Motion-Compensated FDG PET/CT for Oesophageal Cancer

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Research

Keywords: Oesophageal cancer, Radiotherapy, Threshold-based delineation, Positron-emission tomography computed tomography, Four-dimensional computed tomography, Motion-compensated, Lymph node detection, Standardized uptake value, Gross tumour volume, Fluorodeoxyglucose F18

DOI: https://doi.org/10.21203/rs.3.rs-80605/v1

Abstract

Purpose

Respiratory-induced motion of oesophageal tumours and lymph nodes can influence positron emission tomography/computed tomography (PET/CT). The aim was to compare standard three-dimensional (3D) and motion-compensated PET/CT regarding standardized uptake value (SUV), metabolic tumour volume (MTV) and detection of lymph node metastases.

Methods

This prospective observational study (NCT02424864) included thirty-seven newly diagnosed oesophageal cancer patients. Diagnostic PET/CT was reconstructed in 3D and motion-compensated PET/CT. MTVs of the primary tumour were calculated using an automated region-growing algorithm with SUV thresholds of 2.5 (MTV2.5) and ≥50% of SUVmax (MTV50%). Blinded for reconstruction method, a nuclear medicine physician assessed all lymph nodes showing ^{18}F-fluorodeoxyglucose uptake for their degree of suspicion.

Results

The mean (95% CI) SUVmax of the primary tumour was 13.1(10.6-15.5) versus 13.0(10.4-15.6) for 3D and motion-compensated PET/CT, respectively. MTVs were also similar between the two techniques. Bland-Altman analysis showed mean differences between both measurements (95% limits of agreement) of 0.08(-3.60 - 3.75), -0.26(-2.34 – 1.82), 4.66(-29.61 – 38.92)cm^3 and -0.95(-19.9 – 18.0)cm^3 for tumour SUVmax, lymph node SUVmax, for MTV2.5 and MTV50%, respectively. Lymph nodes were classified as highly suspicious (30/34 nodes), suspicious (20/22) and dubious (66/59) for metastases on 3D/motion-compensated PET/CT. No additional lymph node metastases were found on motion-compensated PET/CT. SUVmax of the most intense lymph nodes was similar for both scans: mean (95% CI) 6.6(4.3-8.8) and 6.8(4.5-9.1) for 3D and motion-compensated, respectively.

Conclusions

SUVmax of the primary oesophageal tumour and lymph nodes was comparable on 3D and motion-compensated PET/CT. The use of motion-compensated PET/CT did not improve lymph node detection.

Trial registration

(www.clinicaltrials.gov: NCT02424864)

Highlights

- SUVmax of the primary tumour and lymph node metastases was similar on 3D and motion-compensated PET/CT in a prospective cohort of oesophageal cancer patients.

- Motion-compensated PET/CT image acquisition did not reveal additional lymph node metastases compared to 3D PET/CT.
- Threshold-based tumour lengths showed poor correlation with endoscopic tumour lengths and should be used with caution.
- Metabolic tumour volumes of the primary tumour based on threshold of SUV≥2.5 and ≥50% SUVmax were similar between 3D and motion-compensated PET/CT.

Introduction

Most patients with oesophageal cancer present with locally advanced disease or with distant metastases[1]. ^{18}Ffluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT) has an important role in staging oesophageal cancer patients and therefore in selecting patients for potentially curative treatment. In the Netherlands, potentially curative treatment consists of neo-adjuvant chemoradiotherapy followed by surgery for operable patients and definitive chemoradiotherapy for inoperable patients or patients with irresectable tumours[2, 3].

PET/CT is increasingly incorporated in radiation treatment preparation. Fusion of PET images with those of the planning CT scan facilitates demarcation of the oesophageal gross tumour volume (GTV) and helps to identify regional lymph node metastases that should be included in the radiation volume[4–7]. To improve delineation accuracy, automatic threshold-based delineation has been suggested[8]. Using a threshold with a certain standardized uptake value (SUV) or a predefined percentage of the maximum (SUVmax) has been described[6, 8]. The influence of motion-compensated PET/CT techniques on these PET tumour segmentation volumes is unknown.

Furthermore, detecting all lymph node metastases before start of treatment is of crucial importance, to increase chances of treatment success. Combined PET/CT can reveal lymph node metastases, but its sensitivity is low (approximately 51%) and its specificity is moderate (84%)[9]. Possible explanations for this suboptimal performance are 1) a small proportion (0–32%) of oesophageal tumours is non-FDG-avid[5], 2) small lymph nodes can give a metabolic signal that remains below the detection level and 3) respiratory motion can cause image blurring of the lesions, which can fade out the signal of the lymph node metastases. The technology to reduce the effects of tumor motion induced by breathing was first studied in lung cancer[10–13]. The four-dimensional (4D) PET/CT can be reconstructed in a time-averaged motion-compensated (MC) PET/CT. Compared to 3D PET/CT, image blurring was significantly reduced, resulting in better characterization of lung lesions and lymph nodes. Also for liver lesions, improved diagnostic accuracy was seen with the motion-compensated PET/CT technique[14, 15].

Like lung tumours and liver metastases, oesophageal tumours and mediastinal lymph nodes are subject to substantial respiratory-induced motion[16, 17]. Furthermore, lymph node metastases of tumours at the distal oesophagus or gastro-esophageal junction are expected to be located around the distal oesophagus or celiac trunk where a larger motion is expected than at the upper mediastinum[17]. As yet, the role of motion-compensated PET/CT in oesophageal cancer has not been studied. The aims of this

prospective study were to compare 3D and motion-compensated PET/CT for the measurement of the SUVmax and metabolic tumour volume (MTV) of the primary tumour and for the detection of lymph nodes metastases in patients with oesophageal cancer.

Methods

Between April 2015 and December 2016, this single centre prospective cohort study (www.clinicaltrials.gov: NCT02424864) included newly diagnosed oesophageal cancer patients undergoing diagnostic workup with PET/CT in the Netherlands Cancer Institute. Written informed consent was obtained in all patients according to the International Conference of Harmonisation/Good Clinical Practise (ICH/GCP) and national and local regulations. This study was approved by the institute's medical ethical committee.

