Impact of PET scanner non-linearity on the estimation of hypoxic fraction in cervical cancer patients

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ABSTRACT

Background: Tumor hypoxia is defined as a low oxygen level in tissue and is associated with poor clinical outcome after chemo-/radiotherapy and surgery in many solid tumor types. Positron Emission Tomography (PET) imaging provides a non-invasive means of measuring local variations in the uptake of hypoxia-targeted agents (e.g. FAZA or FMISO). Accurate quantification of uptake is critically dependent on the PET scanner's linear count rate performance. In the context of cervix cancer, high PET agent accumulation in the bladder, low uptake in the tumor, and their relative proximity makes an accurate quantification of the tumor's hypoxic fraction challenging. The purpose of this study was to estimate the impact of PET scanner non-linearity on PET-based estimation of hypoxic fraction.

Material and Methods: The impact of PET scanner non-linearity effect was assessed with a NEMA body phantom, using the cylinder as the “bladder-mimicking” compartment and the water filled background as a surrogate region for the tumor. A simple model of the non-linearity effect was then applied to a set of patient-derived FAZA-PET scans (N = 38) to estimate the impact of the non-linearity on the calculated hypoxic fraction (HF) for each patient.

Results: The NEMA body phantom measurements revealed a substantial overestimate of activity outside the injected “bladder mimicking” cylinder compartment. This uptake resulted in an overestimate in activity between 1.9 and 0.3 kBq/cc corresponding to distances from 1.0 – 7.0 cm from the cylinder. In the patient-derived PET images, the bladder-to-tumor distance ranged between 1.0 and 3.0 cm. For the 38 patients analyzed, the HF was demonstrated to decrease by 1.1–75.0 % [median 27.2 %] depending on distance and relative uptake levels. Additionally, the magnitude of the effect of the non-linearity was found to depend on the pre-scanning hydration protocol employed ($p = 0.0065$).

Conclusion: Hypoxia imaging of tumors of the cervix is challenging due to patient specific activity accumulation in the bladder and the non-linear response of PET scanner performance. This can result in a substantial overestimate of the calculated hypoxic fraction in cervical tumors. Additional effort needs to be invested to improve the linearity of PET scanners in anatomical regions proximal to the bladder.

Background

Tumor hypoxia is defined as a reduced level of oxygen in tissue below 10 mmHg (1.3 kPa) and is attributed in part to accelerated cell proliferation and disordered angiogenesis in tumors [1]. In many solid tumors, tumor hypoxia is also associated with poor clinical outcomes following chemo-/radiotherapy as well as surgery [2–4]. A quantitative

assessment of tumor hypoxia using non-invasive Positron Emission Tomography (PET) imaging promises to help identify, stratify and monitor patients for personalized clinical interventions. PET-based nitroimidazole compounds which become bound in cells with a low oxygen level have been used to capture the heterogeneity of tumor hypoxia and allow the assessment of changes in hypoxia during treatment through repeated measurements. One such compound is 1-(5-[¹⁸F] Fluoro-5-

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deoxy- α -D-arabinofuranosyl)-2-nitroimidazole (FAZA). The use of PET-based patient-specific hypoxic status has been explored in patient specific interventions including dose escalation [1], an improved oxygen supply [5–7], hypoxic cell radiosensitization [8], hypoxic cell cytotoxins [9] and metabolic targeting [10]. An accurate estimate of compound accumulation is required for both effective development and deployment in clinical decision-making. In cervical cancer, the quantification of tumor hypoxia is challenging due to the low uptake in the tumor and its close proximity to the bladder and its associated high accumulation (i.e. due to renal clearance) [11–13]. Approaches to reduce bladder

accumulation via catheterization have shown an enhanced risk for infection [14,15] and patient tolerance for catheter placement is limited. Imaging preparation protocols designed to reduce bladder accumulation have also been applied to reduce activity in the bladder. Therefore, the non-linearity of the PET scanner, also referred to as a ‘spill-in or spill-out effect’ [12], results in the incorrect attribution of activity to locations in the image (see Fig. 1). In this technical note, we i) characterize the measured FAZA uptake in tumor, gluteus maximus and bladder for a cohort of 38 cervical cancer patients in consideration of two different pre-imaging hydration protocols ($N_{\text{cohort1}} = 26$ and $N_{\text{cohort2}} = 12$), ii)

