1. INTRODUCTION

[18F]-fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT) is widely used for the characterization of lung nodules and for staging patients with primary lung cancer. However, the motion of organs during patient breathing can degrade the quality of PET/CT images particularly in the lower chest and upper abdomen [1]. Indeed, the relatively long duration of PET (several minutes), during which thoracic and abdominal lesions and organs are physiologically moving, can determine lesion blurring. CT acquisition performed in free breathing can be degraded by motion artifacts, mostly near the diaphragm; moreover CT captures the patient breathing cycle in an unknown single state. These phenomena decrease the intensity distribution in the reconstructed PET images and can be a source of PET and CT mismatch [2]. The consequence of the misalignment between PET and CT images can be an inaccurate attenuation correction map (AC) with image artifacts and incorrect quantification (*e.g.* SUV - Standardized Uptake Value) [3, 4]. These effects may reduce the diagnostic accuracy of PET/CT, mainly for small lesions that are usually more affected by the partial volume effect [5]. As quantitative indices in PET, such as SUV and total lesion glycolysis (TLG), can be used to monitor the therapeutic efficacy and to provide important prognostic information, great interest is focused on developing tools for motion correction. Up to date, many different tools have been proposed [6, 7], including respiratory gated-RG PET (4D-PET)/CT.

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The aim of this paper was to evaluate the advantages of RG technique on PET/CT performance in lung lesions. The impact of 4D-PET/CT on diagnosis (metabolic characterization), staging and re-staging lung cancer was assessed, including its application for radiotherapy planning. Finally, new technologies for respiratory motion management have also been discussed.

2. MATERIALS AND METHODS

A comprehensive electronic search of the literature was performed in September 2018, by using Medline database (PubMed) searching "PET/CT" and "gated" and "lung". Of the 94 references, all the abstracts available were reviewed by the authors, who examined in detail the most relevant full articles. Original articles, review articles, and editorials published in the last 10 years were included and critically reviewed in order to select relevant articles. Abstracts only and reports from meetings were excluded. Other relevant studies cited in the references of selected papers were also included. A systematic review was not performed, but articles were analysed by authors with the aim to summarize the role of 4D-PET/CT through different phases of management of lung lesions, from diagnosis to treatment.

2.1. 4D-Respiratory Gated PET/CT Techniques

4D-PET/CT technique, by synchronization of PET and CT acquisition to respiratory motion, is a valid tool for improving image quality and lesion characterization. Established hardware gating technology typically tracks the patient's breathing cycle by external sensors, such as a) an elastic belt with associated pressure sensors which fits over the chest, b) infrared markers placed on patient's chest wall, c) sensors measuring air temperature changes during respiration, d) spirometer estimating the volume of air inhaled or exhaled during breathing. RG is achieved through the definition of the patient's respiratory cycle used to reconstruct image data into portions (bins) of the range of amplitude (amplitude-based gating) or the breathing cycle (phase-based gating) [8].

In both options, only counts emitted during the selected interval will be used in the post-processing and image visualization. RG motion management solution is usually based on LIST mode acquisition of PET Field of View (4D FOVs), centered on the anatomical region of interest; the breathing curve is registered by an external tracking device and the PET data acquisition is synchronized with the patient's breathing curve. In this way, PET images are linked not only to the time and spatial position but also to the corresponding breathing phase. The 4D FOVs acquisition time has to be selected in order to have adequate count statistics; as a practical rule, the count statistics of each phase should be similar to the count statistics of a standard Whole-Body FOV and so the 4D PET acquisition should have a duration equal to the number of the phases multiplied by the time of the standard FOV. For example, if the standard time/FOV is 90 seconds and 6 phases are expected from the RG protocol, the total duration of the 4D FOV should be 9 minutes (90 seconds x 6 phases). Commonly, the phases are set between 4 and 10 with each phase visualized separately as a static 3D PET image; a higher value gives more accurate temporal resolution and more precise definition of organs motion but also consistently increases the PET acquisition time. The extended time related to 4D PET acquisition can be a constrain to use RG protocol in patients not compliant and can impact on routine clinical workflow. A Cine CT scan is acquired covering the same 4D PET anatomical volume. The gated PET bins are amplitude or phase matched to appropriate CT bins for attenuation correction [6].