FDG PET/CT scans were acquired using a combined PET/CT scanner (Gemini TF/ Big Bore; Philips Medical Systems, Cleveland Ohia, USA). A PET with low dose CT scan from skull base to thighs was acquired 60 +/- 10 min after injection of FDG (190–260 MBq) at 2 min per bed position in 3D mode. Two bed positions centred around the oesophageal tumour were acquired in 4D mode at 4 min per bed position. Subsequently, the 4D CT of the thorax and upper abdominal region was acquired and reconstructed with a slice thickness of 3 mm. Motion of the tumour was determined by assessing the displacement during the breathing cycle in 10 phases in left-right (LR), craniocaudal (CC) and anterior-posterior (AP) direction with in-house developed software. The 10 breathing phases were used to reconstruct a time-averaged mid position CT and attenuation-corrected motion-compensated PET scan; in addition, the 3D CT scan was used to reconstruct the 3D attenuation corrected PET scan[11]. Details on the 4D PET/CT acquisition and reconstruction are provided in the supplementary material.

The 3D and motion-compensated PET/CT reconstructions were pseudonymised. Observers (EV, FV) were blinded for technique. The nuclear medicine physician (EV) assessed the quality of the scan on a five-point scale (very good, good, acceptable, poor and very poor).

The tumour was manually indicated and subsequently a volume of interest (VOI) was computed around the tumour using an automatic region-growing algorithm based on a minimum SUV threshold using Osirix software (Pixmeo SARL, Geneva, Switzerland). SUVmax was measured. Automatic segmentations with an SUV threshold of 2.5 and a threshold of 50% of the SUVmax were generated[6, 18]. When these segmentations extended into other FDG-avid organs (e.g. heart or liver) they were manually corrected using the anatomical boundaries on CT. Subsequently, of these segmented volumes, the SUVmean, metabolic tumour volume (MTV) and craniocaudal extension were measured and compared between 3D and motion-compensated reconstructions. Craniocaudal tumour length on PET/CT was also compared with the endoscopic tumour length.

An experienced gastrointestinal nuclear medicine physician (EV) scored the degree of suspicion of the lymph nodes on a four-point scale (highly suspicious, suspicious, dubious or unlikely) based on the intensity of the metabolic signal. The two most suspicious lymph nodes were localized and SUVmax per

node was measured. The numbers and locations of highly suspicious, suspicious, dubious or unlikely nodes were compared between 3D and motion-compensated PET/CT.

Measurements between the two groups (3D versus motion-compensated scans) were compared using a Paired Student's t-test, Wilcoxon signed-rank test and Bland-Altman analysis. Pearson correlation coefficients were calculated. *P*-values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS (version 24).

Results

Thirty-nine patients were prospectively recruited for this study. In 2 patients, there was technical failure during 4D reconstruction, resulting in a total of 37 patients available for analysis. The patient characteristics are shown in Table 1. Based on all staging procedures combined, most patients had a clinically node positive adenocarcinoma located in the distal oesophagus or gastro-oesophageal junction. Figure 1 shows images of a patient with a node positive gastro-oesophageal junction tumour. After staging, patients were treated with neoadjuvant chemoradiotherapy (n = 23), definitive chemoradiotherapy (n = 9), neoadjuvant chemotherapy (n = 1) or palliative treatment (n = 4).

Table 1
Patient characteristics

Patient characteristics	All patients (n = 37)
Gender	
Male	20
Female	17
Age, years, median (range)	67 (40–86)
Histology	
Adenocarcinoma	25
Squamous cell carcinoma	12
Location of the primary tumour	
Proximal oesophagus	2
Mid oesophagus	9
Distal oesophagus	11
Gastro-oesophageal junction	15
Clinical T stage*	
cT2	8
cT3	28
cT4	1
Clinical N stage*	
cN0	10
cN1	16
cN2	9
cN3	2
Clinical M stage*	
cM0	35
cM1	2

Abbreviations: *PET: positron emission tomography, CT: computed tomography.*

[*] *Clinical tumour-node-metastasis stage according to 7th edition TNM classification as defined by all staging procedures (computed tomography, endoscopic ultrasound, positron emission tomography) together.*

Patient characteristics	All patients (n = 37)
Endoscopic tumour length, cm, median (range)	5 (2–14)
Treatment after PET/CT staging	
Neoadjuvant chemoradiotherapy	23
Definitive chemoradiotherapy	9
Neoadjuvant chemotherapy	1
Palliative treatment	4
Abbreviations: *PET: positron emission tomography, CT: computed tomography.*	
[*] *Clinical tumour-node-metastasis stage according to 7th edition TNM classification as defined by all staging procedures (computed tomography, endoscopic ultrasound, positron emission tomography) together.*	

Scan quality was rated as good in 65% and 68% of the 3D and motion-compensated PET/CT scans, respectively. Motion amplitude of the oesophageal tumour was largest in the CC direction and CC motion varied between 0 and 21 mm with a median of 6.0 mm. In 6 patients the CC motion amplitude was > 10 mm. There was no correlation between CC amplitude and 3D/motion-compensated differences in SUVmax (r=-0.18, p = 0.29), MTV2.5 (r = 0.05, p = 0.78) or MTV50% (r=-0.01, p = 0.94) (See also Fig. 5).

The results of the quantitative analyses are shown in Table 2 and Fig. 2. In 60% of patients the automatically segmented MTVs based on SUV ≥ 2.5 (MTV2.5) had to be edited manually, because it extended into surrounding organs (such as heart, kidneys or liver). The extension of the volume in the oesophagus or stomach was not edited, because tumour extension and oesophagitis or gastritis could not be distinguished.

Table 2
Qualitative analysis of metabolic activity and metabolic volumes on 3D and MC PET/CT

Measurement	3D			MC			
	Mean +/- SD (95% CI)			Mean +/- SD (95% CI)			*p*
Primary tumour							
SUVmax	13.1	+/- 7.3	(10.6–15.5)	13.0	+/- 7.9	(10.4–15.6)	0.531‡
VOI SUV ≥ 2.5							
-SUVmean	4.5	+/- 1.4	(4.1-5.0)	4.5	+/- 1.5	(4.0–5.0)	0.946‡
-MTV (cm^3)	100.0	+/- 67.8	(77.4-122.6)	95.4	+/- 65.1	(73.7–117.0)	0.114*
VOI SUVmax ≥ 50%							
-SUVmean	8.5	+/- 4.6	(7.0-10.1)	8.6	+/- 5.1	(6.9–10.3)	0.792‡
-MTV (cm^3)	18.5	+/- 15.4	(13.4–23.7)	19.5	+/- 17.2	(13.7–25.2)	0.898‡
Lymph nodes							
SUVmax most intense nodes							
-Node 1;	6.6	+/- 6.2	(4.3–8.8)	6.8	+/- 6.3	(4.6–9.1)	0.549‡
-Node 2;	5.7	+/- 5.6	(3.3-8.0)	5.9	+/- 6.2	(3.3–8.5)	0.587‡
Number of lymph nodes							
-highly suspicious	0.9	+/- 1.5	(0.3–1.4)	1.0	+/- 1.7	(0.4–1.6)	0.206‡
-suspicious	0.6	+/- 0.7	(0.3–0.8)	0.6	+/- 1.0	(0.3-1.0)	0.766‡
-dubious	1.8	+/- 3.7	(0.6–3.2)	1.7	+/- 3.1	(0.6–2.8)	0.608‡