Fig. 1. Exemplary patient geometry highlights the intrinsic variability in patient anatomy and bladder filling compliance despite the use of a standardized imaging and bladder uptake protocol (top: highlighted patient with gross tumor volume [GTV] contours presented in blue). This presented effect challenges the PET scanner’s quantitative performance for low uptake regions in close proximity to high uptake (bottom: schematic). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

quantify PET scanner non-linearity proximal to high uptake regions (i.e. similar to the bladder) using a NEMA body phantom, and iii) quantify the deleterious effect of the non-linear response of the PET scanner on estimates of the tumor hypoxic fraction in 38 patients using a simple model.

Material and Methods

Patient Data – Scanning Protocol, Anatomical Parameters, and Uptake Values

Between 2011 and 2019, 38 patients with stage IB-IVA cervical squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma were enrolled in two distinct Research Ethics Board (REB) approved studies. A total of 38 FAZA-PET scans ($N_{\text{cohort1}} = 26$ and $N_{\text{cohort2}} = 12$) with corresponding CT scans were considered (see Table 1). Both patient cohorts participated in the same FAZA-PET study but with two different pre-imaging hydration protocols (see Table 1) while all other aspects of the imaging protocol remained the same. Both cohorts underwent definitive chemo-/radiotherapy [16,17]. Scans were acquired on either a GE Discovery 610 PET/CT scanner (2014–2019) or a GE Discovery STE PET/CT scanner (2004–2014) (GE Healthcare, Waukesha, WI). These scanners share very similar geometries and detector designs (BGO) and employed consistent OSEM reconstruction parameters (2 iterations, 32 subsets) with a standard Gaussian filter in z-direction (6.4 mm). The basic PET scanner corrections include the detector normalization, dead time correction, scatter correction, random correction and decay correction. Resulting in the following image dimensions of (256 voxels) $\times$ (256 voxels) $\times$ (83 slices) and a voxel size of 1.95x1.95x3.27 mm in the reconstructed image.

For both clinical cohorts, the patient's individual bladder, gross tumor volume (GTV), and a region within the gluteus maximus were contoured by a single radiation oncologist. The GTV was contoured on the CT scan with the aid of co-registered T2-weighted MR image (see Table 1). For each of the regions of interest (ROIs), the mean activity concentrations for the bladder (A_{Bl}), the gluteus maximus (A_{GM}) and the tumor (A_{Tum}) were calculated (MIM 6.8.6, MIM Software Inc., Nelson et al., USA & Matlab-2013b - see Table 2). A minimum 2D distance between a point on the patient's bladder surface and the GTV center was calculated in each of the axial image slices to determine the global minimum 2D distance. For patients without a common image slice between the bladder surface and GTV contour, the average distance across all patient's FAZA-PET scans was employed in the subsequent analysis (average distance 1.7 cm, applied in 3 patients). An offset based on the patient's specific bladder uptake and corresponding bladder-tumor distance was determined (in reference with the NEMA body phantom measurement see Section "Estimating the Degree of PET Scanner Non-Linearity"). For completeness, each patient's individual anatomical geometries, the volume (V) of the patient's bladder (V_{Bl}), and the tumor (V_{Tum}) were also calculated.

Estimating the Degree of PET Scanner Non-Linearity

The NEMA body phantom [18] was employed to mimic the bladder by providing a central region (cylindrical insert: 51 mm in diameter and 108 mm in length) high uptake surrounded by low activity in the background region. The study was performed with the same image acquisition parameters as employed in the patient imaging studies. The injected activity into the "bladder mimicking" central compartment was 55.9 MBq/cc for a multi study experiment. No activity was included in the background region. Images were acquired using two bed positions and image-derived activity concentrations were compared to well-counter measurements. Decay corrections were performed for both scans and a spherical ($r = 2$ cm) volume of interest (VOI) and four additional spherical ($r_1 = 1$ cm) VOIs were used to quantify PET scanner reported activity in the surrounding zero activity region in absolute

Table 1

Overview of the patient data, scanning protocol and anatomical parameters ($N_{\text{cohort1}} = 26$ and $N_{\text{cohort2}} = 12$) used for the study. The patient's individual injected activity was based on the corresponding body weight. Static imaging started 2 h post injection. Differences in the patient's hydration protocols and duration of the image acquisition are highlighted.

