

Thoracic Tumor Volume Delineation in 4D-PET/CT by Low Dose Interpolated CT for Attenuation Correction

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Abstract

Purpose: 4D-PET/CT imaging is an excellent solution for reducing the breathing-induced effects in both CT and PET images. In 4D-PET/CT, 4D-CT images are selected to match those of 4D-PET phase by phase and the corresponding phases are used for attenuation correction in 4D-PET. However, the high radiation dose that patients acquire while undergoing 4D-CT imaging for diagnostic purposes remains a concern. This study aims to assess low-dose interpolated CT (ICT) for PET attenuation correction (PET_{ICT}) in thoracic tumor volume delineation.

Methods and Materials: Twelve thoracic cancer patients (10 esophageal and 2 lung cancer cases) were recruited. All patients underwent 4D-PET/CT scans. The optical flow method based on image intensity gradient was applied to calculate the motion displacement in three dimensions for each voxel on two original extreme CT phases in the respiratory cycle, end-inspiration and end-expiration. The interpolated CTs were generated from two phases of the original 4D-CT using motion displacement.

Results: Tumor motion due to respiration was estimated in the anterior-posterior dimension, the lateral dimension and the superior-inferior dimension by the optical flow method. The PET_{ICT} and ICT (4D-PET_{ICT}/ICT) matched each other spatially in all the phases. The distortion of tumor shape and size resulting from respiratory motion artifacts were not observed in 4D-PET_{ICT}. The tumor volume measured by 4D-PET_{ICT}/ICT correlated to the tumor volume measured by 4D-PET/CT ($p = 0.98$).

Conclusions: 4D-PET_{ICT} consistently represented the interpretation of FDG uptake as effectively as 4D-PET. 4D-PET_{ICT}/ICT is a low-dose alternative to 4D-CT and significantly improves the interpretation of PET and CT images, while solving the respiratory motion problem as effectively as 4D-PET/CT.

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Introduction

Positron emission tomography/computed tomography (PET/CT) enables the precise localization and characterization of sites of radiotracer uptake for tumor detection. In imaging, the hybrid scanners combine anatomic and functional information to improve cancer diagnosis, tumor staging and restaging, and tumor response under treatment. They also aid in target volume delineation in radiotherapy treatment planning, which is required to calculate the optimal radiation dose for the tumor and the surrounding normal tissues [1,2]. Therefore, PET/CT has been widely used in routine clinical practice.

Tumor motion due to respiration creates challenges in PET and CT imaging and makes PET/CT imaging more difficult [3,4]. Motion artifacts on CT imaging not only introduce errors

in localization and the overestimation of tumor volume due to blurring of the tumor volume, but can also cause the underestimation of standardized uptake value (SUV) in PET quantification [5-8]. In PET/CT imaging of thoracic cancer patients, the mis-registration in fusion images between PET and CT because of respiratory motion is still a major problem. In addition, the difference in acquisition time between PET (15 minutes) and CT (10 seconds), which causes spatial misalignment, is another concern when PET/CT imaging is performed [9]. PET/CT imaging that uses Real-Time Position Management (RPM, Varian Medical Systems, Palo Alto, CA, USA), a respiratory motion monitoring system, is referred to as 4D (gated) PET/CT imaging and is an excellent solution for reducing breathing-induced effects on both CT and PET images [10-13]. 4D-CT with gates of equal amplitude, which

Table 1. The clinical characteristics of patients.