Abbreviations: *3D: three-dimensional, MC: motion-compensated, PET: positron emission tomography, CT: computed tomography, CI: confidence interval, SUV: standardized uptake value, max: maximum, SD: standard deviation, VOI: volume of interest, MTV: metabolic tumour volume.*

[*] Statistics calculated with paired t-test

[‡] Statistics calculated with Wilcoxon signed-rank test

The primary oesophageal tumour showed a mean (95% CI) SUVmax of 13.1 (10.6–15.5) on 3D versus 13.0 (10.4–15.6) on motion-compensated PET/CT ($p = 0.809$). The most intense lymph node showed a mean (95% CI) SUVmax of 6.6 (4.3–8.8) on 3D versus 6.8 (4.6–9.1) on motion-compensated PET/CT ($p = 0.176$). MTVs2.5 were not significantly different between 3D and motion-compensated PET/CT. Also, MTVs based on SUVmax ≥ 50% (MTV50%) were similar on both scans ($p = 0.554$). The Bland-Altman analysis showed mean differences between 3D and motion-compensated measurement (and corresponding 95% limits of agreement) of 0.08 (-3.60–3.75), -0.26 (-2.34–1.82), 4.66 (-29.61–38.92)cm^3 and − 0.95 (-19.9–18.0)cm^3 for tumour SUVmax, lymph node SUVmax, for MTV2.5 and MTV50%, respectively (Fig. 2). Percentage differences of 3D and motion-compensated MTV50% showed an interquartile range (IQR) of 92–109%. The two outliers (Fig. 2D, 3 and Fig. 6D) were patients with a relatively low SUVmax (≤ 8) of the primary tumour, resulting in differences in MTV50% between − 81% and + 160% on the 3D and 4D scan.

The median craniocaudal length of the MTV2.5 was 94 mm (range 44–204 mm) on 3D PET/CT and 88 mm (range 56–200 mm) on motion-compensated PET/CT ($p = 0.336$). The median craniocaudal length of the MTV50% was 44 mm (range 12–120 mm) on 3D and also 44 mm (12–124 mm) on motion-compensated PET/CT ($p = 0.645$). A comparison of the length of the tumour on endoscopy and the length of the MTVs is presented in Fig. 4. The MTV based tumour lengths showed poor correlation with the endoscopic tumour length; endoscopic length with MTV2.5 lengths (3D: $r = 0.12$, $p = 0.48$, MC: $r = 0.07$, $p = 0.69$) and endoscopic length with MTV50% (3D: $r = 0.15$, $p = 0.39$, MC: $r = 0.07$, $p = 0.69$).

The degree of suspicion for lymph node metastases based on the 3D respectively motion-compensated method was classified as follows: 30 respectively 34 nodes highly suspicious, 20 respectively 22 suspicious and 66 respectively 59 dubious. A more detailed analysis was performed in a subgroup of patients in whom there was a discrepancy in grade of suspicion that would have a clinical impact. In 8/37 (22%) patients, lymph nodes were scored unlikely to contain metastases on 3D while scored dubious or suspicious on motion-compensated PET/CT or vice versa. These nodes were correlated with the assessment at endoscopic ultrasound (EUS) and pathology if the nodes were investigated with EUS guided fine needle aspiration (EUS-FNA). In 7 of 8 discrepant cases, the nodes defined at motion-compensated PET/CT as “unlikely” nodes were negative at EUS/pathology and “dubious” or “suspicious” nodes were positive at EUS/pathology, while this was conversely for 3D PET/CT. In one patient the dubious node at motion-compensated PET/CT was suspicious at EUS, but FNA was not representative. These cases with discrepancies were reassessed on both scans. Direct comparison of the 3D with the motion-compensated PET/CT showed no clear differences in the intensity or clarity of these discrepant nodes. If those nodes would be reclassified, they would be scored with an equal degree of suspicion on 3D and motion-compensated PET/CT.

Discussion

In this study, motion-compensated PET/CT revealed no clear clinical benefit compared to 3D PET/CT imaging in oesophageal cancer patients. SUVmax of the primary tumour and lymph nodes was similar between 3D and motion-compensated PET/CT. The MTV2.5 and MTV50% were also similar on both scans for the complete group. In a subgroup of patients (SUVmax of the primary tumour of ≤ 8), large differences of the MTV50% were observed between 3D and motion-compensated PET/CT, probably caused by uptake around a SUV of 4 in inflammatory tissue surrounding the tumour, with the result that minor differences in SUVmax could show large impact on the MTV50%. In addition, threshold-based and endoscopic-based tumour lengths were poorly correlated. Furthermore, the motion-compensated technique did not improve the detection rate of lymph node metastases.

Prior studies on 4D PET/CT in oesophageal cancer focused on the primary tumour volumes only. Guo et al. evaluated the clinical target volumes (CTV) and planning target volumes (PTV) based on 3D CT, 4D CT and 3D PET/CT[19]. Volumes generated with 3D PET with 4D CT were significantly larger than those generated with 3D CT or 4D CT. Direct comparison of 3D PET/CT with 4D PET/CT was, however, not performed. Wang et al. determined GTV volumes on the average 4D PET/CT with auto-contouring methods using eight different thresholds and compared these PET-derived GTVs with a CT-derived GTVs[20]. SUV $\geq$ 2.5 and SUV $\geq$ 20% volumes correlated best with tumour length on CT. However, 4D PET/CT was not compared with 3D PET/CT. Scarsbrook et al. compared PTVs on 3D PET/4D CT with 4D PET/CT in 15 oesophageal cancer patients[21]. Volumes on both scans were similar, but overlap analysis demonstrated a median Dice similarity coefficient of 0.88 between both scans, leading to chance of under-coverage. However, the lack of pathology confirmation in this study obviates the clinical interpretation when this part of the volume is excluded from the PTV.