2.1.1. 4D-PET/CT for Lung Lesion Characterization

The intensity of FDG uptake of a pulmonary lesion is crucial since it is the base for the nodule classification and consequently impacts on the management of the patient (follow-up or biopsy, respectively) [9]. The respiratory motion not only causes a distortion in the lesion morphology with worse shape definition but also can decrease the FDG activity detected, possibly limiting the sensitivity of PET/CT [10].

The increase in quantification (SUVmax) is one of the most important benefits obtained from gated technique, as shown by published papers in Table **1** [5, 9, 11-18].

The mean rate of increase of SUVmax for lung lesions ranged from 4 to 83%. Park *et al*. [19] found that signal loss is related to the grade of displacement and the pattern of respiratory motion. In addition, the increase in quantification with RG PET/CT is more evident for small lesions [5, 9, 12, 14, 15]. Recently Farid *et al*. [12] compared SUVmax values of 32 solitary pulmonary nodules evaluated with gated and ungated PET/CT, demonstrating an increase in the SUVmax for all gated lesions; they also found the highest increase in smaller nodules (< than 10 mm) compared to the larger ones (respectively, 45% and 31%). Lupi *et al*. [14] analyzed separately lung lesions smaller than 20 mm at CT and demonstrated a mean increase of SUV max of 103%, ranging from -3.85% to 312.5%. In a recent paper by Robin *et al*. [15], the mean change in SUVmax resulted in 31% for lung lesions with CT diameter < 15mm, 20% for lesions between 15-30mm and 11% for lesions with CT diameter > 30mm. This information could also be considered for a more appropriate selection of patients who can have more benefits from RG.

Several authors have demonstrated that quantitative data of PET/CT images changes especially when lesions are located in the lower lung lobes, more influenced by respiratory movement [13, 15]. Conversely motion amplitude is lower in upper lobe lesions that usually have limited displacement during the respiratory cycle [20]. Robin *et al*. [15] considered 140 lung lesions comparing phase-gated and ungated SUV values. The mean change in SUVmax resulted in 5% for upper lobes, 17% for medium lobes and 20% for lower lobes. Similarly, Grootjans *et al*. [13] using an amplitude-based RG found large changes in SUV values for lesions located in the middle and lower lobes. In addition, centrally located lesions showed less changes in SUV with respect to peripheral lesions.

Beyond the increase in quantification, the gated technique can improve the diagnostic performance of the PET/CT imaging (*i.e.* sensitivity, specificity and accuracy). Table **2** shows published studies focused on the diagnostic accuracy of the gated technique [5, 9, 21].

Table 1. Differences in SUVmax values comparing gated and ungated lung lesions.

Author	N. Les	Gating	SUVmax Ungated	SUVmax Gated	% Difference	p
Chang [11]	21	Amplitude	7. 9 ± 4,9	9.9 ± 6,3	27%	<0.05
Farid [12]	32	Phase	2.5 ± 1,6	3.2 ± 1,9	38%	< 0.001
Grootjans [13]	83	Amplitude	10.5 ± 6.7	10.9 ± 6.7	6.1% ± 10.2	0.001
Guerra [5]	206	Phase	5.2+/-5.1	6.8+/-6.1	31%	< 0.0001
Lupi [14]	21	Phase	9.2+/-6.9	13.4+/-11.7	60%	< 0.05
Robin [15]	140	Phase	-	-	23 ± 29%	<0.05
Suzawa [16]	50	Phase	6.9 ± 4.9	7.6 ± 5.4	14.8 %	0.001
van Elmpt [17]	26	Phase	13.1±5.4	13.7±5.6	4.9±4.8%	<0.001
Garcia Vicente [9]	42	Phase	1.33+/-0.59	2.26+/-0.87	83.3%	<0.05
Werner [18]	26	Phase	9.2+/-4.8	11.8+/-5.5	22%	<0.001

Table 2. Impact of Gated technique on diagnosis of lung lesione.

Author	N Lesion	n°(%) of Lesions Equivocal/Negative at 3D Shifted to Positive in Gated Studies	Ungated Sensitivity, Specificity, Accuracy	Gated Sensitivity, Specificity, Accuracy
Callahan *et al*. [21]	20	3/20 (15%)	73%, 56%, 65%	75%, 63%,70%
Garcia Vicente A.M. *et al.* [9]	42 *	17/42 (40%)	NA, 100%, 45%	52%, 74%, 62%
Guerra L. *et al.* [5]	206	33/206 (16%)	72%, 91%, 80.5%	96.6%, 91%, 94.2%

*(only lesions with low or no uptake at PET/CT without gating acquisition).

