Biases affecting tumor uptake measurements in FDG-PET

M. Soret, C. Riddell, S. Hapdey, and I. Buvat

***Abstract*-- The influence of tumor diameter, tumor-to-background activity ratio, attenuation, spatial resolution, tumor location, tumor non-uniformity and spatial sampling on the biases affecting tumor-to-background activity ratio (TBR) estimates in FDG PET was studied using analytical simulations of an anthropomorphic phantom. Major parameters affecting the bias amplitudes appeared to be the tumor diameter, the tumor-to-background activity ratio, whether attenuation had been performed, the spatial resolution of the PET scanner and the spatial sampling used to define the anatomical regions of interest used for TBR estimation.**

I. Introduction

Accurate estimates of tumor uptake in FDG PET would be useful for lesion characterization and patient follow-up. However, tumor uptake measurements are challenging given the small size of many tumors and the limited spatial resolution of PET imaging. A common index used to differentiate benign from malignant tumors is the tumor-to-background activity ratio (TBR) [1]. The effect of limited spatial resolution on activity estimates in small spheres surrounded by uniform background has already been studied in PET using simple geometric models [2, 3]. In this work, we determined the effect of tumor diameter (D), tumor-to-background activity ratio, attenuation, spatial resolution, tumor location, tumor non-uniformity and spatial sampling on the biases affecting tumor-to-background estimates in FDG PET using simulations of an anthropomorphic phantom.

II. Material and Methods

3D numerical phantom. Various factors potentially affecting tumor uptake measurements in FDG PET were studied by performing analytical simulations using the 3D numerical Zubal thoracic phantom [4] sampled with 1 mm × 1 mm × 1 mm voxels. Activity and attenuation distributions were defined to respect anatomical and physiological properties (Fig. 1). Realistic FDG activity concentrations were set in the heart (1850 kBq/ml), lungs (296 kBq/ml) and soft tissues (370 kBq/ml). Three spheres representing tumors were added in the lungs, soft tissues and in between. Attenuation coefficients at 511 keV were set to 0.099, 0.024, 0.098 and 0.097 cm^{-1} in tumors, lungs, muscle and heart respectively.

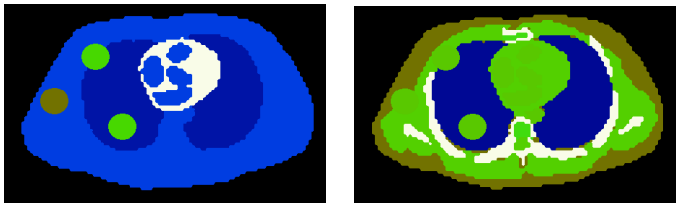

Fig. 1. Examples of axial slices through the simulated activity and attenuation distribution.

Analytical noise-free simulations. Noise-free emission projections with or without attenuation were simulated. All simulations included 300 projections 512× 512 with 1 mm × 1 mm pixels. The point spread function (PSF) of the PET system was modeled by convolving the projected data with a 2D Gaussian function of full width at half maximum (FWHM) equal to 4 mm. Transmission data were also simulated using the same PSF.

The attenuated emission projections were corrected for attenuation by multiplying the sinograms by the attenuation correction factors derived from the noise-free transmission simulations. Images were reconstructed using the Ordered Subset Expectation Maximization (OSEM) algorithm (16 subsets, 4 iterations), yielding 40 slices 128× 128 with 4 mm × 4 mm × 4 mm voxels. Spatial resolution in the reconstructed images was around 6.5 mm.

Effect of tumor diameter and tumor-to-background activity ratio. To study the effect of tumor diameter (D), different simulations were performed involving tumors with diameters D of 0.5, 1, 1.5, 2, 3 and 4 cm. Tumor-to-surrounding tissue (background) uptake ratios (TBR) were varied from 3 to 13.

Effect of attenuation. Three data sets were obtained to investigate the effect of attenuation: data without simulation of attenuation (NA), data with simulation of attenuation and without attenuation correction (NAC) and data with simulation of attenuation and attenuation correction (AC) (Fig. 2). These 3 data sets were used to study the impact of attenuation by comparison of NAC and AC and to check the efficiency of attenuation correction by comparison of NA and AC.