	Cohort 1	Cohort 2
Number of patients	26	12
Hydration protocol and time to imaging	The patient was asked not to drink fluids 3 h prior to the FAZA-PET scan. Small sips of water with medications were permitted and the patient was asked to completely empty her bladder. The patient was positioned supine on the imaging couch to facilitate starting PET-CT imaging immediately after FAZA-PET injection. Her arms were positioned above her head if possible, away from the primary region of interest in the abdomen and pelvis.	Patients were asked to drink 250 mL of water 2 h prior to the FAZA-PET scan. After FAZA injection, participants were asked to drink up to 1 L of water (target 10 mL/kg with max 1 L) within 20–30 min and were asked to completely empty their bladder whenever necessary.
Intravenous injection based on body weight	FAZA was administered by intravenous injection at a dose of 5.2 MBq/kg [minimum of 100 MBq (2.7 mCi) and maximum 600 MBq (16.2 mCi)] in Cohort 1 and Cohort 2.	
FAZA-PET/CT imaging sequence and acquisition time	Static FAZA PET scan: The static FAZA PET scan began approximately 2 h after FAZA injection. The patient was asked again to completely empty her bladder and then was repositioned supine on the imaging couch with her arms above her head and asked to remain as still as possible. A static PET scan acquired over approximately 30 min.	The static FAZA PET scan was comparatively acquired over a longer time of approximately 10–30 min.
CT-imaging	A low dose CT scan of the abdomen and pelvis (1–2 mSv) was performed for emission attenuation correction in Cohort 1 and Cohort 2.	
CT-imaging: Accessed regions of interest for the image analysis	Bladder, Gluteus Maximus	
T2-weighted MR	The GTV was contoured on the CT scan with the aid of co-registered T2-weighted MR image. Registration in MIM 6.8.6 imaging software.	
PET image reconstruction	OSEM reconstruction parameters (2 iterations, 32 subsets) with a standard Gaussian filter in z-direction (6.4 mm). Image dimensions of (256 voxels) $\times$ (256 voxels) $\times$ (83 slices) and a voxel size of 1.95x1.95x3.27 mm.	

Table 2

FAZA-PET image analysis for the cervical cancer patients ($N_{\text{cohort1}} = 26$ and $N_{\text{cohort2}} = 12$), characterizes the mean bladder, tumor and GM activity concentrations with corresponding standard deviations and volumes measured in the FAZA-PET scans. Median values are reported in ranges of minimum and maximum of the observed parameters. Data is presented in units of activity concentrations [kBq/cc] and volumes [mL].

Image Analysis- Activity concentration (A) in kBq/cc	Cohort 1	Cohort 2	Both Cohorts
Mean A_{Bladder}	65.0 ± 26.9	41.3 ± 27.2	57.6 ± 29.1
Mean A_{Tumor}	4.0 ± 1.4	4.1 ± 0.9	4.0 ± 1.3
Mean A_{GM}	2.6 ± 0.5	2.7 ± 0.3	2.6 ± 0.4
Image Analysis- Activity concentration (A)- after offset in kBq/cc	Cohort 1 – after offset	Cohort 2 – after offset	Both cohorts – after offset
Mean A_{Bladder}	63.7 ± 26.3	40.6 ± 26.8	56.4 ± 26.3
Mean A_{Tumor}	2.7 ± 1.4	3.3 ± 1.1	2.9 ± 1.3
Image Analysis- Volume (V) in mL	Cohort 1	Cohort 2	Both cohorts
Mean V_{Bladder}	61 ± 33	69 ± 28	64 ± 32
Mean V_{Tumor}	50 ± 40	37 ± 28	46 ± 37
Mean V_{GM}	62 ± 26	122 ± 102	81 ± 67
Image Analysis- Activity concentration (A) in kBq/cc	Cohort 1	Cohort 2	Both cohorts
Median A_{Bladder}	64.6 [15.3–134.0]	32.4 [17.0–116.0]	54.6 [15.3–134.0]
Median A_{Tumor}	3.8 [1.8–8.4]	4.0 [3.0–6.6]	3.9 [1.8–8.4]
Median A_{GM}	2.5 [2.0–4.1]	2.7 [2.3–3.3]	2.6 [2.0–4.1]
Image Analysis- Activity concentration (A)- after offset in kBq/cc	Cohort 1 – after offset	Cohort 2 – after offset	Both cohorts – after offset
Median A_{Bladder}	63.2 [14.9–131.2]	31.7 [16.6–114.7]	53.5 [14.9–131.2]
Median A_{Tumor}	2.5 [0.8–6.6]	3.3 [1.8–6.1]	2.7 [0.8–6.6]
Image Analysis- Volume (V) in mL	Cohort 1	Cohort 2	Both cohorts
Median V_{Bladder}	48 [31–141]	58 [25–106]	51 [25–141]
Median V_{Tumor}	37 [10–171]	29 [9–107]	35 [9–171]
Median V_{GM}	63 [15–119]	75 [52–391]	67 [15–391]