Table 3. Percentage difference in average size of planning target volume/internal target volume (PTV/ITV) evaluated in three-dimensional (3D) positron emission tomography/computed tomography (PET/CT) or four-dimensional (4D) CT compared with 4D PET/CT reported by different studies. Adapted from Frood *et al.* [25].

-	N of Lesion	-	Compared with	% Difference	P value
Callahan [32, 37]	29	PTV	3D PET/CT	40% larger	0.0013
Chirindel [33]	21	ITV	4D CT	38.7% larger	0.0006
Guerra [38]	13	PTV	4D CT	3.4% larger	n.s.
Wijsman [29]	29	PTV	3D PET/CT	3.8% smaller	0.036

The RG PET/CT can make the physician more confident in the interpretation of PET images and consequently can reduce the number of undetermined findings, not useful for clinical patient management.

Garcia-Vicente *et al*. [9] assessed the change in classification due to 4D PET/CT technique of 42 pulmonary lesions with a SUVmax value < 2.5 at ungated FDG PET/CT. They found 40% (17/42) of lesions changed in the final classification from benign to malignant attending to 4D PET-CT and 52% (12/17) of malignant lesions were confirmed. The decrease in specificity has to be ascribed to the intrinsic characteristic of FDG not able to differentiate malignant for inflammatory lesions rather than to the gating technique, as the main aim of gating acquisition is the compensation for motion related artifact of the lesions and increase in the metabolic signal of the lesion, independently from its nature (inflammation or malignancy). In the work of Callahan *et al*. [21], the impact of 4D PET/CT on the classification of solitary lung nodule using a 5-point probability classification in 20 patients was evaluated. The authors reported no change in lesions characterization as benign or malignant at standard 3D-PET/CT but found a slight increase in sensitivity and accuracy of PET/CT lesions classified as indeterminate at 3D. Guerra *et al*. [5], in a multicenter experience, enrolled 206 lung lesions; for each lesion, SUVmax was calculated and the lesions were visually analyzed and classified as posi-

tive, negative or equivocal for malignant. The results showed great discrepancy between equivocal findings found in ungated and gated PET/CT. Indeed about 24% of the lesions (50/206) were considered equivocal in ungated studies whereas only about 4% (9/206) in 4D PET/CT scans. Among these, 30/50 (60.0 %) equivocal lesions were shifted to positive in 4D PET/CT scans on the basis of the increased metabolic signal. Moreover, 28% (14/50) of the lesions (28.0 %) were defined as definitely negative, mainly because of a more precise location of lesions. These results could have a great impact on the clinical activity, improving diagnostic performance of PET/CT in detecting metastatic lung lesions. Other quantitative parameters as metabolic tumor volume (MTV: the volume of a lesion with increased FDG uptake) and Total Lesion Glycolysis (TLG: the product of MTV and SUV mean of the lesion) have been investigated as prognosticators in a variety of cancers, including lung cancer [22]. The respiratory motion can cause blurring of PET avid lesions in the lung with a consequent apparent increase in the lesion's size. In a study on anthropomorphic thorax phantom containing a spherical ball simulating the tumors, 4D PET imaging reduced the effect of motion on MTV compared with 3D PET [23]. Robin *et al*. [15] performed tumor delineation using an adaptive threshold method, comparing MTV and TLG of 140 lung gated lesions with respect to the standard technique. The author found a mean decrease of 18% for MTV and 7% for TLG in gated images, in comparison to the standard technique. However, there are no specific indications (*i.e*. guidelines) regarding the standardized automatic delineation MTV and the differences in SUVmax in ungated and gated studies, which may introduce further complications to the auto contour process when a % of SUVmax or fixed SUVmax values are utilized as a threshold.

