Single-source Dual-energy CT as a Part of ^{18}F -FDG PET/CT: Direct Comparison of Iodine-related and Metabolic Parameters in Non-small Cell Lung Cancer

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Abstract. *Aim: The aim of the study was to assess possible correlation of fluorodeoxyglucose (FDG) uptake and iodine-related attenuation values derived from positron-emission tomography/computed tomography (PET/CT) using single-source dual-energy CT scan (DE-CT) in non-small cell lung cancer (NSCLC). Materials and Methods: Forty-eight patients with histologically-proven NSCLC underwent ^{18}F -FDG-PET/CT within their staging process. PET/CT included single-source DE-CT in late post-contrast phase. Direct comparison of PET and DE-related values was performed. A sub-study regarding different histological types and various thresholds for quantification of volume metabolic values was also performed. Results: A strong correlation was found of metabolic tumor volume and total lesion glycolysis with total iodine content using Pearson correlation analysis ($r=0.965-0.983$; $p<0.0001$) with various thresholds for FDG lesion segmentation. The strongest correlations with iodine content were reached using 10% threshold for segmentation. Only a weak correlation was found between iodine content and the maximal standard uptake value. A significant difference between adenocarcinomas and other histological subtypes was found for selected parameters of metabolic PET and DE-CT data. Conclusion: Our study demonstrated a strong correlation of the iodine content calculated from single-source DE-CT with volumetric FDG parameters in NSCLC, without a significant effect of the threshold value for FDG lesion segmentation.*

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Positron-emission tomography (PET)/computed tomography (CT) with ^{18}F -labeled fluorodeoxyglucose (FDG) is currently the most accurate method for the detection and assessment of lung carcinoma, with higher sensitivity and specificity than CT alone (1, 2). In this respect, PET/CT is the recommended method for staging, however, it was recently demonstrated that level of FDG uptake has also a prognostic value determining the probability of successful therapy (3-5). At the same time, there is a presumption that the vascularization of lung tumors is related to their aggressiveness, that can be assessed by dynamic contrast-enhanced CT (DCE-CT) (6-8).

Standard CT imaging without the use of metabolic or perfusion parameters is still the most commonly used method for evaluating the response to selected anticancer therapy due to technical demands, a higher radiation burden and the economic costs of PET/CT. Although morphological assessment is standard for monitoring the effect of anticancer therapy, this assessment has fundamental limitations, particularly in targeted therapy. Therefore, the metabolic or perfusion response should be preferred. CT-based therapy-response monitoring can be used subsequently after treatment completion; on the contrary, FDG-PET can reflect the response to treatment within a short interval (*e.g.* within the second week of chemoradiotherapy) with the possibility of enabling early adaptations to therapy (9-11).

Dual-energy CT (DE-CT) is a relatively simple method for objective evaluation of tumor vascularization using iodine-related attenuation (IRA). To date, only a limited number of studies have been performed comparing IRA parameters obtained from DE-CT and FDG values. Schmid-Bindert *et al.* demonstrated a correlation between the maximum standard uptake value (SUVmax) and IRA (12).

The aim of our study was to directly compare the different metabolic parameters and IRA values obtained from ^{18}F FDG PET/CT with those from single-source DE-CT in patients with non-small cell lung cancer (NSCLC).

Materials and Methods

Study design and population. In 2015 and 2016, a total of 48 patients (23 males; average age 66 years) were prospectively included in the study. Patient characteristics are detailed in Table I. All patients were referred for FDG-PET/CT including single-source DE-CT scan due to staging of lung cancer. No interim examinations were performed. The use of defined PET/CT examination protocol was approved by the local Ethics Committee and all patients gave their informed consent to participation. Only patients with histologically proven NSCLC without contraindications for administration of iodine contrast agent underwent the defined scanning protocol.