values and percent of the injected bladder mimicking center concentration (see Fig. 2 and Section “NEMA Body Phantom Measurement”). These VOIs were placed along a radially line at 1 cm, 3 cm, 5 cm and 7 cm from the surface of the cylinder and a continuous fitting approach was used (see Fig. 2). Based on this approach, misplaced activity concentrations for each individual patient were determined by indexing to the appropriate distance from the bladder and scaling according to patient-specific bladder concentrations.

Estimation of Non-Linearity on the Quantification of Hypoxic Fraction

The hypoxic fraction for each tumor was calculated for each tumor using the pattern of FAZA uptake in the tumor activity and the muscle tissue of the gluteus maximus ROI [19] as a reference. Each patient’s muscle histogram was normalized by its own mean, all GM histograms were average-pooled and a standard deviation calculated, resulting in a calculated threshold of 1.2 (mean + three standard deviations). Based on the NEMA phantom results, the non-linearity contribution from the bladder to the muscle was less than 0.01% of the average muscle signal and therefore no correction was applied to the gluteus maximus. The hypoxic fraction was then re-calculated for each tumor based on an individualized estimate of the contaminating signal due to PET scanner non-linearity. This estimate was selected using the minimum 2D distance between the bladder and tumor as described above. The impact of the non-linearity on the calculated hypoxic fraction was quantified in percentage relative to the original hypoxic fraction estimates.

Results

The results of the patient cohort analysis are summarized in Table 2 with mean and corresponding standard deviations as well as median values in ranges of minimum and maximum. The two cohorts represent two different hydration protocols. A threshold value of 1.2 resulted for Cohort 1, Cohort 2 and both Cohorts (see Section “Estimation of Non-Linearity on the Quantification of Hypoxic Fraction”).

Patient Cohort Parameters

For Cohort 1 ($N_{\text{cohort1}} = 26$), a mean bladder activity concentration of $65.0 \text{ kBq/cc} \pm 26.9 \text{ kBq/cc}$ in a range of 64.6 kBq/cc [15.3–134.0] kBq/cc was observed. A much lower mean activity concentration in the tumor of $4.0 \text{ kBq/cc} \pm 1.4 \text{ kBq/cc}$ was observed. The average bladder

Fig. 2. The NEMA body phantom was employed to mimic the bladder by providing a central high uptake region without activity in the background. Regions of interest were placed at 1 cm, 3 cm, 5 cm and 7 cm from the surface of the cylinder to measure uptake in the background and were fitted in a continuous approach (left: measurement, right: visual aid in a schematic).

volume was measured to be $61 \text{ mL} \pm 33 \text{ mL}$ in Cohort 1 and $69 \text{ mL} \pm 28 \text{ mL}$ in Cohort 2 and all other parameters are presented in Table 2. For Cohort 2 ($N_{\text{cohort}2} = 12$), a mean bladder activity concentration of $41.3 \text{ kBq/cc} \pm 27.2 \text{ kBq/cc}$ in a range of 32.4 kBq/cc [17.0–116.0] kBq/cc was observed. The mean activity concentration of the tumor was $4.1 \text{ kBq/cc} \pm 0.9 \text{ kBq/cc}$.