M. Soret, S. Hapdey and I. Buvat are with U494 INSERM, CHU Pitié-Salpêtrière, Paris, France (telephone: 33 1 53 82 84 14, e-mail: soret@imed.jussieu.fr).

C. Riddell is with GE Medical System, Buc, France (e-mail: Cyril.Riddell@med.ge.com).

0-7803-7324-3/02/$17.00 © 2002 IEEE

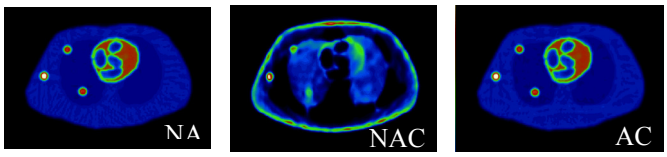

Fig. 2. Reconstructed activity distribution corresponding to data without simulation of attenuation (NA), with simulation of attenuation and without attenuation correction (NAC), with simulation and correction of attenuation (AC).

Effect of spatial resolution. Influence of the PET system resolution was studied by simulating a system resolution of FWHM equal to 8 mm in addition to the 4 mm FWHM initially used. Such 8 mm resolution is more representative of a gamma-camera based PET scanner than of a dedicated PET scanner [4]. These simulations were used to assess the importance of PET system resolution on quantitative performances. Influence of a PSF in transmission ($FWHM_T$) different from the PSF in emission ($FWHM_E = 4$ mm) was also studied in two cases: a "smoothed" transmission data corresponding to $FWHM_T = 8$ mm and a CT transmission data corresponding to $FWHM_T = 1$ mm.

Effect of tumor location. Tumors were simulated in the lungs, soft tissues and in between to investigate the influence of tumor location.

Effect of tumor non-uniformity. A lung tumor with non-uniform uptake was simulated using two concentric spheres: the inner sphere representing necrosis had a diameter D_N varying from 2 to 3.5 cm and a TBR_N varying from 0 to 2 while the external sphere (D = 4 cm) had a TBR = 3. Such simulation was used to assess the quantitative changes that would be observed when a tumor with uniform uptake turned to a tumor with non-uniform uptake due to a necrosis process.

Quantitative index. For each reconstructed image, uptake was measured in regions of interest (ROIs) corresponding to the anatomical regions used to define the original activity distribution. Estimated TBR were deduced from uptake measurements. Percent errors affecting TBR estimates were defined as:

100*(estimated TBR – true TBR)/(true TBR).

Effect of sampling. Two sampling schemes were used to estimate tumor uptake and associated TBR. In the first approach, the reconstructed volume (40 slices with a 4 mm × 4 mm × 4 mm voxels) was resampled using trilinear interpolation to a 1 mm × 1 mm × 1 mm voxel size identical to the sampling of the original activity distribution. ROI uptakes were estimated by applying the anatomical 1 mm × 1 mm × 1 mm anatomical regions defined on the original activity maps onto the interpolated reconstructed images. In the second scheme, the anatomical ROIs defined in the 1 mm × 1 mm × 1 mm sampling were resampled in 4 mm × 4 mm × 4 mm. A 4 mm × 4 mm × 4 mm voxel was considered as belonging to an ROI i if and only if the majority of the 64 1 mm × 1 mm × 1 mm voxels it included belonged to ROI i. Regional uptakes were then estimated in these binary ROIs applied on the 4 mm × 4 mm × 4 mm reconstructed volume.

III. Results and Discussion

A. Effect of tumor diameter

Fig. 3 shows that the smaller the tumor diameter, the greater the underestimation of TBR. For example, for a lung tumor with TBR = 13, with attenuation correction, TBR was underestimated by about 24% for D = 4 cm and by more than 85% for D = 0.5 cm. When the true TBR changed from 10 to 5 (50% decrease), the observed TBR reduction was 47% for a 4 cm diameter tumor but was only 25% for a 0.5 cm diameter tumor. When both tumor and background activities varied but TBR remained unchanged, observed TBR remained almost constant. For instance, for TBR = 6.5 with 592 kBq/ml in the background and D = 4 cm, observed TBR was 5.25, while for TBR = 6.5 with 148 kBq/ml in the background, observed TBR was 5.31. Curves shown in Fig. 3 are therefore valid for a wide range of background activities.