Patient #	Histology	Location	Tumor motion (mm)			Type	Stage
			AP	LAT	SI		
1	Squamous cell carcinoma	Esophageal cancer (Lower)	3.01	1.75	3.48	Primary	ii
2	Squamous cell carcinoma	Esophageal cancer	0.95	1.15	2.63	Primary	ii
3	Squamous cell carcinoma	Esophageal cancer (Upper)	1.33	0.93	5.34	Primary	ii
4	Squamous cell carcinoma	Esophageal cancer (Middle)	5.28	6.13	5.36	Lymph node	iii
5	Squamous cell carcinoma	Esophageal cancer (Lower)	2.82	2.25	3.32	Lymph node	iii
6	Dysplastic squamous cells	Esophageal cancer (Middle to lower)	2.51	1.04	1.54	Lymph node	iii
7	Squamous cell carcinoma	Esophageal cancer (Lower)	2.67	5.35	7.81	Lymph node	iv
8	Squamous cell carcinoma	Esophageal cancer (Lower)	1.59	0.50	1.14	Lymph node	iv
9	Squamous cell carcinoma	Esophageal cancer (Upper)	1.06	1.13	1.84	Lymph node Lymph node	ii
10	Squamous cell carcinoma	Esophageal cancer (Lower)	2.89	1.87	4.49		iv
11	Squamous cell carcinoma	Lung cancer, Left lower lobe	3.49	1.78	3.85	Lymph node	iii
12	Squamous cell carcinoma	Lung cancer, Right lower lobe	2.54	1.70	4.18	Lymph node	iii

Abbreviations: AP = anterior-posterior, LAT = lateral, SI = superior-inferior

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divide the respiratory signal with reference to the magnitude of the breathing signal by RPM, is currently the one of the most optimal equipment for capturing lung motion and is frequently used for motion correction in PET. In 4D-PET/CT, 4D-CT images are selected to match those of the 4D-PET phase by phase and are used for attenuation correction in the corresponding 4D-PET. Nehmeh et al reported that 4D PET/CT increases the accuracy of the coregistration of PET and CT, the SUV and the accuracy of tumor volume calculation in PET [14]. Pan et al derived the average CT (ACT) from 4D-CT for attenuation correction to achieve better matching between PET and CT and also, to reduce the SUV loss due to respiration [15]. Although previous studies have presented excellent methods for correcting image artifacts from respiration, the high radiation dose acquired by patients from diagnostic 4D-CT remains a concern.

We previously developed interpolated CT (ICT), which is generated from the end-expiration and end-inspiration phases of CT and interpolated phases using deformable image registration, for PET attenuation correction (AC). This allows for the correction of misalignment artifacts and SUV quantification errors for thoracic tumors with high dose reduction [16]. Its clinical merits in six oncologic patients and its potential application in cardiology have also been reported [17]. ICT has been reported to be a robust, accurate, low-dose alternative to 4D-CT and it works well for a large range of respiratory motion amplitudes [18]. This study aims to assess the interpretation of 4D-PET using ICT for AC on 4D-PET/CT in the spatial matching of PET and CT, localization of tumors, quantification of tumor volume and quantitation of SUV for clinical thoracic cancer patients.

Materials and Methods

Patients

Twelve thoracic cancer patients (10 esophageal and 2 lung cancer cases) were retrospectively recruited in this study. All

patients were male and ranged in age from 37 to 63 years, with a median age of 53 years. The tumors were mostly in the lower section of the esophagus and lower lobe of the lung, and consisted of squamous cell carcinoma and dysplastic squamous cells. The patients' clinical characteristics are listed in Table 1. Written informed consent was obtained from all patients, and the collection of clinical patient data was approved by the ethics committees of the China Medical University Hospital, Taiwan (DMR98-IRB-171-2).

4D-PET/CT

The 4D-PET/CT data were acquired using GE PET/CT-16 slice, Discovery STE (GE Medical Systems, Milwaukee, Wisconsin, USA), incorporated with Varian real-time position management (RPM system, Varian Medical Systems, Inc. Palo Alto, CA) for respiratory motion tracking. For 4D-CT, sine-mode scanning was used to provide images of 10 phases of a breathing cycle. The CT image in each phase was binned according to the RPM respiratory signal based on the motion amplitude. The 4D sinograms were reconstructed on a 512 x 512 image matrix. The pixel size in the transaxial slice of the 4D CT images was approximately 0.98x0.98 mm², and the slice thickness was 2.5 mm. The 10 respiratory phases were labeled as T5%, T15%, ... T95% phases, with the T5% phase corresponding approximately to the normal end-inspiration and the T55% to the end expiration, as illustrated in Figure 1.