2.1.2. 4D-PET/CT in Staging and Restaging Lung Cancer

Grootjans *et al*. [13] evaluated the impact of RG on staging and management of 55 patients affected by lung cancer. The number and anatomical location of the lesions were scored and a TNM stage was assigned to each patient according to non-gated and gated images. Histopathological data and follow-up CT imaging were considered as a standard reference to determinate staging accuracy. In addition, for each patient, an experienced pulmonologist defined a management plan on the basis of non-gated and gated images results. For observer 1 and 2, gated PET/CT detected more lesions in 5 and 8 patients (9% and 15%) respectively, but these results did not significantly influence T or M stages as mainly due to the recovery of satellite lesions and locoregional metastatic lesions, otherwise obscured by tumor motion. Gated images found a higher number of positive lymph nodes; in particular, N stage was changed in 4 and 7 patients for reviewers 1 and 2 respectively, more frequently for hilar lymph nodes. Furthermore, RG also recovered aortic, inferior and superior mediastinal lymph nodes, however to a lesser extent. In a few cases, lymph nodes were considered positive on the non-gated images and negative on respiratory-gated images, probably because of spatial mismatch between PET and CT images in the ungated study. Gated PET/CT slightly improved staging accuracy, but without significant effect on patient management, probably due to the prevalence of advanced disease stages in the population (75% stage IIIA or higher with bulky primary tumors and multiple lymph nodes involvement). However, these results point out that RG could be important for the management of patients with early disease stages.

Aristophanous *et al*. [24] evaluated 3D and 4D FDG-PET/CT scans acquired before and after radiation treatment in 12 lung cancer patients for a total of 16 lesions, with the aim to investigate the effect of 4D PET on uptake changes due to therapy, in comparison to 3D PET. SUVmax of the lesions was significantly higher (p-value <0.005) in 4D PET images. The decrease of SUV on PET scan acquired pre and post-RT was 62% (range 36-89%) and 67% (range 30-89%) in 3D and 4D images, respectively with a mean absolute difference in SUV change on 3D versus 4D scans of 4.9% and a range 0-15% (p-value = 0.07). Considering that a 30% SUV variation is recommended by PERCIST criteria as a threshold to classify response to therapy, the differences of PET quantification related to 4D PET scan could potentially impact response evaluation. Authors indicated that other factors can play a role in the evaluation of PET scans if acquired with different uptake time (time elapsed between tracer injection and PET acquisition) and after the patients have been submitted to radical treatment [24]. Changes in the breathing pattern or in the location of the maximum SUV can influence the evaluation by altering the amount of signal lost in the pre and post-RT 3D scans. The recovery of the signal by 4D scan could be more reliable. However, up to date there are no studies establishing the correlation between PET-based response assessment and clinical outcomes.

2.1.3. 4D-PET/CT for Radiotherapy Planning of Lung Cancer

Radiotherapy planning generates a clinical target volume (CTV) with the aim to encompass the gross tumor volume (GTV) and adjacent areas potentially involved in microscopic disease. The internal target volume (ITV) is then defined to account for the movement of the GTV/CTV due to breathing. Finally, further enlargement is added to account for set-up variability and uncertainties in dose delivery to create a planning target volume (PTV) [25].

Respiratory motion is a crucial factor of uncertainty in the definition of the PTV and can be the cause of "missing" of the target lesion during the dose delivery or increased toxicity to the risk organs. Consequently, the use of technologies dedicated to the management of the movement of organs and lesions during the breathing of the patient is strongly recommended in radiation therapy planning, mostly gated CT [26].

Currently RG PET is not included in these recommendations, but it can be useful for a more precise definition of target volumes. PTV obtained with gated PET/CT can be significantly different from that obtained with ungated PET [27, 28]; the differences can be not only in absolute values of volume but also in its shape; in this case, portions of gated PTV can be not included in ungated PTV, even when the absolute value of ungated PTV is larger than gated PTV [1]. The usefulness of respiratory gated PET/CT has been demonstrated when it has been coupled with high precision radiotherapy technique (*i.e*. stereotactic ablative body radiotherapy). The rationale of this treatment is to deliver the