These results demonstrate that Partial Volume Effect (PVE) makes tumor-to-background ratio estimates strongly dependent on tumor size. Correction for PVE is therefore a key correction for accurate TBR estimation in oncology imaging. It is often considered that PVE correction is needed for tumor diameter less than 2 or 3 times the FWHM characterizing the spatial resolution [3], i.e. 2 cm in for the 6.5 mm spatial resolution observed in our reconstructed images. Our results show that even for a 4 cm diameter tumor, PVE has an impact. This is because we considered the anatomical tumor ROIs to estimate TBR, while the values of 2 to 3 times the FWHM are valid when one considers only the maximum pixel value within a given region. As noise makes measurements based on maximum values subject to high variability, we rather used averaged counts within anatomical ROIs, which increased the TBR bias caused by PVE.

Correction of TBR underestimation introduced by PVE can be performed using recovery coefficients [1, 2, 3]. As the PVE bias strongly depends on tumor diameter, the appropriate recovery coefficients have to be determined by assuming the tumor diameter is known.

Fig. 3 shows that, had the data been corrected for attenuation or not, the smaller the tumor diameter, the greater the underestimation of TBR. When the data are not corrected for attenuation, the rate with which TBR underestimates vary with tumor diameter strongly depends on whether the tumor is located in lungs or soft tissues. This is because PVE interferes with attenuation in this instance, as will be explained in section C.

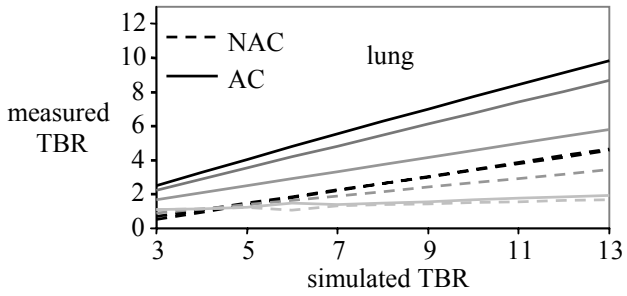

Fig. 3a. Measured TBR in a lung tumor with or without AC as a function of simulated TBR for lesion diameters of 4 cm (—), 2 cm (—), 1 cm (—) and 0.5 cm (—).

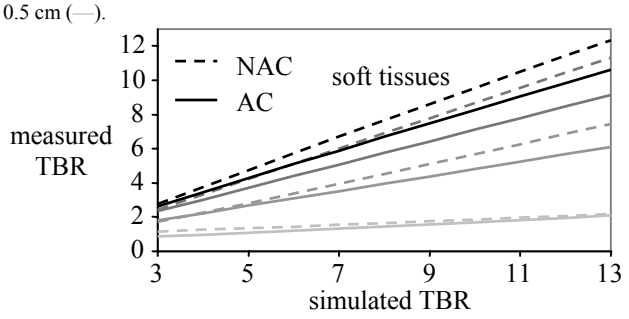

Fig. 3b. Measured TBR in a soft tissue tumor with or without AC as a function of simulated TBR for lesion diameters of 4 cm (—), 2 cm (—), 1 cm (—) and 0.5 cm (—).

B. Effect of TBR

Fig. 3 showed that the greater the TBR, the larger the TBR underestimation expressed as a percentage of the true TBR. For example, for a lung tumor with D = 0.5 cm, the TBR was underestimated by 63% for TBR = 3 and by 85% for TBR = 13.

Indeed, for TBR close to 1, the spill-out (tumor activity detected outside the tumor) almost compensates the spill-in (background activity detected inside the tumor). The greater the TBR, the larger the discrepancy between spill-in and spill-out and the higher the percent error in tumor uptake estimates.

These results show that recovery coefficients appropriate for PVE correction in a specific configuration actually depend on the true TBR (obviously unknown).

C. Effect of attenuation

Efficiency of attenuation correction. The TBR estimated using the images reconstructed from the attenuation corrected projections (AC) and using the images reconstructed from the projections simulated without modeling attenuation (NA) were almost identical (results not shown). The average difference between TBR obtained with NAC and with AC calculated over all tumor diameters and over lung and soft tissue tumors was around 2%.