FDG with an activity of approximately 10 mCi was administered to the patients, and the PET/CT scan session was performed approximately 40 minutes after injection. 4D-PET was acquired in 10 bins in synchrony with the breathing cycle during gated PET acquisition using RPM to monitor the respiration, as is the case in 4D-CT. PET images were reconstructed on a 128 x 128 image matrix with a voxel size of 4.46 x 5.46 x 3.27 mm³. The ordered subset expectation maximization reconstruction method was used with 2 iterations and 20 subsets. For the scans, a post-reconstruction Gaussian filter was applied with a full-width at half-maximum of 7 mm.

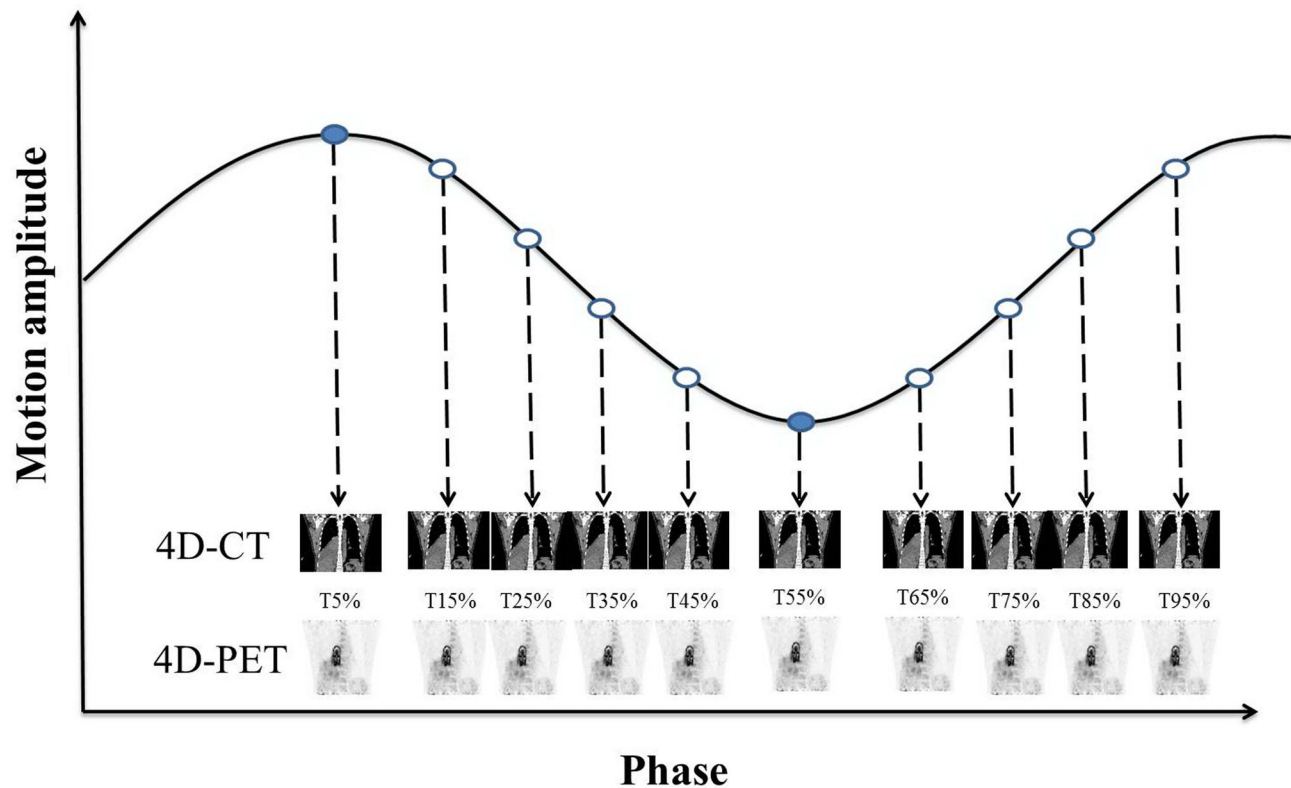


Figure 1. 4D-CT and 4D-PET imaging. The respiratory cycle was divided into 10 phases based on motion amplitude. The 10 respiratory phases were labeled T5%, T15%, ... T95%, with the T5% phase corresponding approximately to the normal end-inspiration and T55% to the end-expiration for both CT and PET. 4D-CT was used for attenuation correction of 4D-PET on a phase-by-phase basis so that they would match each other spatially.

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4D-CT scan was used for attenuation correction of 4D-PET on a phase-by-phase basis, such that they matched each other spatially, as show in Figure 1.

Interpolated average CT (ICT) and PET_{ICT}

The optical flow method (OFM), a deformable image registration algorithm based on the image intensity gradient, was applied to calculate the motion displacement in three dimensions for each voxel on two original extreme CT phases in the respiratory cycle, end-inspiration (phase T5%) and end-expiration (phase T55%) [16,18]. The interpolated phases were generated using the deformation matrix from the OFM registration. The total motion