higher dose to the target sparing from radiation as much as possible the health tissue; consequently the probability to cure the tumor is maximized whereas the probability of toxicity can be minimized. In a recent meta-analysis [25], 3D and 4D PET/CT tumour volumes [3, 11, 13, 16-18, 29-36] of 13 studies were compared (Table **3**); in some cases, 4D PET/CT (16-50%) resulted in significantly smaller volumes (6.9-44.5%) [3, 11, 13, 16, 18, 29, 31, 34], while in others, volumes were significantly larger [30, 32, 35]. Although the differences in GTV described above may affect radiotherapy planning, ITVs and PTVs can be more reliable parameters [25]. Five studies compared target volumes or studied geographic misses [25, 29, 32, 33, 37, 38]. In two studies [32, 37], target volumes were significantly larger (19-40%) in 4D PET/CT than 3D PET/CT. Callahan *et al*. [32, 37] showed that 3D- PET/CT and the enlargement of 15 mm of PTV margins, commonly used for lung lesions, can determine an increased risk of significant geographic miss when tumor motion is increased, in particular for peripheral lesions. Siva *et al*. [39] demonstrated that in the delineation of pulmonary targets using 3D PET/CT, the calculated dose delivered resulted in lower than the expected dose to the PTV when compared with target volumes generated from 4D PET/CT, more often in case of tumors in the lower lobes. Conversely, Wijsman *et al*. [29] did not find a clinically relevant difference in radiation dose to the organs at risk, although median volumes of gated PTV were statistically significantly smaller than the corresponding non-gated volumes. In another study [38], 4D-PET/CT and 4D CT target volumes were compared; no significant differences were found among 4D PET/CT and 4D CT target volumes. On the opposite, another study reported significantly larger PTVs (38.7%) for 4D-PET/CT in comparison to 4D-CT [33].

These differences vary depending upon gated techniques, segmentation, considered margins for PTV and the clinical impact currently remains uncertain. For example, Jani *et al*. [35] on phantom and clinical studies showed that target volumes that originated from amplitude-based gated images were larger compared to those from temporal phase-based gating. Other authors proposed a possible correlation of pretreatment target volumes originated from 3D and 4D PET/CT with postsurgical histology; it would be ideal but technically challenging [25]. Finally, evaluation of patient outcomes based on 3D versus 4D PET/CT derived treatment volumes warrants further investigation

2.1.4. 4D PET/CT and Radiomics

In recent years, evidence has shown that the radiomics approach through texture analysis of medical images, like computed tomography (CT) and positron emission tomography (PET), can provide additional information regarding tumor phenotype, therapeutic response and prognosis of lung cancer patients in various clinical settings [40]. Several texture features, derived from different mathematical models of the relationship between multiple voxels and their neighborhood are proposed to describe tumor heterogeneity. As fine texture features are likely to be blurred during 3D PET acquisition of lung tumors, some authors investigated the impact of 4D-PET/CT on the assessment of textural features in lung cancer patients [41-43].

Grootjans *et al*. evaluated 60 lung cancer patients scanned with an amplitude gated PET/CT. Some features of lesion texture were: "entropy" and "dissimilarity" (representing variation in intensity and disorganization in the lesion), and "zone-percentage" and "high-intensity emphasis" (representing heterogeneity). Overall, the authors did not find any significant difference in texture analysis of ungated and gated lesions. However, lesions located in the middle and lower zone of the lungs demonstrated a significant difference in all textural parameters except "entropy".

Yip *et al*. [41] evaluated 3D and 4D PET images to study heterogeneity of 35 lung lesions. The authors found significant differences in "maximal correlation coefficient", "long run low gray-level emphasis", "coarseness", and "busyness" (NGTDM-based). When measuring tumor heterogeneity characteristics, reduced motion blurring by 4D PET acquisition offers a significantly better spatial resolution of textural features. 3D PET textures may lead to inaccurate prediction of treatment outcome, hindering optimal management of lung cancer patients. The authors concluded that 4D PET textures may have a better prognostic value as they are less susceptible to tumor motion. Oliver *et al*. [42] evaluated 23 patients and showed that image feature extraction using 3D versus 4D acquisition revealed significant different feature values. In particular, the features with the least variability were "sphericity", "spherical disproportion", "$entropy_{Hist}$", "$entropy_{GLCM}$", "sum entropy", "information measure of correlation", "short-run emphasis", "long-run emphasis", and "run percentage", while the features with the largest differences (>50%) were "kurtosis", "low gray-level run emphasis", "short-run low gray-level emphasis", and "long-run low gray-level emphasis". In addition to the movement caused by respiration, the authors identified deformation of lesions between 3D PET and 4D PET, consisting of variation of tumor axis lengths and angles with respect to the XY plane; this factor can affect image feature values.