To our knowledge, the presented study is the first study in which the influence of motion-compensated PET/CT on the detection rate of pathological lymph nodes in oesophageal cancer was studied. Unfortunately, motion-compensation did not improve the lymph node detection rate. PET/CT is superior to CT in the detection of distant metastases. However, for the identification of regional lymph node metastases, the sensitivity of PET/CT is insufficient[9, 22]. Moreover, the location of suspicious lymph nodes may influence radiation target volumes and/or choice of surgical approach. Suspicious nodes are included in the radiation target volumes[4], but larger radiation volumes increase the chance of toxicity[23, 24]. Postoperative complications increase with an extended mediastinal lymph node dissection; a possible long-term benefit should thus be carefully weighed against the risk of a more complicated postoperative course[25]. Preferably, suspicious nodes are cytologically confirmed by EUS-FNA[26].

In this study, the additional value of motion-compensated PET/CT for the metabolic characterisation of oesophageal cancer was limited. There are several possible explanations for this finding. Firstly, the amplitude of the tumour motion was relatively small; on average 6.0 mm in craniocaudal direction. Zhao et al. described an average oesophageal tumour motion of 8.7 mm in craniocaudal direction using 4D CT[16]. The modest motion amplitude in our study might be explained by the 1 hour resting phase prior to PET/CT acquisition, which is not applicable in the abovementioned CT studies, resulting in more relaxed

patients with a more superficial breathing pattern. Kruis et al. investigated the influence of motion amplitude on 4D PET/CT in lung tumours and liver metastases[11]. For targets with a CC motion of less than 5 mm the benefit of motion-compensated PET/CT was limited, while a clear effect was seen with amplitudes of more than 10 mm. This effect was not observed in our study, possibly since only six patients had a peak-to-peak amplitude of > 10 mm.

Secondly, the identification of the borders of the oesophageal tumour on PET/CT imaging may also be difficult. Oesophageal tumours frequently show submucosal spread along the oesophagus and proximal stomach, which might complicate demarcation of the tumour boundaries[27]. Also, oesophagitis and gastritis can give an increased metabolic signal and are often seen in oesophageal cancer patients, limiting differentiation of tumour from inflammation. In patients with tumours with relatively low FDG avidity, this can be even more difficult. These factors hamper demarcation of the tumour, even if the blurring due to the respiratory signal has been compensated for. In this study, the craniocaudal extension of MTVs showed large differences with the tumour length as determined during endoscopy.

And lastly, the accuracy of threshold-based delineation is not only influenced by object motion, but also by other factors, such as metabolic activity of the tumour, homogeneity of uptake, voxel size and signal-to-noise ratio[28]. In this study, we only investigated the influence of object motion.

The threshold-based volumes in this study showed low agreement with tumour length on endoscopy. Currently, semi-quantitative PET analyses are increasingly investigated in oesophageal cancer[29, 30]. Threshold-based volumes are proposed for delineation purposes and SUVmax or metabolic changes are proposed for response assessment or as prognostic factors. However, current segmentation methods show shortcomings[28]. Advanced image segmentation algorithms are emerging that can cope with such challenges[31]. Also, different methodologies for segmentation or combined thresholds can contribute to the robustness of semi-quantitative volumes. However, most of these new segmentation methods have not yet been validated and the most reliable and robust delineation method remains to be found.

The limitations of our study are the relative low motion amplitude of both tumour and lymph nodes during PET/CT acquisition, prohibiting proper analysis of motion-compensated PET/CT in patients with larger amplitude motion. Furthermore, cytological confirmation of lymph node involvement was only available for a limited number of patients and pathological assessment of the actual pre-treatment tumour length was not possible due to neoadjuvant chemoradiotherapy or a non-surgical approach. Despite these limitations, the prospective study design with a relatively large patient sample contributes to current available literature.

In the future, the impact of PET-based measurements may even increase further. In the prospective dose-escalation phase I/II study of Yu et al., definitive chemoradiotherapy was given with an escalated simultaneous integrated boost to the volume of ≥ 50% SUVmax[32]. Encouraging local control rates and acceptable toxicity were seen. Unfortunately, the PET scan technique and segmentation algorithm were not described in the manuscript. For interpretation and implementation of results of studies using PET-volume guided treatment, uniform segmentation methods and PET technique are necessary.

Conclusions

Metabolic tumour volumes of the primary tumour and the SUVmax of the primary tumour and lymph nodes metastases were similar between 3D and motion-compensated PET/CT in the majority of patients. Motion-compensation during PET/CT in oesophageal cancer patients did not improve the detection rate of lymph node metastases. Automatic segmentation should be used with caution, especially in patients with a primary tumour with a relatively low SUVmax.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained in all patients according to the International Conference of Harmonisation/Good Clinical Practise (ICH/GCP) and national and local regulations. This study This study was approved by the medical ethical committee of the Netherlands Cancer Institute- Antoni van Leeuwenhoek hospital (METC AVL).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Prof JJS reports a patent on Computed Tomography Scanning with royalties paid by Elekta AB, a patent Motion Artefact Reduction in CT Scanning, a patent Methods and System for Protecting Critical Structures During Radiation Treatment with royalties paid by Elekta AB, and a patent Radiotherapy and Imaging Methods and Apparatus with royalties paid by Elekta AB. These patents are not correlated to this manuscript.

All other authors declare that they have no competing interests.

Funding

This study was funded by the Netherlands Cancer Institute- Antoni van Leeuwenhoek

Authors' contributions

FV, EV generated all the data from the scans. ST and JvK were involved in reconstruction of the 4D scans with the new software used for these reconstructions. FV, EV, JJS, BA were involved in design of the

protocol and interpretation of the data. FV, EV, JvK, JvS, JvD, ST, JJS, CG, AB, BA were involved in drafting the work and revising it. All authors read and approved the final manuscript.

Acknowledgements

We acknowledge Tineke Vijlbrief, Mark Kroon, Lyandra Rooze en Linda de Wit for their contribution on image acquisition and logistics.