displacement field for each voxel in the forward motion map was divided equally into five intervals, resulting in four sets of interpolated CT (ICT) images representing the mid-phases from inspiration to expiration. Similarly, the backward motion map was used to calculate the four mid-phases from expiration to inspiration. Then, PET_{ICT} was acquired by its own-phase ICT with attenuation correction. The two original, plus the eight interpolated phases, composed a complete respiratory cycle, as illustrated in Figure 1.

Tumor volume evaluation

The tumor volume in PET was defined for each of the ten phases of the 4D-PET and $4D-PET_{ICT}$. The tumor volumes in PET were manually identified by an experienced physician and all the delineations were manually performed in all phases. In addition, each phase of the PET image was superimposed with the corresponding CT phase to investigate the misalignment between the PET and CT images. The difference in tumor volume between 4D-PET and $4D-PET_{ICT}$ was compared phase by phase, except in the two original phases (T5% and T55%). We also defined the percentage difference (PD) in the tumor volume as follows:

$$PD = \frac{TumorVolume_{4D-PET} - TumorVolume_{4D-PET_{ICT}}}{TumorVolume_{4D-PET}} \times 100$$

Results

Tumor motion due to respiration was estimated in the anterior-posterior dimension, the lateral dimension and the superior-inferior dimension by the optical flow method (Table 1). Figure 2 illustrates the sagittal views of PET and CT fusion images across the ten phases of a complete respiration cycle.

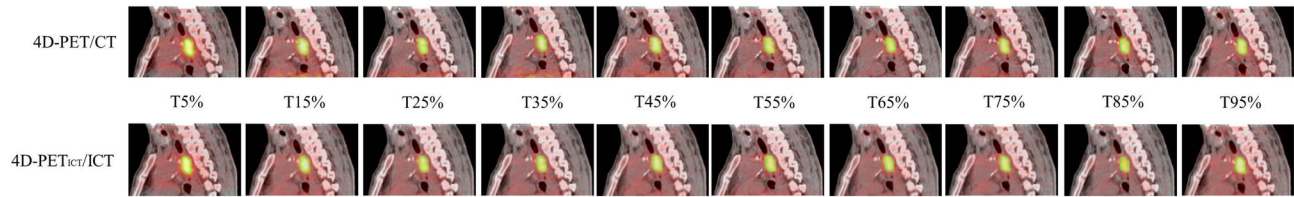


Figure 2. Sagittal views of PET and CT fusion images across the ten phases of a complete respiration cycle. One example for 4D-PET/CT and 4D-PET_{ICT}/ICT are shown from patient 3.