In addition, it is well known that segmentation is a critical step of the radiomics process because features are extracted from the segmented volumes. Manual delineation of tumor volume suffers from high interobserver and intraobserver variability, whereas fixed thresholding can significantly underestimate the true metabolic active tumor volume extent by considering only the tumor subvolume with the highest uptake [44, 45]. Both approaches may bias the heterogeneity assessment and the associated ranking of intratumor heterogeneity levels. Orlhac *et al*. [46] evaluated a consistent number of texture indices on a variety of tumors (including 24 NSCLC); all histogram indices strongly depended on the tumor delineation method. Similarly, "$contrast_{NGTDM}$", "busyness" (NGTDM-based), "low gray-level run emphasis", "short-run low gray-level emphasis", "long-run low gray-level emphasis" (GLRLM-based), "low gray-level zone emphasis", and "short-zone low gray-level emphasis" (GLSZM-based) were highly sensitive to the segmentation method, while "$homogeneity_{GLCM}$" and "$entropy_{GLCM}$" were found to be robust with respect to tumor segmentation [40]. However further studies and standardization of features extraction processes are needed to clarify the impact of 4D on radiomics features in lung lesions.

2.1.5. Open Issues

Although it has been demonstrated that RG techniques can improve PET/CT image quality, quantification and diagnostic accuracy, as also shown in Fig. (**1**), there are still some open issues that need to be considered. Firstly, the standardization of the procedures, a fundamental prerequisite to guarantee the comparability of the results and harmonization. Currently, RG protocol is utilized with different tracking systems (elastic belt, infrared camera, probes for air temperature) and different gating approaches (phase-based, amplitude-based) [7], but there are no data demonstrating which is the best approach in terms of detectability and quantification [1].

The second important point is the compliance of the patient, particularly his/her capability to adapt to the breathing requirements of the protocol. Depending on the acquisition protocol used for gated PET/CT, the patient is asked to breathe regularly along with the whole acquisition or to keep the breath during a specific time of the examination. Unfortunately, breathing compliance is not always obtainable, in particular in very compromised patients or in case of chronic pulmonary disease, locally advanced lung cancer and massive neoplastic pleural effusion [1]. The third point is the extended acquisition time needed for gated PET/CT. In some cases, patients do not tolerate prolonged acquisition and, in addition, prolonged acquisition can impact on diagnostic workflow, reducing department throughput [1].

A preliminary evaluation of patient's compliance is often suggested to avoid inadequate results. In RG protocols for radiotherapy planning, the patient is often asked to be trained with a sort of simulation of the PET/CT scan before proceeding with the acquisition, particularly to check for his/her ability to sustain regular breathing over time comparable to the RG acquisition one.

During the training and the PET/CT acquisition, the patient should be positioned in the same way of radiotherapy treatment, by using a flat table and the same immobilization devices applied during dose delivery. Regular breathing can be also obtained by some devices for patient coaching during RG acquisition. The simplest is a vocal instruction saying to the patient alternately "breath in" and "breath out" according to the intervals of time averaged on a consistent number of patient's breathing cycles previously acquired. Using another device, the breathing patient's curve can be displayed on a monitor inside the diagnostic room; the patient is asked to follow his/her own breathing rhythm and to stay within amplitude limits calculated from few cycles acquired before starting the scan.

The last critical point is the dose to the patient, mainly due to the 4D CT acquired for the attenuation correction of gated PET data. The cine 4D CT has been estimated to have a mean additional exposure of 4.18 mSv, ranging from 2.28mSv (for 30mA) to 6.08 (for 80mA). The estimation has been performed from DLP data by using the conversion fac-