Yet, partial volume effect affected the transmission measurements through small tumors located in the lung: the smaller the tumor, the greater the underestimation of the attenuation coefficient of the tumor. For instance, the tumor attenuation coefficient was underestimated by 33% for a 2 cm diameter tumor and by 55% for a 1 cm diameter tumor. This bias in attenuation coefficient value was observed only for tumors of density significantly different from the density of surrounding tissues (typically lung tumors) because for tumor density similar to background density (as observed for soft tissue tumors), spill-in compensated spill-out. The bias affecting the lung tumor attenuation coefficients did not affect attenuation correction accuracy however, because the partial volume effect affecting transmission measurements similarly affected the attenuation factors in emission measurements. Thus, the partial volume effect affecting transmission measurements in PET does not introduce any bias during the subsequent attenuation correction, provided spatial resolution affecting the emission measurements is identical to that used for the transmission measurements. The case of a different spatial resolution in emission and in transmission is studied in section D.

It should be noted that the excellent performances of attenuation correction reported in this study were obtained using noise-free emission and transmission measurements. In clinical practice, both transmission and emission data are noisy. The precise impact of the noise affecting both emission and transmission measurements on TBR estimates will be the subject of future studies.

Effect of attenuation correction. The change in TBR estimates introduced by attenuation correction varied depending on the tumor location. For lung tumors, TBR was greater with attenuation correction than without, while for soft tissue tumors, TBR was smaller with attenuation correction than without. For example, for a TBR = 13 and D = 2cm, TBR of a lung tumor was underestimated by 64% without AC and by 24% with AC. If the same tumor was located in soft tissues, TBR was underestimated only by 5% without AC and by 19% with AC.

Without attenuation correction, TBR estimates are affected by attenuation and by partial volume effect. With attenuation correction, TBR estimates are mostly biased by partial volume effect. Without AC, the way TBR estimates are affected by attenuation depends on the ratio between tumor density and surrounding tissue density. The higher this ratio, the more TBR is underestimated. For example, for a 4 cm soft tissue tumor with true TBR=13 and tumor density 1.2 greater than soft tissue density, estimated TBR was 10.5. For a soft tissue tumor of same size and same TBR with a tumor to soft tissue density ratio of 0.9, estimated TBR was 12.5. For a tumor of same size and same TBR located in the lung, the tumor-to-background density ratio was 3 times greater than when surrounding tissues were soft tissues, hence a very large TBR underestimation: estimated TBR was only 4.2.

Our results agree with previously reported results [5] obtained for a chest phantom and which showed that tumor contrast (defined as TBR-1) for lung tumors was higher with attenuation correction than without. The variable impact of attenuation correction depending on tumor-to-surrounding tissues density ratio partially explains the current controversy

regarding the benefit of attenuation correction for tumor detection. Indeed, the fact that attenuation correction actually decreases TBR in some cases (here, for soft tissue tumors) is consistent with the fact that lesions can get more difficult to detect after attenuation correction.

D. Effect of spatial resolution

Identical emission and transmission spatial resolution. Changing the spatial resolution of the detector PSF from 4 to 8 mm FWHM decreased the spatial resolution in reconstructed images from 6.5 to 9 mm. Such a change increased the tumor uptake underestimation from 28% to 42% for a 2 cm lung tumor and TBR = 13. Whatever the tumor location, with attenuation correction, TBR was 8% to 30% lower with FWHM = 8 mm than with FWHM = 4 mm (Fig. 4). Indeed, the poorer the spatial resolution, the greater the biases introduced by PVE. For accurate quantitative measurements, recovery coefficients should also depend on spatial resolution.

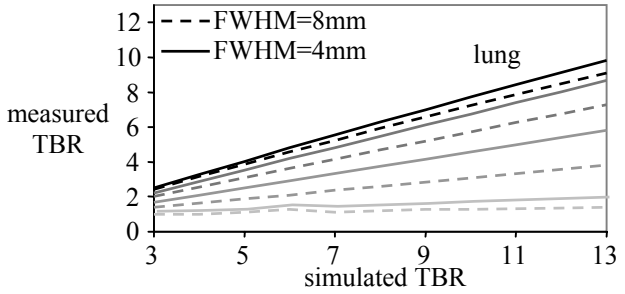

Fig. 4. Measured TBR with AC in a lung tumor with $FWHM_{ET}$ = 8mm or FWHM = 4mm as a function of simulated TBR for lesion diameters of 4 cm (—), 2 cm (—), 1 cm (—) and 0.5 cm (—).