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One example of 4D-PET/CT and 4D-PET_{ICT}/ICT from patient 3 is shown. The PET_{ICT} and ICT (4D-PET_{ICT}/ICT) in all the phases matched each other spatially. The distortion of tumor shape and size resulting from respiratory motion artifacts was not observed. 4D-PET_{ICT} consistently represented the interpretation of FDG uptake to a similar extent as 4D-PET. Table 2 shows the percentage difference (PD) in tumor volume observed between the 4D-PET and the 4D-PET_{ICT} by phase. The average PD in tumor volume ranged from 0.76% (patient 2) to 5.79% (patient 9). Figure 3 shows a bar graph of the average tumor volumes from 4D-PET and 4D-PET_{ICT} for each patient, with the percentage difference between two volumes shown on top of the bars. Positive PD values represented a larger 4D-PET_{ICT} volume in most cases. SUV_{max} is the threshold level for tumor detection, according to its fluorodeoxyglucose (FDG) uptake. Figure 4 shows the average SUV_{max} from 4D-PET and 4D-PET_{ICT}, with the percentage difference shown on the top of bar. The SUV_{max} was smaller on 4D-PET_{ICT} than 4D-PET, with the exception of patient 9.

Discussion

Respiratory motion artifacts cause blurring in the detection of FDG uptake and the resulting tumor size and volume measurement, and also causes the mislocalization of tumors in PET and CT fusion images of PET/CT. Accurate information can be obtained with 4D-PET, as well as by 4D-CT, in 4D-PET/CT when respiration artifacts are present in images of the thorax. In this study, ICT was successfully applied as a low-dose alternative to 4D-CT, and the PET_{ICT} reconstructed by ICT improved the interpretation of PET, while solving the respiratory motion problem as effectively as 4D-PET/CT. No misalignment between PET_{ICT} and ICT was observed. The potential role of 4D-PET_{ICT}/ICT in providing accurate anatomic and functional fusion images for delineating tumor volume contours with low radiation doses was investigated by contrasting the tumor volumes calculated by 4D-PET. The tumor volume from 4D-PET_{ICT}/ICT was correlated to the tumor volume from 4D-PET/CT ($R^2 = 0.98$).

As the reconstruction of PET using CT for temporal correction in PET/CT is necessary, in PET, CT number,

representing electron density, is correlated to SUV. In this study, ICT was calculated from the interpolated images to generate PET_{ICT}. The loss of CT intensity usually appeared within the interpolated images, especially with large-amplitude respiratory motion. This factor caused a slightly lower SUV_{max} in 4D-PET_{ICT}, and there was a 4.88% loss in average percentage difference of SUV_{max} in our study. Furthermore, the strong correlation between SUV_{max} changes and tumor motions was not observed in our patient cohort.

The limitation of this study was the accurate estimation in movement of respiration. In the interpolation of the mid-phase of CT, the equal spacing of total motion displacement was based on the assumption that patient's breath is smooth and that the amplitude of the breath in a whole respiration cycle follows a sine curve. If the patient does not breathe in such a normal pattern, the present ICT method based on two original phases and the linear interpolation would not be a good representation of real breath. Active breathing control (ABC) devices, which capture the respiratory phases of the patients, might be an alternative approach to ensure that the phase used is appropriate. Another concern, which is regarding the OFM-based motion displacement, is that OFM was derived from the distribution of the apparent velocities of movement in the brightness patterns between the images. As the "smoothness constraint" for the motion component in the direction of the local gradient was applied, when the tumor moves rapidly with respiration, the displacement estimation using OFM is as a consequence, inaccurate [19]. Third, more investigations are required to reconfirm our preliminary findings that were obtained in a limited number of patients.