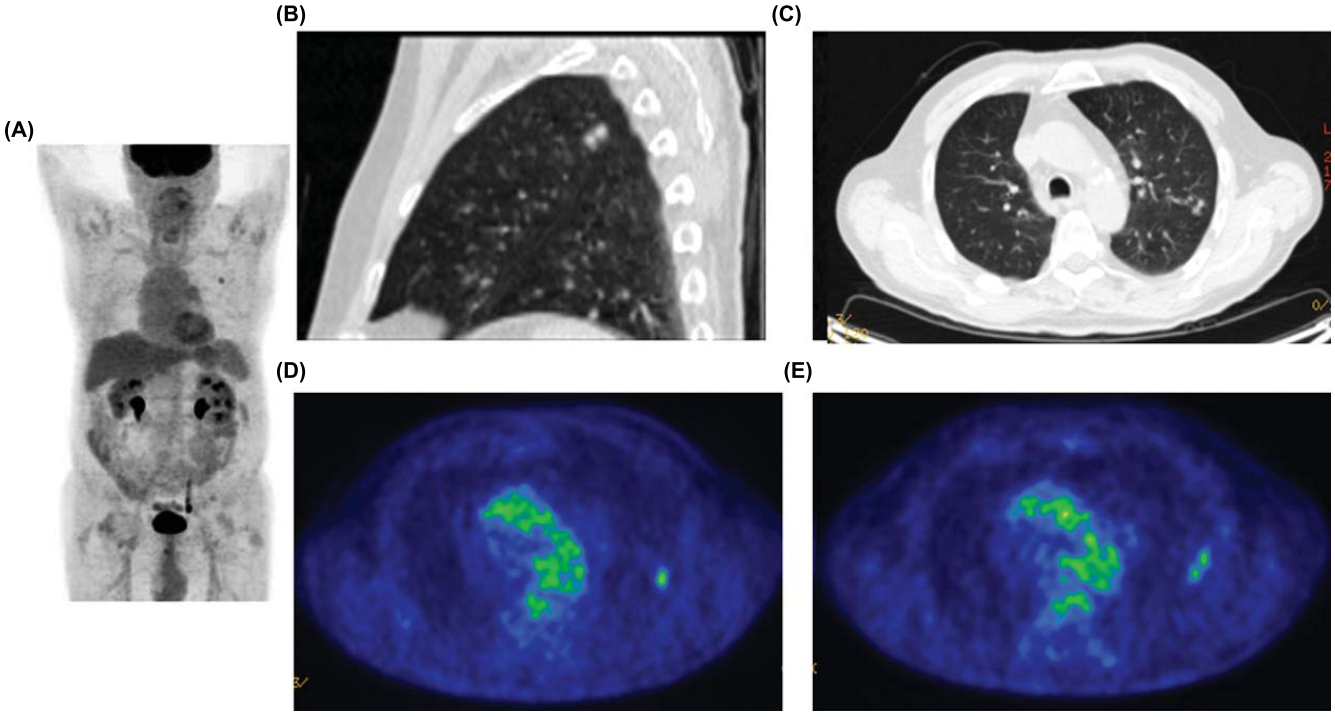

Fig. (1). WB 18F-FDG PET /CT study (**A**) conducted to characterize 2 lung nodules in an oncologic patient. Sagittal (**B**) and axial (**C**) CT images confirmed the presence of two nodules in the upper lobe of the left lung. The PET data on the chest (1 FOV) were acquired in LIST mode and then reconstructed with and without respiratory-gated synchronization. The WB ungated study (**D**) shows only one focal uptake of the tracer, whereas the gated PET axial image (**E**) clearly demonstrates that both nodules have metabolic activity. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

tor to an effective dose, for adult patients, taken from AAPM report n.96, considering CT parameters used in a previous multicentric study [5]. The additional dose can be justified only if the information derived from gated image has an impact on patient management. Consequently, a precise knowledge of the patient's clinical situation is required. Furthermore, appropriate dose reduction strategies need to be considered, such as mA modulation for CT component and injected activity reduction obtained by TOF (time of flight) or high-sensitivity scanners for PET component.

Finally, other techniques for non-GATED acquisition protocol are available to manage breathing motion, such as deep-inspiration breath-hold (DIBH); according to this acquisition protocol, patients hold their breath at deep inspiration for a relatively short time while both CT and PET data are acquired. DIBH has been demonstrated to be feasible on current PET/CT scanners. However, patient compliance and good technologist-patient interaction are essential prerequisites to coordinate and optimize data acquisition. Nevertheless, studies have shown that approximately 60% of lung cancer patients cannot perform the DIBH technique successfully [47].

2.1.6. Novel Techniques and Software

Data-driven or software RG techniques are available on the latest generation PET/CT scanners. These techniques do not require external hardware to detect respiratory motion, involve direct mathematical modeling of the motion of organs and lesions on the basis of PET acquisition data and have been shown to have good accuracy [8, 25, 31, 48, 49].

In more recent years, several semi-automated database algorithms [50] and fully automated database algorithms have been developed with the goal to extract respiratory signals directly from raw PET data. The semi-automated algorithms showed that it was possible to extract respiratory information from raw data and to create gated scan from that. However, these methods requires reconstructing images, manually defining objects within the field of view (if visible) and tracking their geometric motion (if possible).