¹⁸F-FDG-PET/CT protocol. All examinations were performed on an integrated clinical PET/CT 128-row CT and 4-ring PET subsystems (Biograph mCT 128; Siemens Healthcare, Knoxville, TX, USA). The examination was initiated with CT scanning performed by the 128-slice single source CT sub-system following administration of iodine contrast agent (Iomeron 350; Bracco, Milano, Italy). A uniform amount of 100 ml iodine contrast agent was injected (flow rate 4 ml/s) *via* antecubital vein using an over-pressure injector (Ulrich Motion, Ulm, Germany) followed by saline flush (50 ml). The first scan (single-energy) was performed for the whole body (skull base to groin) in arterial phase. The timing of the scan was performed using dedicated monitoring system (BolusTracking, Siemens Healthcare, Forchheim, Germany). The subsequent DE scan was performed only in the extent of chest using a scanning prototype protocol which consisted of two separate scans with different fixed tube voltage, quality referenced miliampere seconds and pitch factor (80 kV/298 mAs/0.6 and 140 kV/71/1.2). Other scanning parameters were constant for both scans (collimation=128×0.6 mm, rotation time=0.5 s). The default delay of the single-source DE scan was set to 75 s after the end of the first, single-energy scan. Two datasets with slice thickness of 1.0 mm (increment 0.6 mm; kernel B26) were reconstructed.

The PET scan was initiated 60-70 min after administration of ¹⁸F-FDG (activity of 2.5 MBq/kg). The scan was performed by step-and-shoot technique and the whole body was covered by 5-6 scanner positions ('beds'). The acquisition time was 90 s/bed. PET raw-data were reconstructed in a 400×400 pixel matrix in transaxial field-of-view with 46 cm diameter using the ultraHD algorithm, which combines the time-of-flight and point-spread function algorithms, and 2 mm full width at half maximum. Each PET dataset with attenuation correction using single-energy scan was reconstructed for subsequent analysis.

Image analysis. Each PET dataset was analyzed in consensus by two experienced radiologists (11 and 9 years' experience with hybrid imaging) in dedicated software application Syngo *via* MM Oncology (Siemens Healthcare). Segmentation of the FDG uptake in the lung tumours was performed using an automatic algorithm with five different isocontour thresholds (10%, 20%, 30%, 42% and 50%) of absolute SUV. Various SUV parameters were calculated by body weight [measured activity concentration (Bq/ml)/injected dose (Bq) × patient weight (g)]: maximal SUV (SUV_{max}), peak SUV (SUV_{peak} – highest average 1 cm³ equivalent); mean SUV (SUV_{mean}); and metabolic tumor volume (MTV). Total lesion glycolysis (TLG) was calculated as: MTV × SUV_{mean}. Diameters in orthogonal projections and volumes were calculated in segmented lesions.

Table I. Baseline characteristics of patients.

Characteristic	Value
Age, years	
Mean (range)	66 (40-81)
Gender, n (%)	
Male	25 (53%)
Female	23 (47%)
Histology, n (%)	
Adenocarcinoma	20 (42 %)
Squamous cell carcinoma	25 (52 %)
Non-differentiated	3 (6 %)
Stage, n	
IA/IB	6/8
IIA/IIIB	7/5
IIIA/IIIB	13/3
IV	6

DE-CT datasets were analyzed in dedicated software prototype eXamine (Siemens Healthcare, Forchheim, Germany) in consensus by the same experienced radiologists. Tumors were segmented using a semi-automatic algorithm with the possibility of manual corrections of peripheral borders (Figure 1). The total iodine content (mg) and iodine uptake relative to tumor size (mg/ml) were acquired for all tumors.

Statistical analysis. Complete statistical analysis was performed using commercially available software (MedCalc Software, Ostend, Belgium). Standard descriptive statistics were used to assess the observations of different variables (mean, standard deviation). Pearson correlation coefficient was used for comparison of FDG and DE-CT parameters measured in individual tumors (*r*: 0-0.2 without correlation; >0.2 and <0.5 weak correlation; >0.5 and <0.7 moderate correlation; >0.7-0.9 strong correlation). Subgroup analysis of different histological types (adenocarcinomas *vs.* non-adenocarcinomas) was performed using the two-sample *t*-test. Box plots and bar charts were used for visual comparison of the selected samples. All tests were performed at the 5% level of significance.

Results

Results of analysis of PET and DE images are presented in Table II, including measurements with different thresholds for automatic delineation of lesions. Histological sub-types were determined according biopsy or post-resection assessment.