For the combined cohort, a mean bladder activity concentration of $\bar{A}_{\text{BJ}} = 57.6 \text{ kBq/cc} \pm 29.1 \text{ kBq/cc}$ with a median of 54.6 kBq/cc was observed for both cohorts (see Table 2). Most importantly for this study, the range of observed activity concentrations in the bladder is substantial (range [15.3–134.0] kBq/cc). Likewise, a mean tumor activity concentration $4.0 \text{ kBq/cc} \pm 1.3 \text{ kBq/cc}$ in a range of [1.8–8.4] kBq/cc with median 3.9 kBq/cc and a mean GM activity concentration $2.6 \text{ kBq/cc} \pm 0.4 \text{ kBq/cc}$ in a range of [2.0–4.1] kBq/cc with median 2.6 kBq/cc was calculated. Similarly, to the wide observed range in the bladder activity concentration, the range of observed bladder volumes within Cohort 2 was high with a median of 51 mL [25.0–141.0] mL (see Table 2).

NEMA Body Phantom Measurement

The NEMA body phantom scans had an average mean activity concentration in the bladder mimicking center of $80.2 \text{ kBq/cc} \pm 5.3 \text{ kBq/cc}$ and this corresponds well to the mean observed activity concentration plus one standard deviation in both patient cohorts. The four outside ROIs at distances of 1 cm, 3 cm, 5 cm and 7 cm had observed activity concentrations in the background of $1.9 \pm 0.2 \text{ kBq/cc}$ (corresponding to 2.4 % of bladder mimicking center concentration), $1.5 \pm 0.2 \text{ kBq/cc}$ (corresponding to 1.9 % of bladder mimicking center concentration), $0.7 \pm 0.1 \text{ kBq/cc}$ (corresponding to 1.0 % of bladder mimicking center concentration) and $0.3 \pm 0.1 \text{ kBq/cc}$ (corresponding to 0.04 % of bladder mimicking center concentration) (see Fig. 2). These activity concentrations were observed without injected activity in the surrounding background.

Impact of Scanner Non-Linearity on the Quantification of Hypoxic Fraction

The hypoxic fractions for each tumor are shown in Fig. 3. Correcting for the estimated effect resulted in a 1.1 to 75.0 % [median 27.2%] decrease in the hypoxic fraction based on the bladder-induced activity contamination estimated using the NEMA body phantom body (see Fig. 2 and Fig. 3).

Fig. 3. Estimation of the hypoxic fractions HF in cervical cancer FAZA-PET scans in activity concentrations (Bq/cc). HF were calculated for each patient before (HF) and after considering (HF*) for the bladder-induced activity contamination estimated using the NEMA body phantom measurement. The patient index corresponds to both clinical cohorts ($N_{\text{cohort}1} = 26$ and $N_{\text{cohort}2} = 12$) presented in the following order: Cohort 1: 1–26 and Cohort 2: 26–38.

Effect of Hydration Protocol

The previously presented observations for both clinical cohorts lead to further results specific to differences in the hydration protocols between Cohort 1 and Cohort 2 (see Fig. 4 and Table 1). Point biserial correlations between the bladder volume, the bladder activity concentration and the bladder-tumor distance were calculated (see Fig. 4). Statistical significance ($p = 0.0025$) was observed for the cohort's mean activity concentrations in the bladder. An overall significance ($p = 0.0065$) was also observed of the calculated weighting factor between the patients in the two cohorts with Cohort 2 having a significantly lower bladder activity concentration with similar bladder-tumor distances compared to Cohort 1. A bi-linear regression of the applied correction with the bladder activity and the bladder-tumor distance resulted in a R^2 value of 0.9. Therefore, the applied weighting factor is significantly lower as well. This suggests pre-imaging preparation protocols can reduce the deleterious impact of bladder accumulation on the accuracy of hypoxic fractions.