Different emission and transmission spatial resolutions. A difference between emision and transmission spatial resolutions has a large influence for lung tumors only (Fig. 5) (results for soft tissue tumors not shown). For lung tumors, the better the transmission resolution, the smaller the biases affecting TBR. For a 1 cm tumor in lung and TBR = 3, changing $FWHM_T$ from 4 to 1 mm induced TBR underestimation decreases from 41% to 27%. Changing $FWHM_T$ from 4 to 8 mm induced TBR underestimation increases from 41% to 66%. For the same tumor located in soft tissues, TBR underestimation was between 35% and 40% for $FWHM_T$=8 mm, 4 mm or 1 mm.

Indeed, when the emission and transmission spatial resolution are different, the partial volume effect affecting the attenuation coefficient measurement during the transmission scan does not compensate exactly the partial volume effect affecting the attenuation factors in the emission transmission, as was observed for identical transmission and emission resolutions (see section C). For lung tumors, the better the transmission resolution, the less the transmission measurements are affected by PVE, hence the smaller the biases in TBR. This is not the case for soft tissue tumors, as tumor and soft tissue densities are similar: the transmission spatial resolution does not change the bias in TBR estimates.

High resolution CT transmission maps, segmented transmission maps or transmission maps with lower resolution than emission data due to smoothing operations will therefore affect TBR estimates for lung tumors but not soft tissue tumors (assuming those have an attenuation coefficient close to that of soft tissues).

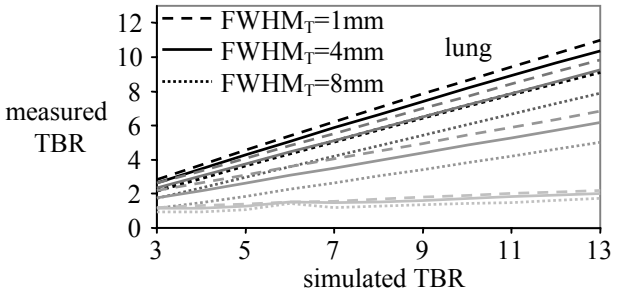

Fig. 5. Measured TBR with AC in a lung tumor with $FWHM_T$ = 1mm, 4mm or 8mm and $FWHM_E$=4mm as a function of simulated TBR for lesion diameters of 4 cm (—), 2 cm (—), 1 cm (—) and 0.5 cm (—).

E. Effect of tumor location

With attenuation correction, for a given TBR, biases in tumor uptake estimates were similar regardless the tumor location.

Results of comparison between NA and AC have demonstrated the efficiency of attenuation correction (see section C). As PVE does not depend on location for a given TBR, bias affecting the TBR after attenuation correction is also independent of tumor location.

Recovery coefficients calculated for PVE correction of attenuation corrected images could therefore be the same for tumors located in the lung or in soft tissues.

F. Effect of tumor non-uniformity

For the non-uniform lung tumor of 4 cm diameter, the tumor TBR averaged over the whole tumor was underestimated by 13% for a inner (necrotic) region of 2cm diameter with respect to the true TBR value. This averaged error actually corresponded to a 15% TBR underestimation in the external region with true TBR of 3 and to a 13% TBR overestimation in the inner region with true TBR of 2. For this object simulating a necrosis process in the tumor, the averaged TBR measured over the whole tumor was only 1% smaller than the averaged TBR that would be measured if the tumor presented a uniform activity concentration (i.e. no necrosis process) with TBR=3. For a necrosis with a constant diameter, the more amplified the necrosis process (i.e. the smaller the inside TBR_N), the greater the difference between the measured TBR and the TBR which would be measured without necrosis with TBR=3 (Table I). Also, for a necrotic part presenting a constant TBR_N, the larger the necrosis diameter, the larger the difference between the measured TBR and the TBR that would be measured had no necrosis be

present. For a necrotic part of diameter equal to 3 cm with TBR_N= 2, the TBR measured over the whole tumor would be 12% smaller than that measured without necrosis, and for a diameter of 3.5 cm, it would be 20% smaller. Assuming that at least a 15% TBR difference is needed for detecting a change, the volume of the necrotic region that would make the necrosis process detectable depends on the intensity of the necrosis, i.e. on TBR_N. For a TBR_N = 2 (compared to TBR = 3 in the rest of the tumor), the necrosis would get detectable if the necrotic volume was at least 75% of the total tumor volume. For TBR_N=0 or 1, the necrosis would get detectable for a necrotic volume greater than 50% of tumor volume.