PET *vs.* DE correlation. A strong correlation was generally shown between MTV and total iodine content using Pearson correlation analysis (*r*=0.965-0.983; *p*<0.0001) (Figure 2). Strong correlation between TLG and total iodine content was also found at all SUV thresholds used for lesion segmentation (*r*=0.965-0.972; *p*<0.0001) (Figure 3). Only weak correlation was found between total iodine content and SUV_{max} (*r*=0.459; *p*=0.004), SUV_{peak} (*r*=0.467; *p*=0.003) and

Figure 1. Multimodal assessment of peripheral non-small cell lung cancer. A: Iodine map B: Fluorodeoxyglucose uptake segmentation with 10% (purple line) and 50% (green line) threshold.

Table II. Overview of fluorodeoxyglucose uptake and iodine-related parameters.

Parameter	Overall (n=48)	Adenocarcinoma (n=28)	Non-adenocarcinoma (n=20)	<i>p</i> -Value
SUVmax	19.5 (16.0)	17.58 (7.1)	29.45 (18.2)	0.006
SUVpeak	14.4 (13.2)	11.8 (5.9)	21.76 (15.0)	0.006
SUVmean_42%	11.5 (9.2)	10.16 (4.5)	15.28 (8.9)	0.021
Iodine uptake (mg/cm ³)	1.5 (0.7)	1.88 (0.76)	1.38 (0.51)	0.018
Maximal iodine density (HU)	124.0 (68.5)	133.9 (49.7)	155.92 (77.4)	0.332
Mean iodine density (HU)	33.1 (15.5)	43.61 (18.3)	31.42 (11.7)	0.014

Values of parameters are expressed as mean (standard deviation). SUV: Standard uptake value; SUVmean_42%: SUV_{mean} with 42% segmentation threshold; HU: Hounsfield unit.

SUVmean ($r=0.379-0.466$; $p=0.008-0.015$). Weak and moderate correlation was demonstrated when comparing maximal iodine density and all SUV parameters. For other parameters, there was no or negative correlation between SUV parameters and iodine-related attenuation values calculated in DE analysis. Complete results are presented in Table III.

Comparison of SUV thresholds. Values of SUVmean, MTV and TLG were acquired using multiple thresholds (10-50%). Using all parameters, the highest correlation with total iodine content was reached using 10% ($r=0.983$; $p<0.001$) and

lowest with 50% ($r=0.965$; $p<0.001$). Complete results are presented in Table III.

Comparison of histological subtypes. Significant differences between adenocarcinomas and other histological subtypes were found for selected parameters of metabolic and DE data. Statistical analysis revealed significantly lower glucose metabolic parameters and, on the contrary, higher iodine-related attenuation values in the histological subgroup of adenocarcinomas (Figures 4 and 5). Complete results are presented in Table II.

Table III. Summary of Pearson correlation analysis of fluorodeoxyglucose uptake and iodine-related parameters.

Parameter	Threshold	Total iodine content (mg)		Iodine uptake (mg/ml)		Mean iodine density (HU)		Maximal iodine density (HU)	
		r	p-Value	r	p-Value	r	p-Value	r	p-Value
SUVmax		0.459	0.0037	-0.277	0.084	-0.273	0.089	0.51	0.0008
SUVpeak		0.467	0.003	-0.323	0.042	-0.323	0.042	0.482	0.002
SUVmean	50%	0.379	0.015	-0.257	0.101	-0.263	0.101	0.435	0.004
	42%	0.414	0.009	-0.27	0.092	-0.266	0.097	0.48	0.002
	30%	0.412	0.009	-0.281	0.079	-0.276	0.085	0.471	0.002
	20%	0.419	0.009	-0.254	0.124	-0.245	0.138	0.476	0.003
	10%	0.466	0.008	-0.342	0.056	-0.334	0.062	0.414	0.019
MTV	50%	0.965	<0.0001	-0.201	0.214	-0.209	0.196	0.556	0.0002
	42%	0.969	<0.0001	-0.208	0.198	-0.216	0.18	0.56	0.0002
	30%	0.972	<0.0001	-0.219	0.175	-0.228	0.158	0.572	0.0001
	20%	0.973	<0.0001	-0.231	0.164	-0.239	0.148	0.587	0.0001
	10%	0.983	<0.0001	-0.257	0.155	-0.264	0.145	0.658	0.0001
TLG	50%	0.965	<0.0001	-0.235	0.144	-0.240	0.136	0.579	0.0001
	42%	0.972	<0.0001	-0.236	0.143	-0.241	0.134	0.588	0.0001
	30%	0.968	<0.0001	-0.239	0.138	-0.244	0.129	0.595	0.0001
	20%	0.966	<0.0001	-0.245	0.127	-0.250	0.120	0.603	0.0001
	10%	0.965	<0.0001	-0.302	0.105	-0.308	0.098	0.607	0.0004