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Figures

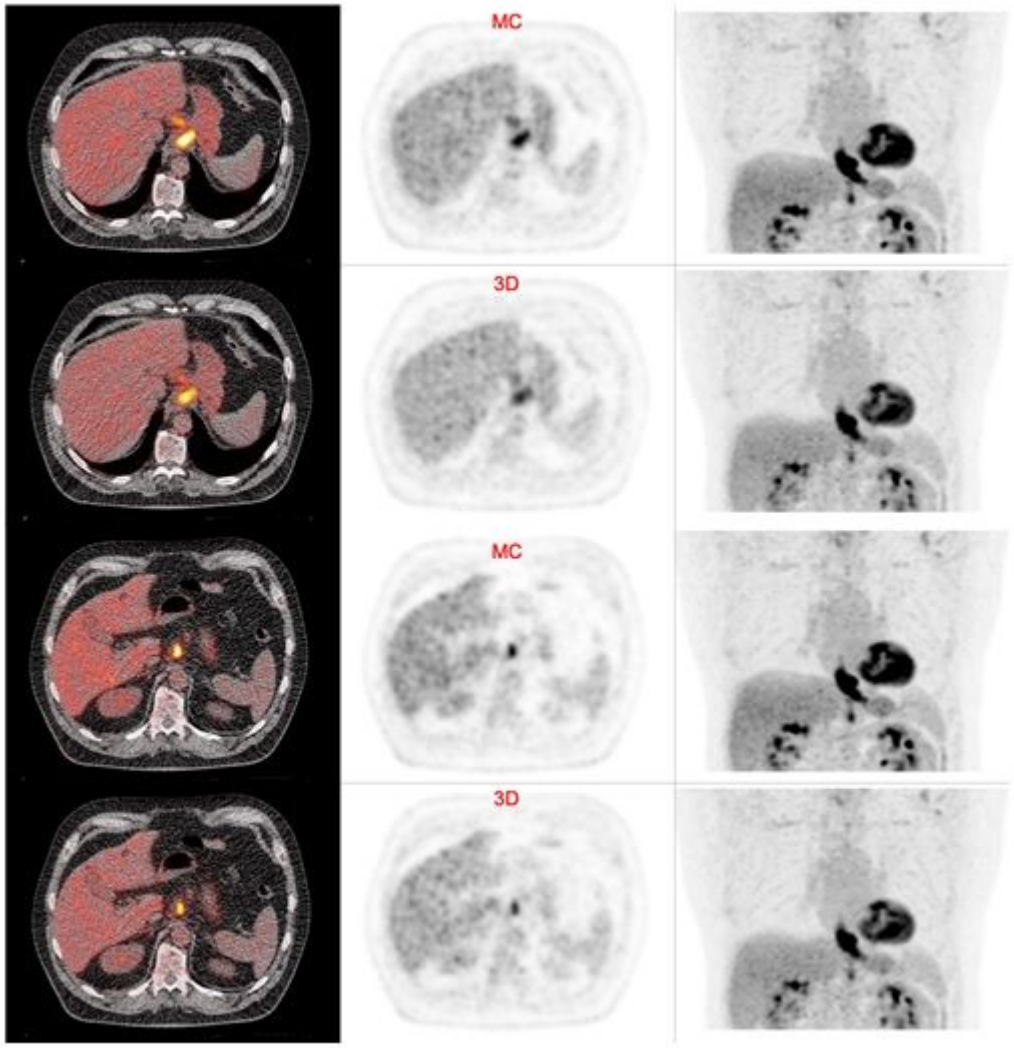

Figure 1

Motion-compensated and 3D PET/CT of a patient with a gastro-oesophageal junction tumour. Fused PET/CT (left) and PET only (middle) transversal slices, and maximum intensity projection (right) images of the primary tumour are shown in the upper panels, and a highly suspicious lymph node at the celiac trunk is shown in the lower panels. The primary tumour showed a SUVmax of 12.0 on 3D PET/CT and 14.7 on MC PET/CT. The pathological lymph node showed a SUVmax of 6.6 on 3D PET/CT versus 7.6 on MC PET/CT. Abbreviations: 3D: three-dimensional, MC: motion-compensated, PET: positron emission tomography, CT: computed tomography, SUVmax: maximum standardized uptake value.