Conclusions

In this study, we have evaluated the effectiveness of PET_{ICT} from ICT attenuation correction compared to 4D-PET in thoracic cancer patients. 4D-PET_{ICT}/ICT is a low-dose alternative to 4D-CT and significantly improves the interpretation of PET and CT images while solving the respiratory motion problem as effectively as 4D-PET/CT.

Table 2. The tumor volume from 4D-PET and 4D-PET_{ICT} for each phase, and the results of t tests comparing 4D-PET and 4D-PET_{ICT}.

Patient #	Tumor Volume (mL)	T15%	T25%	T35%	T45%	T65%	T75%	T85%	T95%	Average
1	4D-PET	85.15	86.99	84.67	83.35	83.35	85.05	85.23	84.35	84.77
	4D-PET _{ICT}	88.57	87.68	86.02	85.07	87.02	85.99	86.95	85.97	86.66
	PD	4.02	0.79	1.59	2.06	4.40	1.11	2.02	1.92	2.24
2	4D-PET	71.27	72.07	71.89	71.91	72.02	71.41	71.82	72.1	71.81
	4D-PET _{ICT}	71.88	72.21	72.56	72.45	72.88	71.92	72.26	72.69	72.36
	PD	0.86	0.19	0.93	0.75	1.19	0.71	0.61	0.82	0.76
3	4D-PET	79.03	78.05	76.76	77.46	77.85	79.37	81.61	77.87	78.50
	4D-PET _{ICT}	78.63	79.27	79.36	77.47	79.58	79.21	79.43	79.66	79.08
	PD	0.51	1.56	3.39	0.01	2.22	0.20	2.67	2.30	1.61
4	4D-PET	101.79	99.97	111.15	105.55	107.91	105.58	104.09	114.13	106.27
	4D-PET _{ICT}	104.89	101.97	111.5	106.24	105.98	106.23	108.09	117.95	107.86
	PD	3.05	2.00	0.31	0.65	1.79	0.62	3.84	3.35	1.95
5	4D-PET	100.64	101.01	100.93	90.39	91.6	92.9	91.7	97.85	95.88
	4D-PET _{ICT}	93.12	102.84	102.23	92.51	91.5	91.55	92.93	99.74	95.80
	PD	7.47	1.81	1.29	2.35	0.11	1.45	1.34	1.93	2.22
6	4D-PET	93.24	100.26	96.86	96.17	101.11	93.81	94.23	95.44	96.39
	4D-PET _{ICT}	94.14	102.21	97.61	96.67	105.19	94.56	93.64	96.07	97.51
	PD	0.97	1.94	0.77	0.52	4.04	0.80	0.63	0.66	1.29
7	4D-PET	133.63	143.9	140.95	138.88	129.95	147.99	157.49	141.09	141.74
	4D-PET _{ICT}	132.91	142.5	139.75	132.57	132.74	146.48	141.33	136.66	138.12
	PD	0.54	0.97	0.85	4.54	2.15	1.02	10.26	3.14	2.93
8	4D-PET	158.32	136.48	142.96	168	144.88	153.72	129.66	147.96	147.75
	4D-PET _{ICT}	157.77	144.1	151.42	172.19	155.32	169.27	141.98	155.62	155.96
	PD	0.35	5.58	5.92	2.49	7.21	10.12	9.50	5.18	5.79
9	4D-PET	77.79	78.32	75.58	76.8	77.59	78.87	78.3	77.22	77.56
	4D-PET _{ICT}	78.37	79.57	77.13	78.22	79.86	79.74	79.9	78.85	78.96
	PD	0.75	1.60	2.05	1.85	2.93	1.10	2.04	2.11	1.80
10	4D-PET	105.78	118.06	109.99	112.67	104.58	106.05	99.44	110.77	108.42
	4D-PET _{ICT}	108.69	112.97	106.47	109.67	101.73	108.87	105.04	110.61	108.01
	PD	2.75	4.31	3.20	2.66	2.73	2.66	5.63	0.14	3.01
11	4D-PET	327.89	302.82	309.82	297.29	298.8	283.59	317.43	308.54	305.77
	4D-PET _{ICT}	321.96	295.69	296.34	289.76	310.98	289.88	310.8	314.62	303.75
	PD	1.81	2.35	4.35	2.53	4.08	2.22	2.09	1.97	2.68
12	4D-PET	217.39	217.37	209.33	252.93	217.58	210.56	214.04	223.91	220.39
	4D-PET _{ICT}	209.67	201.29	214.38	236.93	214.56	206.81	199.37	227.77	213.85
	PD	3.55	7.40	2.41	6.33	1.39	1.78	6.85	1.72	3.93