SUV: Standard uptake value; HU: Hounsfield unit; MTV: metabolic tumor volume; TLG: total lesion glycolysis; r: Pearson correlation coefficient.

Discussion

The main finding of our study is a very strong correlation between volumetric FDG values (MTV and TLG) and total iodine content in NSCLC. We consider this to be important in terms of the possible combined use of ¹⁸FDG PET/CT and DE-CT in determining prognosis and, in particular, when monitoring the effects of therapy. To our knowledge, a similar study with the direct comparison of these two modalities has not yet been conducted. Moreover, there are only a limited number of studies comparing FDG with IRA parameters derived from DE-CT. Schmid-Bindert *et al.* demonstrated a strong correlation between maximal SUV and maximal IRA values not only in primary lung tumors, but also in mediastinal lymph nodes (12). The maximal SUV is routinely used to assess the level of metabolic activity of malignant lesions; on the other hand, its predictive value for therapy response can be limited in the case of larger lesions or lesions with a significantly non-homogeneous distribution of FDG uptake (13). The same limitation applies for the maximal IRA value, especially if the examination is performed in the early post-contrast phase (14). Several studies have confirmed that volumetric FDG parameters are also significant parameters for the prognosis of disease recurrence or disease-free survival (15-17). Moreover, Satoh *et al.* found that for NSCLCs larger than 3 cm, MTV and TLG have a higher predictive ability than SUVmax. At the same time, these parameters have been found to be

predictive independently of the clinical stage, and a low variability among evaluators has been demonstrated (18).

DE-CT, a still developing technology, is no longer limited to dual-source CT scanners. However, different types of devices and scanning techniques cause problems with the comparability of absolute values in reported studies. In addition to basic IRA determinations using Hounsfield units, direct iodine quantification (mg) is also available, possibly relative to the tumor volume (mg/ml). In our study, we used a prototype dedicated software, but these features are now a part of commercially available solutions and allow volumetric quantification of iodine uptake and total iodine content. The accuracy of iodine quantification by DE has been demonstrated by comparing different technologies (19).

The time interval between the administration of an iodinated contrast agent and imaging is an important difference between assessment of vascularization by DCE and that by DE. 'First-pass' perfusion is evaluated in DCE-CT, while a longer interval (more than 70 seconds) is recommended for DE-CT, *i.e.* already in the equilibrium phase when the saturation of the contrast agent in the tumor is relatively stable (14, 20, 21). Our patients were scanned 75 seconds after the completion of the single energy scan in the arterial phase, about 90-100 seconds after the administration of the contrast agent. The reason for the long delay was the use of a single-source DE scan that comprises two consecutive scans. This technique is not widely used, but allows performance of the DE scan with single-source CT

Figure 2. Scatter-plot of the correlation between metabolic tumor volume (MTV) and iodine content.

Figure 3. Scatter-plot of the correlation between total-lesion glycolysis (TLG) and iodine content.

devices (22). It can be assumed that modern PET/CT devices will be equipped with CT subsystems enabling DE scan.

Previously published studies showed that DE-CT parameters correlates with perfusion parameters calculated from DCE-CT in vascularization assessment. The accuracy of IRA was demonstrated both using dedicated phantom tests or in comparison with dynamic perfusion CT (23, 24). DCE-CT scanning is technically more challenging than DE-CT with a limited range in the scanning axis, and also represents a higher exposure to ionizing radiation, as well as to a higher amount of iodinated contrast agent. In addition to these facts, no method for processing and interpreting the results of perfusion CT from the entire tumor volume has yet been defined. Several kinetic models are available for calculating perfusion parameters and perfusion mapping, and quantification itself is a problem. The most common method in commercially available software is the use of a manual border with a region

Figure 4. Box-plot diagrams showing maximal standard uptake (SUVmax) values for adenocarcinomas (n=20), and non-adenocarcinomas (n=28). Boxes represent 25th-75th percentiles; lines represent the median values, and bars the range.