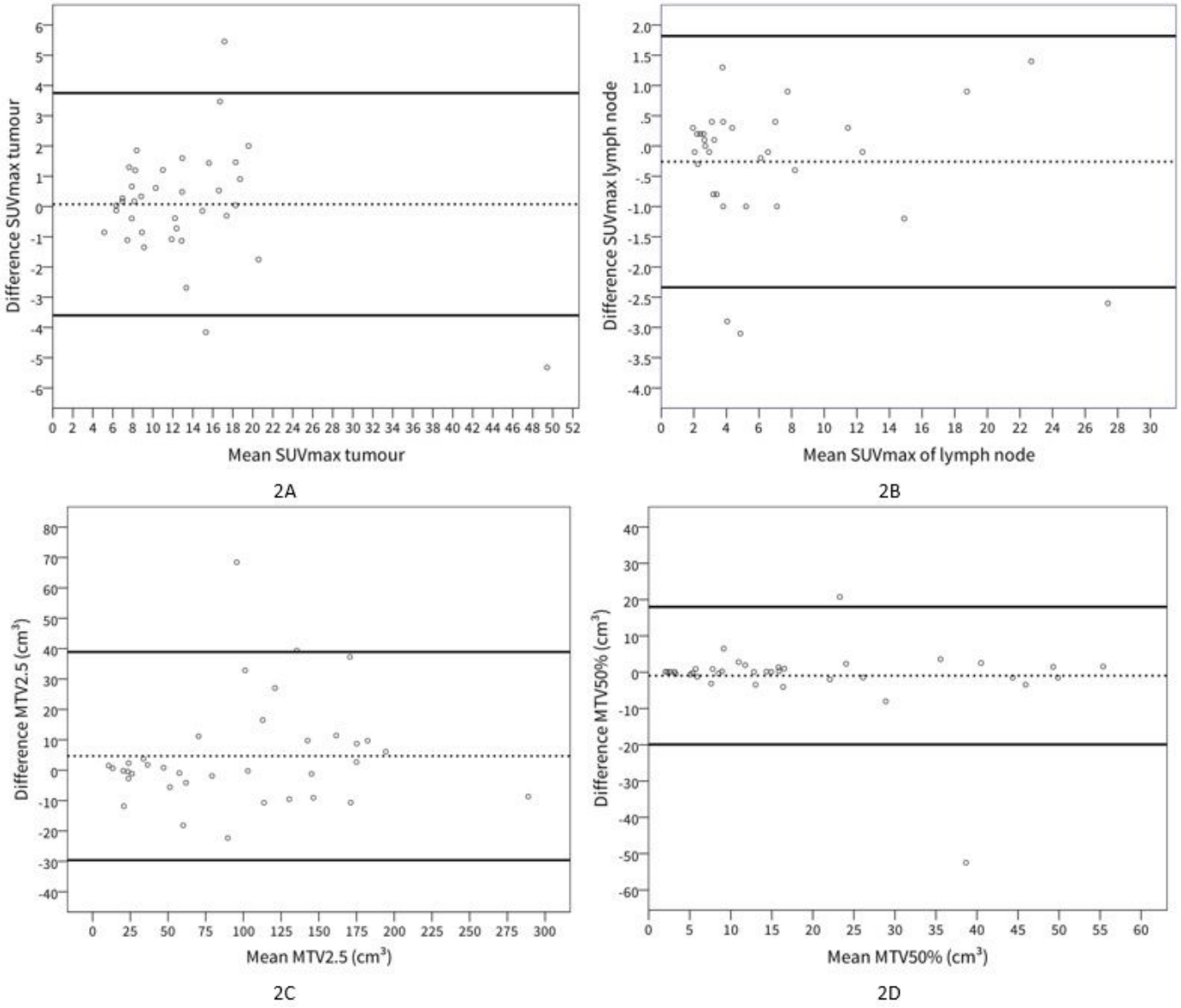

Figure 2

Bland-Altman plot of SUVmax of the tumour (A), SUVmax of the most intense lymph node (B), MTV2.5 (C) and MTV50% (D) measurements on 3D PET/CT and motion-compensated PET/CT. The x-axis shows the mean of the measurement on 3D PET/CT and motion-compensated PET/CT and the y-axis shows the difference between the both measurements. The dotted lines show the mean differences (3D-MC) between both methods. The solid lines show the upper and lower 95% limits of agreement. Abbreviations: 3D: three-dimensional, MC: motion-compensated, PET: positron emission tomography, CT: computed tomography, SUVmax: maximum standardized uptake value, MTV2.5: metabolic tumour volume with SUV threshold of 2.5, MTV50%: metabolic tumour volume with threshold 50% of SUVmax.

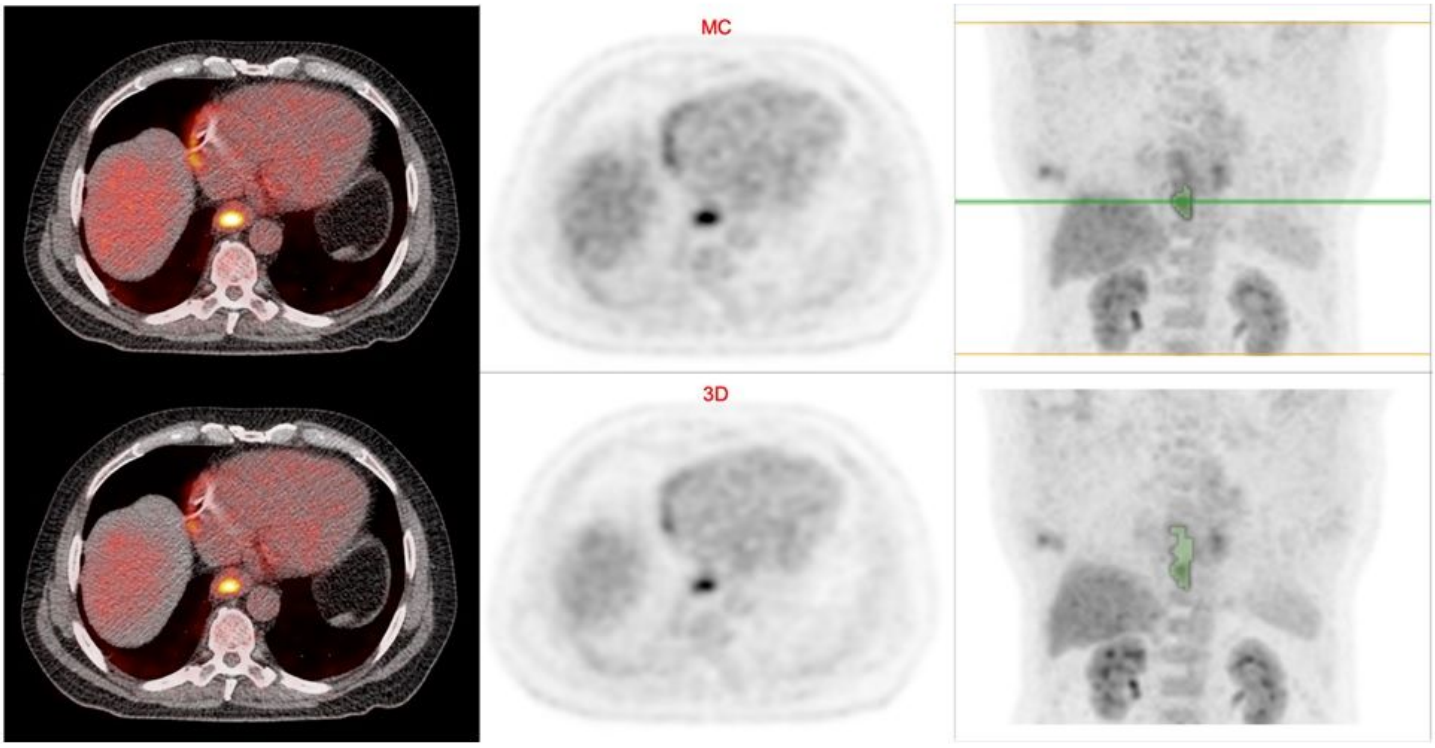

Figure 3

Image of a patient with a distal oesophageal tumour with motion-compensated and 3D reconstruction. The primary oesophageal tumour showed a SUVmax of 8.0 on MC PET/CT and 6.9 on 3D PET/CT. The corresponding metabolic tumour volume of ≥ 50% SUVmax was 5.89 cm3 on MC PET/CT versus 12.38 cm3 on 3D PET/CT. This was probably caused by extension of the VOI to an area of oesophagitis due to the lower SUVmax on 3D PET/CT. Abbreviations: 3D: three-dimensional, MC: motion-compensated, PET: positron emission tomography, CT: computed tomography, SUVmax: maximum standardized uptake value, VOI: volume of interest