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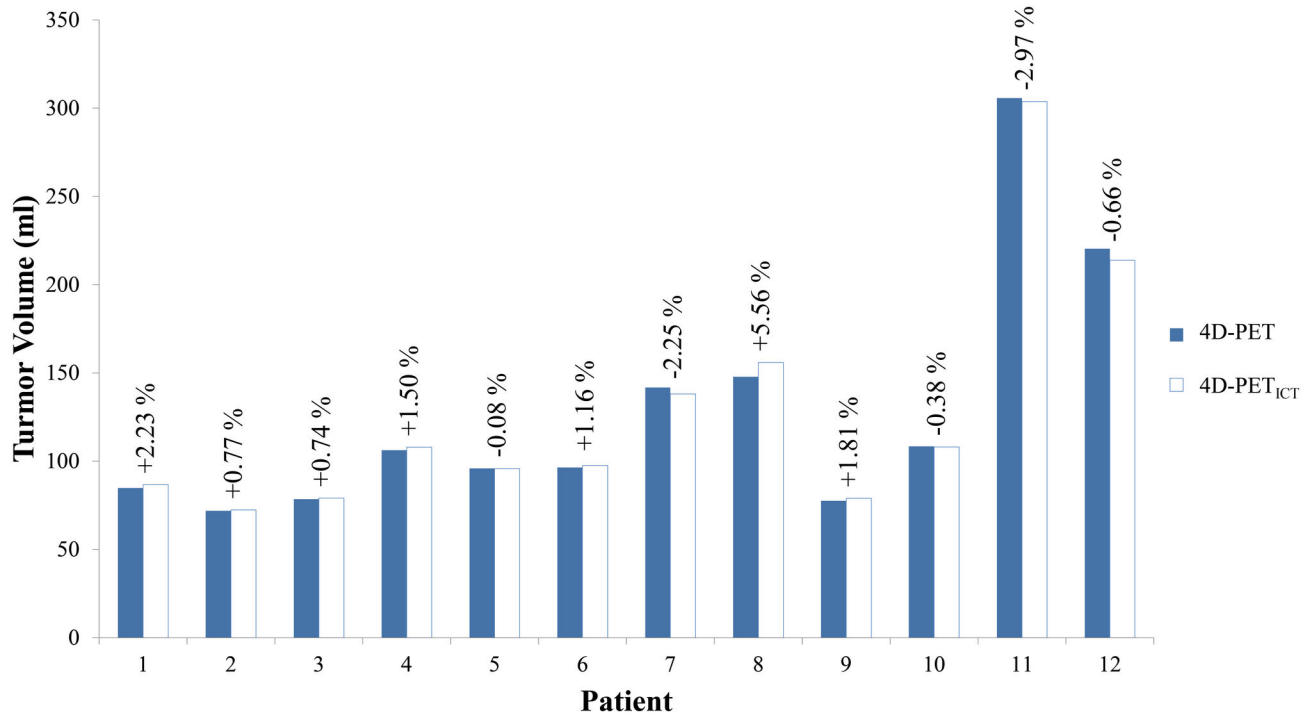


Figure 3. A bar graph showing the mean tumor volume from 4D-PET and 4D-PET_{ICT} for each patient. The percentage difference between 4D-PET and 4D-PET_{ICT} is indicated on the top of each bar.