Fully automated algorithms not only endorse the characteristics of semi-automated algorithms but also have several advantages as well. Particularly, they are operator independent and do not require additional hardware infrastructure or changes to routine clinical protocols. Thus, they have the potential to be easily implemented in clinical practice. In contrast to semi-automated algorithms or external devices, fully automated algorithms do not operate by following the geometric movement of markers or structures but utilize specific scan and scanner characteristics [48, 51].

Buther *et al*. [31] investigated the feasibility and impact of RG PET in a clinical trial including 164 lesions. The authors compared conventional hardware-based gating (Belt-Gating, BG) with a data-driven approach (DDG). Both gating methods revealed respiratory shifts of lesions (4.4 mm ± 3.1 for BG vs 4.8 mm ± 3.6 for DDG, P = 0.76). Gated SUVmax of the lesions compared with ungated values did not differ significantly between both the methods (SUVmax: +7% ± 13 for BG vs +8% ± 16 for DDG, P = 0.76). Similarly, gating significantly reduced metabolic lesion volumes with both methods (−6% ± 26 for BG vs −7% ± 21 for DDG, P = 0.44) compared with ungated reconstructions. Blinded reading revealed a significant increase in image quality with gating, but no difference between the gating methods was observed (DDG was judged to be inferior to BG in 22 cases, equal in 12 cases, and superior in 15 cases; P = 0.32). Similarly, Kesner *et al*. [48] studied 116 patients with pulmonary nodules and compared ungated images to gated images obtained with the hardware and software approach. After blind review, the software was selected as superior 16.9% of the time (111 of 657 image sets; 95% confidence interval [CI]: 14.0%, 19.8%), and hardware was selected as superior 6.2% of the time (41 of 657 image sets; 95% CI: 4.4%, 8.1%). About 76% of the gated image sets (505 of 657; 95% CI: 73.6%, 80.1%) were considered comparable regarding motion management quality. Quantitative analysis demonstrated similar performance for the two gating strategies, in both cases significantly different from that of non-gated images. The mean increase ± standard deviation in SUV lesion was 42.2% ± 38.9 between ungated and software-gated images, and lesion full width at half maximum values decreased by 9.9% ± 9.6. This study indicates that software solutions can perform as hardware solutions, with the benefit of eliminating the overhead (except some additional image reconstruction time). Fully automated motion characterization methods require no additional equipment or changes to current clinical procedures and are more likely to be accepted by clinicians and patients; this would allow the routine application of gating technique, with the improvement of lesion detectability and quantification, particularly in the subset of patients with small moving lesions near the diaphragm. However, these recent advances require standardization and validation in multicenter clinical trials.

CONCLUSION

Breathing movement can introduce heavy bias in PET/CT imaging of lung lesions. The RG technology has shown significant improvement in image quality, reduction of motion-related artifacts, increased quantification and lesion detectability. Also MTV, TLG and textural-features presented differences comparing 4D and 3D acquisition. Although the role of 4D-PET/CT in staging and therapy response assessment has not yet been defined, it can be used for radiation therapy planning with the purpose to reduce the uncertainty in target definition, to optimize the target treatment and to reduce the probability of "missing" during the dose delivery. Lastly, up to date technologies defining the movement of lesions and organs directly from the PET sinogram can solve some problems (*i.e.* extended acquisition time, radiation exposure), currently limiting the clinical use of gated PET/CT. If these new technical improvements for motion compensation will be clinically validated, the gated technique could be applied routinely in any PET/CT scan.

LIST OF ABBREVIATIONS

BG	=	Belt-Gating
CI	=	Confidence Interval
CT	=	Computed Tomography
CTV	=	Clinical Target Volume
DDG	=	Data-Driven Gating

DIBH = Deep-Inspiration Breath-Hold

FDG = Fluorodeoxyglucose

FOV = Field Of View

GTV = Gross Tumour Volume

ITV = Internal Target Volume

MTV = Metabolic Tumor Volume

PET = Positron Emission Tomography

PTV = Planning Target Volume

RG = Respiratory Gating

SUV = Standardized Uptake Value

TLG = Total Lesion Glycolysis

WB = Whole-Body

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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