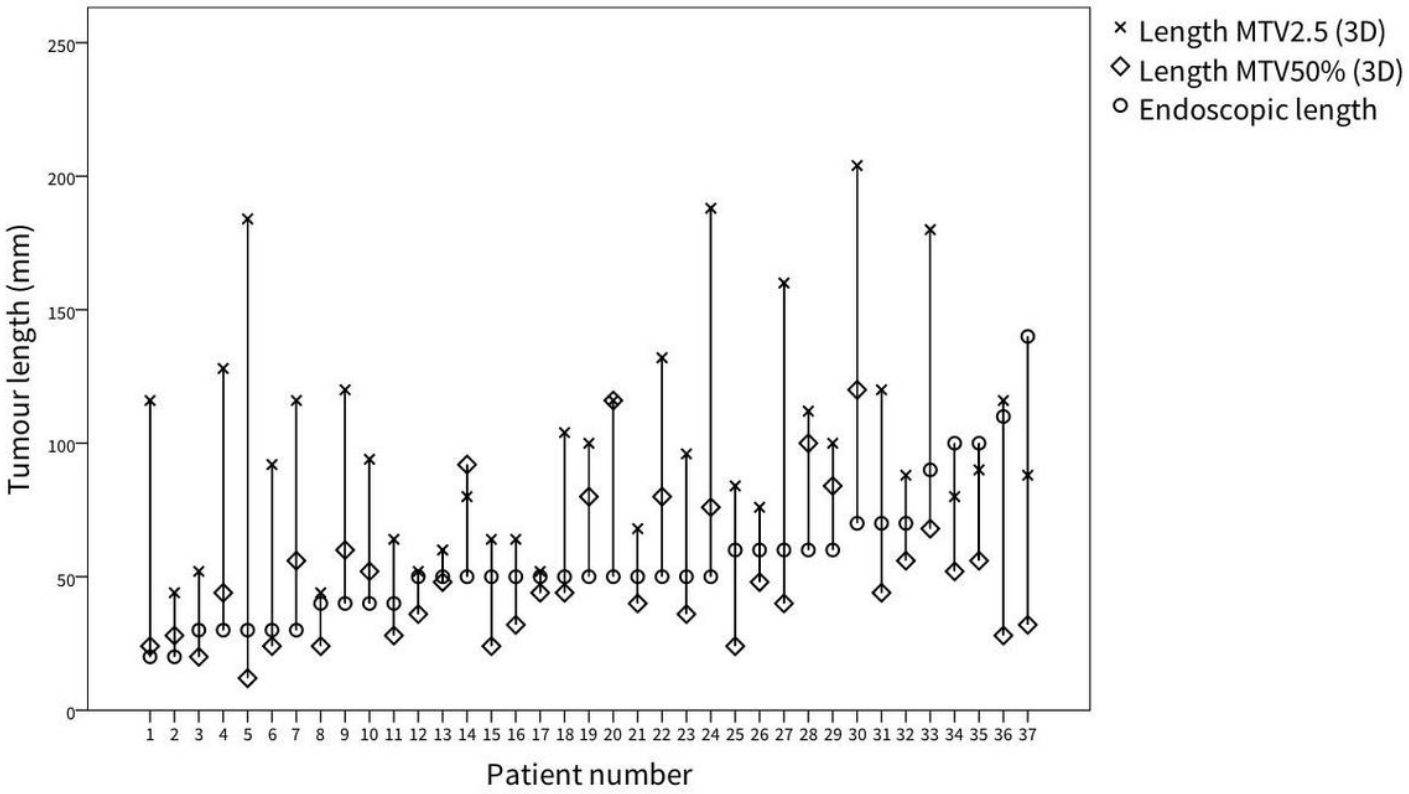

Figure 4

Tumour length (mm) in craniocaudal (CC) direction as measured during endoscopy (black circles), length of MTV2.5 (grey squares) and length of MTV50% (black crosses). Patients are ordered by endoscopic tumour length. Abbreviations: 3D: three-dimensional, CC: craniocaudal, SUVmax: maximum standardized uptake value, MTV2.5: metabolic tumour volume with SUV threshold of 2.5, MTV50%: metabolic tumour volume with threshold 50% of SUVmax.