Figure 5. Box-plot diagrams showing iodine for between adenocarcinomas (n=20), and non-adenocarcinomas (n=28). Boxes represent 25th-75th percentiles; lines represent the median values, and bars the range.

of interest. More advanced data processing techniques from perfusion testing are often performed in dedicated software. The resulting perfusion parameters are greatly influenced by many factors (*e.g.* the amount and mode of administration of the contrast agent, or patient characteristics).

In addition to a better comparability and limited dependency on the patient and the delivery of the contrast agent, another advantage of DE-CT over CT perfusion is the better representation of different compositions of tumor when assessing the extravascular/extracellular component. It is well known that in lung tumors, especially in adenocarcinomas, not only necrotic, but also fibrotic changes are often present which have a major effect on post-contrast saturation, especially in the late phase. This is a probable reason for the negative

correlations of the maximal and peak SUV values with iodine uptake demonstrated in our study. A possible reason why there was not a strong correlation between the SUV values and iodine content is the heterogeneity of histological types and grading. Iwano *et al.* demonstrated the dependence of the degree of differentiation and measured IRA values (14). In our substudy, we also demonstrated a statistically significant difference in the SUV_{max} and DE values between adenocarcinomas and other histological types (25).

Our findings regarding the very strong correlation of MTV and TLG with iodine content may contribute to the further implementation of DE-CT in algorithms for the evaluation of NSCLC. While studies using FDG uptake to determine patient prognosis have already been reported, only a small number have addressed the prognostic value of DE-CT in cancer (26, 27). In addition to their prognostic value, MTV and TLG parameters are also beneficial in assessing the actual response to therapy. In particular, the possibility of determining an early response to different types of anticancer therapies is important in enabling possible effective adjustment (28). Both MTV and iodine content are affected not only by tumor size, but also by the distribution of the SUV. The inhomogeneity of tumor vascularization and FDG uptake are significant limitations of the maximal SUV and iodine uptake. The TLG value is also affected by the mean SUV. The use of volumetric FDG parameters is limited by the inconsistency in quantification of the MTV, when different threshold values (as a percentage) are used for segmentation of the FDG uptake foci (29). Our study included a comparison of different threshold values, including the frequently used 42%, for segmentation. A strong correlation with MTV and TLG was demonstrated in all fixed percentage thresholds, however, the strongest was at 10%.

Our study demonstrated only a moderate correlation of the maximal and peak SUV with DE parameters (iodine uptake and iodine content). The results of previously published studies also confirm a marked inconsistency in the correlation of these or similar parameters. Iwano *et al.* demonstrated a significant negative correlation between iodine volume and SUV_{max}, while a strong positive correlation between the maximum IRA and SUV_{max} was demonstrated by Schmid-Bindert *et al.* (12, 14). It should be noted that their examination and contrast agent administration protocols differed, mainly in the time of the DE scan after administration. In addition, different techniques for quantification of the parameters compared were used in both cases.

There are several limitations of our study that need to be mentioned. In addition to the low total number of patients, these limitations include non-homogeneity of the population in terms of histological evaluation and clinical stage. The use of a single-source DE protocol is also a limitation, and we did not perform lymph node analysis. Our analysis was only of pre-treatment assessment, no interim or post-treatment analysis was included.

It can be concluded that our study demonstrated the strong correlation of the iodine content calculated from single-source DE-CT with volumetric FDG parameters in primary NSCLC without a significant effect of the threshold value for FDG lesion segmentation. The probable prognostic value of iodine content and its value in therapy monitoring related to FDG uptake needs to be assessed in the future. Integration of dual-source subsystems into PET/CT scanners cannot be expected to be expanded in the future, however, new types of single-source scanners allowing dual-energy scanning could be integrated. This could provide a unique possibility of combining dual functional assessment of tumor tissue.

Conflicts of Interest

Thomas Flohr, Martin Sedlmair and Bernhard Schmidt: Employees of Siemens Healthcare, Forchheim, Germany. These co-authors were not involved in performance and analysis of examinations.

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