Obviously, "averaging" two TBR in a single anatomical ROI makes it more difficult to detect necrosis. Our results give some insights into the volume of necrotic tissues needed to detect an overall change in TBR as a function of the amplitude of the necrosis process.

TABLE I. MEASURED TBR AVERAGE OVER THE WHOLE TUMOR AND TBR UNDERESTIMATION COMPARED WITH A UNIFORM TUMOR WITH TBR=3.

TBR	TBR_N=0	TBR_N=1	TBR_N=2
D_N=2cm	2.2 (-10%)	2.4 (-5%)	2.5 (-1%)
D_N=3cm	1.4 (-45%)	1.8 (-32%)	2.2 (-12%)
D_N=3.5cm	0.7 (-70%)	1.3 (-46%)	2.0 (-20%)

G. *Effect of sampling*

Biases in uptake estimates were always larger when measurements were performed on the reconstructed images interpolated to a 1 mm × 1 mm × 1 mm sampling than when they were performed on the reconstructed images sampled in 4 mm × 4 mm × 4 mm. For instance, for a 2 cm diameter tumor with a TBR of 13, the uptake was underestimated by 30% with the 1 mm sampling and by 17% with the 4 mm sampling. This surprising result comes from the way we resampled the ROIs to the 4 mm sampling. When using the 1 mm sampling, the tumor volume as calculated from the anatomical ROI was overestimated by 1%, while when using the 4 mm sampling, it was underestimated by 15%. Because the way we convert tumor ROIs from the 1 mm × 1 mm × 1 mm sampling to the defined on the 4 mm × 4 mm × 4 mm sampling made the tumor ROIs systematically smaller when defined on the 4 mm sampling than when defined on the 1 mm sampling, PVE was reduced for the 4 mm sampling and the biases in mean uptake estimate were smaller than when considering the 1 mm sampling.

IV. CONCLUSION

Tumor-to-background uptake ratios are strongly underestimated in FDG PET with accurate attenuation correction because of limited spatial resolution. TBR underestimation up to 85% can be observed for a 5 mm tumor seen using a PET scanner with a 4 mm spatial resolution. We provided data to give indications regarding the amplitude of tumor-to-background uptake ratio underestimation as a function of tumor size, tumor-to-background activity ratio, attenuation, spatial resolution, non-uniform uptake of the tumor and spatial sampling. Such data should assist the quantitative interpretation of tumor-to-background uptake measurements in FDG PET.

V. REFERENCES

[1] N. Avril, S. Bense, I. Ziegler, J. Dose, W. Weber, C. Laubenbacher, W. Römer, F. Jänicke, M. Schwaiger, "Breast imaging with fluorine-18-FDG PET: Quantitative image analysis," *J. Nucl. Med*., vol. 38, pp.1186-1191, 1997.

[2] E. J. Hoffman, S. C. Huang, and M. E. Phelps, "Quantitation in positron emission computed tomography: effect of object size," *J. Nucl. Med.*, vol. 3, pp.299-308, 1979.

[3] R. M. Kessler, J. R. Ellis and M. Eden, "Analysis of emission tomographic scan data: limitations imposed by resolution and background," *J. Comput. Assist. Tomogr.*, vol. 8, pp.514-522, 1984.

[4] I. G. Zubal, C. R. Harrell, E. Smith, "Computerized three dimensional segmented human anatomy," *Med. Phys*., vol. 21, pp.299-300, 1994.

[5] R. E. Coleman, C. M. Laymon and T. G. Turkington, "FDG Imaging of lung Nodules: A phantom study comparing SPECT, camera-based PET, and dedicated PET," *Radiology*., vol. 210, pp.823-828, 1999.