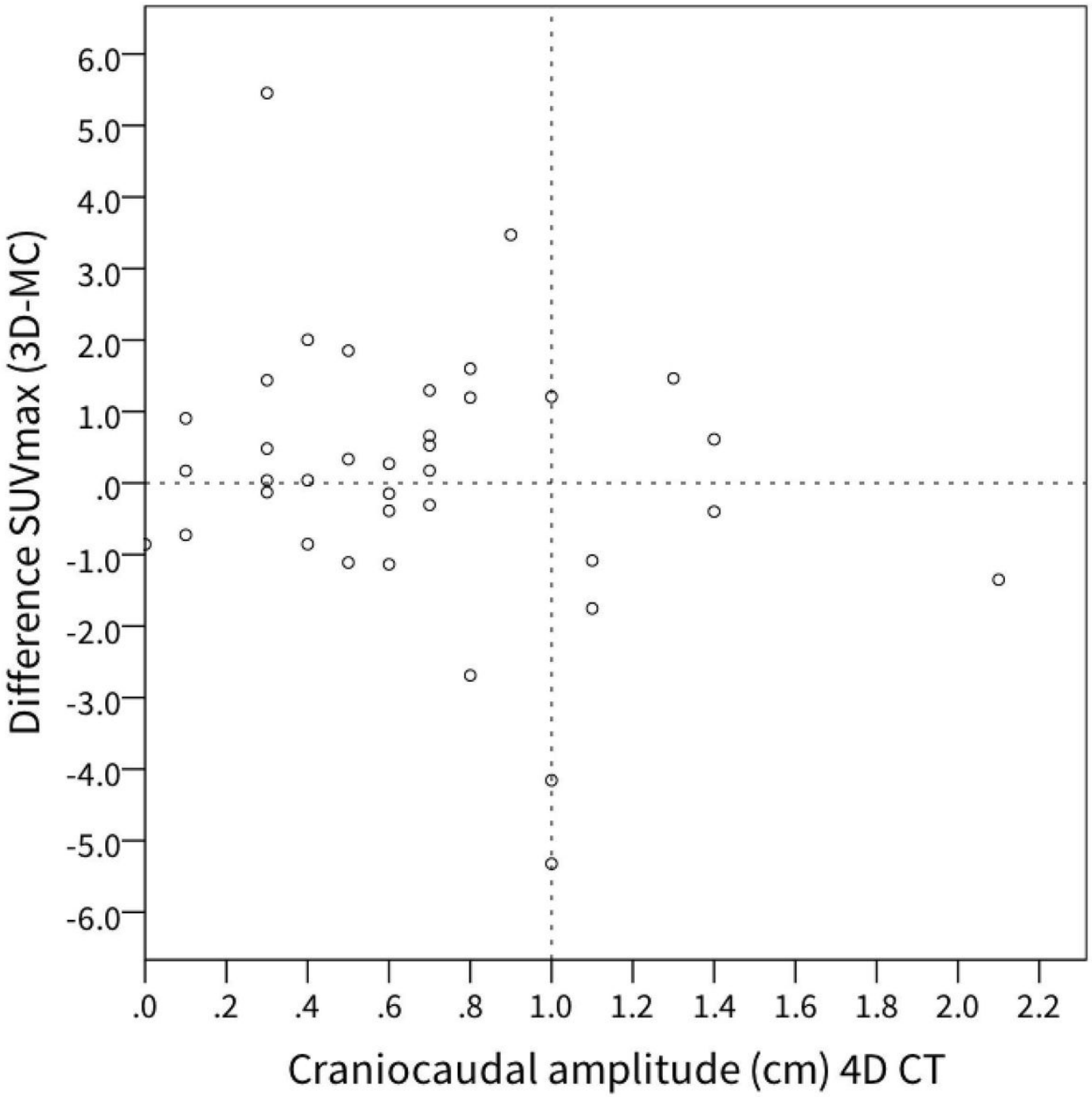

Figure 5

Difference in SUVmax of the tumour between 3D and MC, plotted as a function of peak-to-peak craniocaudal amplitude of the tumour. The horizontal dashed line represents difference=0. The vertical dashed line represents craniocaudal amplitude = 1.0 cm. Abbreviations: 3D: three-dimensional, MC: motion-compensated, SUVmax: maximum standardized uptake value, CT: computed tomography.

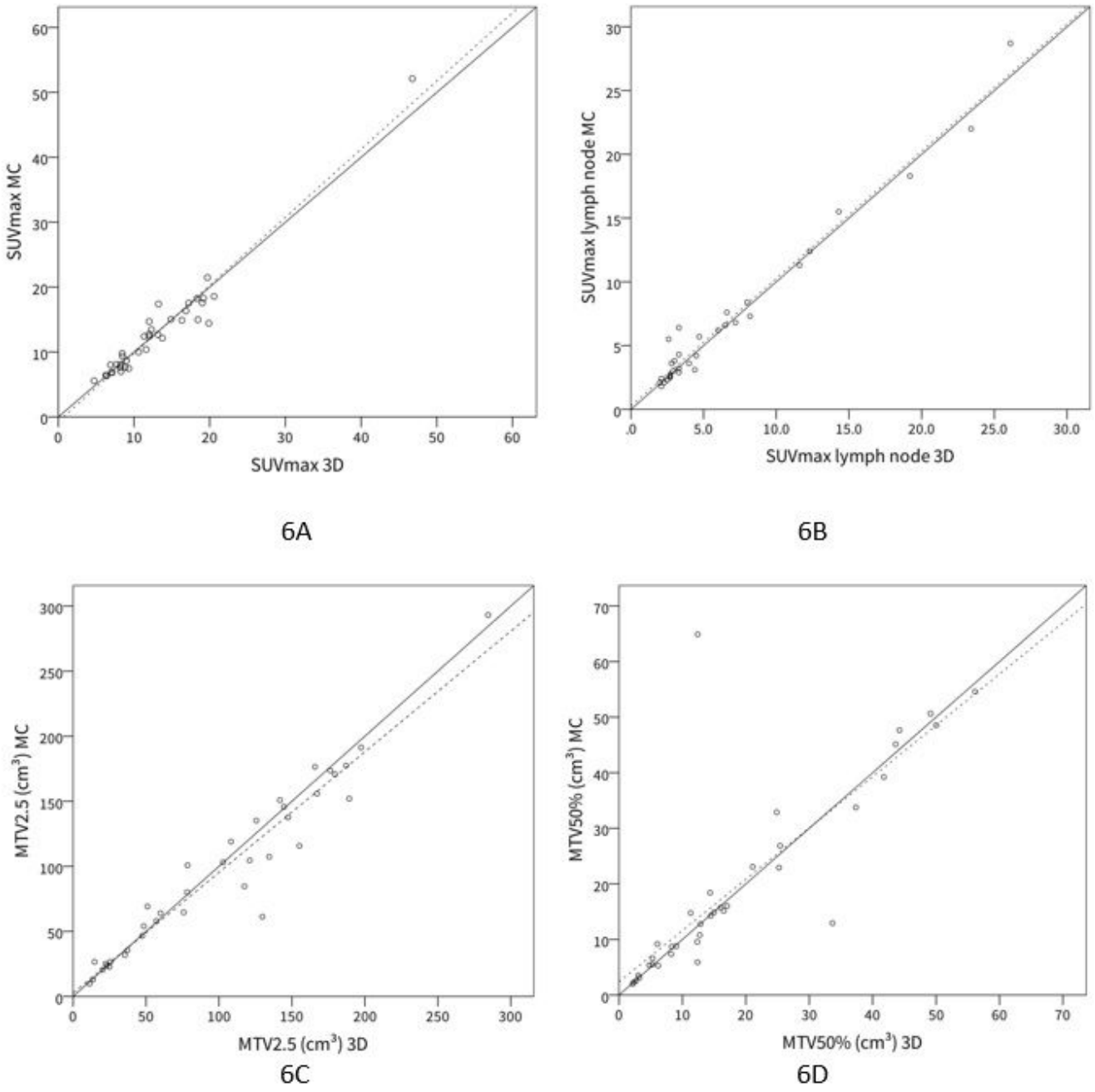

Figure 6

Scatter plots of (6A) SUVmax of the tumour, (6B) SUVmax of the lymph node, (6C) MTV2.5 and (6D) MTV50% on 3D PET/CT versus motion-compensated (4D) PET/CT. The solid lines represent y=x. The dashed lines represent the linear fit. Abbreviations: 3D: three-dimensional, MC: motion-compensated, 4D: four-dimensional, PET: positron emission tomography, CT: computed tomography, SUVmax: maximal standardized uptake value, MTV2.5: metabolic tumour volume with SUV threshold of 2.5, MTV50%: metabolic tumour volume with threshold 50% of SUVmax.