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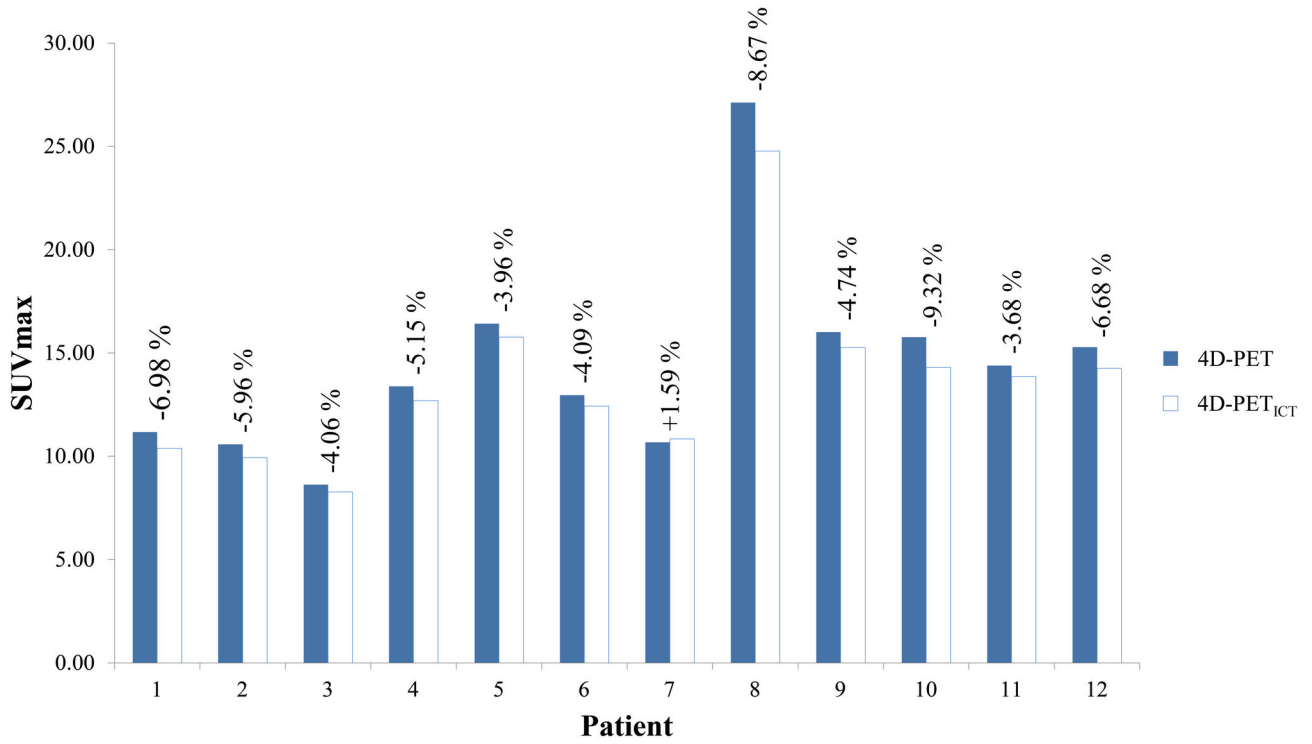


Figure 4. A bar graph representing the SUV_{max} from 4D-PET and 4D-PET_{ICT} for each patient. The percentage difference between 4D-PET and 4D-PET_{ICT} is indicated on the top of each bar.

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Author Contributions

Conceived and designed the experiments: TH. Performed the experiments: TH YW CK. Analyzed the data: TH. Contributed

reagents/materials/analysis tools: TH. Wrote the manuscript: TH.

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