Discussion

The NEMA body phantom measurements provide a simple means to assess the presence and scale of the non-linearity in a PET scanner. While more complex, anatomically representative phantoms could be used to assess the effect, the large anatomical variations in bladder size and proximity to the tumor as illustrated in our patient cohort suggest that any single phantom would be limited in representing the effect. Therefore, the use of a standard phantom was chosen to allow others to replicate this work on other scanners with other experimental conditions. To simplify the experimental effort, the 'mimicked bladder' activity concentration in the phantom was fixed at a value within one-standard deviation of that found in clinical cohorts and the correction was scaled by the bladder activity itself for each patient. The lack of a background activity was also a simplification in our approach and both a 'spill-out and spill-in' effect should be considered as a limitation of the method as described earlier [12]. Ultimately, a more complete set of phantom studies with additional variations in activity and patterns would be helpful to inform computational approaches to estimating PET scanner non-linearity.

In general, the study contributes to the field of quantitative PET imaging by highlighting a technical consideration inherent in the absolute quantification of uptake regions proximal to high activity regions such as the bladder. This further emphasizes the need to develop methods that address the non-linearity. This includes improved collimation, the use time of flight methods [15], or computational corrections (e.g. Monte Carlo based approaches) to correct patient-specific acquisitions as has been proposed in other imaging modalities such CT [20–22]. Our quantitative analysis of the 38 patients highlights the intrinsic variability in patient anatomy and bladder filling compliance despite the use of a standardized imaging and bladder uptake protocol. While all patients were asked to drink defined quantities of water (target 10 mL/kg) and empty their bladder just prior to imaging, the observed bladder retention and filling ranged by a factor of 5 between [25.0–141] mL across the patient cohort. This highlights the relevance of the time-dependent bladder filling even within a 10 min PET bed position (see Fig. 1, Fig. 4, Table 1 and Table 2). Of greater relevance to signal non-linearity is the variation in activity concentration in each bladder ranging by a factor of 9 across the patient cohort [15.3–134.0] kBq/cc . To put these numbers in context, the total FAZA-PET signal in the cervical tumor (FAZA and contamination) is much smaller (1.8–8.4 kBq/cc). Corresponding to non-linearity related deviations in HF ranging from 1.1 to 75.0 % in the patient cohorts considered here.

It is important to point out that we have employed a very simple anatomy-specific estimation based on a simple 2D minimum bladder-to-tumor distance look-up scheme. Of course, more complex and time-dependent calculations might offer a more refined estimate of the

Fig. 4. A patient derived characterization of uptake parameters suggest an informed imaging strategy for the patient cohorts and its associated bladder-tumor distance, bladder volume and measured activity concentration. Patient Cohort 2 had a lower activity concentration in the bladder ($p = 0.025$) and non-linearity ($p = 0.0065$) compared to Patient Cohort 1 (pearson correlation). The 3D-scatter plot aids the visual distinction between Patient Cohort 1 and Patient Cohort 2 regarding a lower calculated off-set value and bladder activity concentration.

correction that reflects the complexity of the anatomical geometry and the tumor's location. This is the topic of future work. Other approaches such as a deconvolution filter, or a distance quantification of a 3D a voxelized map would be an approach which could be added in a future study or a Monte Carlo based approach could be used to develop a more

accurate correction method.

To our knowledge, this is the first report to quantitatively estimate the deleterious impact of bladder filling on hypoxic fraction estimates in cervix cancer. These observations reinforce the need to improve the quantitative performance of PET scanners for quantitative assessment of

hypoxic fractions in tumors proximal to the bladder. Ultimately, quantitative estimations must be derived from patient-specific, scanner-specific information and the adoption of hydration protocols can further minimize the vulnerability. Without this, PET-based hypoxic fraction based clinical decision-making for sites in the pelvis will be difficult to evaluate in clinical trials, and further, will be challenged to advance through to clinical utility.

Conclusion

Patient specific activity accumulation in the bladder during FAZA-PET imaging introduces non-linear effects in the surrounding image that can result in a substantial overestimate of the calculated hypoxic fraction in cervical cancer. This technical limitation in the quantification of activity concentrations by current PET imaging systems impacts quantitative image interpretation and can be expected to limit the development of evidence in hypoxia-directed interventions and ultimately challenge the accuracy of clinical decision-making based on PET-based agents and current PET imaging technology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This research was funded by NIH (U01 CA190256) and CIHR (OQI – 137992).

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