Anatomical accuracy of lesion localization

Retrospective interactive rigid image registration between ^{18}F-FDG-PET and X-ray CT

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PET, CT, image registration, image fusion, FDG

Summary
The **aim** of this study was to evaluate the anatomical accuracy and reproducibility of retrospective interactive rigid image registration (RIR) between routinely archived X-ray computer tomography (CT) and positron emission tomography performed with ^{18}F-deoxyglucose (FDG-PET) in oncological patients. **Methods:** Two observers registered PET and CT data obtained in 37 patients using a commercially available image fusion tool. RIR was performed separately for the thorax and the abdomen using physiological FDG uptake in several organs as a reference. One observer performed the procedure twice (O1a and O1b), another person once (O2). For 94 malignant lesions, clearly visible in CT and PET, the signed and absolute distances between their representation on PET and CT were measured in X-, Y-, and Z-direction with reference to a coordinate system centered in the CT representation of each lesion (X-, Y-, Z-distances). **Results:** The mean differences of the signed and absolute distances between O1a, O1b, and O2 did not exceed 3 mm in any dimension. The absolute X-, Y-, and Z-distances ranged between 0.57 ± 0.58 cm for O1a (X-direction) and 1.12 ± 1.28 cm for O2 (Z-direction). When averaging the absolute distances measured by O1a, O1b, and O2, the percentage of lesions misregistered by less than 1.5 cm was 91 % for the X-, 88 % for the Y-, and 77 % for the Z-direction. The larger error of fusion determined for the remaining lesions was caused by non-rigid body transformations due to differences in breathing, arm position, or bowel movements between the two examinations. Mixed effects analysis of the signed and absolute X-, Y-, and Z-distances disclosed a significantly greater misalignment in the thorax than in the abdomen as well as axially than transaxially. **Conclusion:** The anatomical inaccuracy of RIR can be expected to be $<$1.5 cm for the majority of neoplastic foci. Errors of alignment are bigger in the thorax and in Z-direction, due to non-rigid body transformations caused, e.g., by breathing.

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Schlüsselwörter
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Zusammenfassung
Ziel: Evaluierung der anatomischen Genauigkeit und Reproduzierbarkeit der Lokalisierung von malignen Herden mittels der retrospektiven, interaktiven, starren Bildfusion von FDG-PET und CT. **Methodik:** Bei 37 onkologischen Patienten wurden innerhalb von 30 Tagen eine Ganzkörper-FDG-PET und ein Spiral-CT gemäß klinischen Standardprotokollen aufgenommen. Zwei Untersucher fusionierten unabhängig voneinander PET und CT. Die Fusion erfolgte für Thorax und Abdomen getrennt. Hauptorientierungsmarken waren Zwerchfell, Leber, Harnblase, Mediastinum und Lungengrenzen. 94 PET- und CT-positive maligne Läsionen wurden evaluiert. Die Abweichung zwischen der Darstellung in PET und CT wurde in den 3 Ebenen ermittelt. Wir bestimmten den absoluten Betrag der Abweichung sowie die vektorielle Richtung in der X-, Y- und Z-Achse durch das Setzen eines Vorzeichen. **Ergebnisse:** Die absoluten Werte für die Fehlregistrierung der Läsionen reichten von 0,57 cm ± 0,58 (X-Richtung) bis 1,12 cm ± 1,28 (Z-Richtung). Die Ergebnisse beider Untersucher unterschieden sich um maximal 3 mm in allen Ebenen für die vektorielle oder absolute Fehlregistrierung der Läsion im fusionierten Bild. Die Inter- und Intraobservervariabilität war niedrig und statistisch nicht signifikant. Eine Fehlregistrierung von weniger als 1,5 cm wurde bei 91% (X-Richtung), 88% (Y-Richtung) und 77% (Z-Richtung) der Läsionen erreicht. Größere Abweichungen wurden v. a. durch unterschiedliche Atemlage und Armposition in PET und CT oder durch Peristaltik-bedingte Lageveränderungen von Magen und Darm zwischen den Untersuchungen verursacht. Die statistische Analyse ergab eine signifikant höhere Fehlregistrierung im Thorax als im Abdomen sowie eine höhere Abweichung in Z-Richtung (kranio-kaudal) als in der X/Y-Ebene. **Schlussfolgerung:** Der Registrierungsfehler bei der retrospektiven, interaktiven Fusion von PET- und CT beträgt bei den meisten neoplastischen Läsionen $<$1,5 cm. Bedingt durch die Atmung ist der Registrierungsfehler im Thorax größer als abdominell sowie ausgeprägter in Z-Richtung als in der axialen Bildebene.

Genauigkeit der Lokalisierung maligner Herde mittels retrospektiver, interaktiver starrer Bildfusion von FDG-PET und CT

The mainstay of to-date diagnostic imaging are morphologic imaging procedures such as ultrasonography and X-ray computed tomography (CT). However, these imaging techniques are suffering from low sensitivity and specificity for vital tumour tissue. Positron emission tomography (PET) using ^{18}F fluorodeoxyglucose (FDG) has proven its value in staging and restaging of patients affected by cancer and in defining the biological characteristics of neoplasms and their response to therapy (7, 8, 17, 21, 24, 27, 34). Undoubtfully, both morphologically and biochemically oriented diagnostic approaches are useful and often clinically necessary (37). However, the main disadvantage of PET is its lack in anatomical details leading to difficulties in localizing FDG-positive lesions.

Although the visual comparison of the unregistrated images may also be useful (3, 23), the complexity of the data from both imaging techniques hampers their mental integration. Therefore, computer-assisted support appears helpful. Since dedicated PET/CT scanners seem to offer precisely matched anatomical and functional information, the problem seems to be solved. However, the comparatively high costs of hybrid cameras may limit their availability. Furthermore, in an as yet undetermined proportion of tumour patients, the indication for a PET examination is derived from an independently performed CT so that a second CT examination would be of little additional use and constitutes an unnecessary radiation burden. The retrospective registration of PET and CT may therefore still be necessary (15).

Several investigators have confirmed the clinical utility of retrospective image registration (4, 6, 9, 13, 14, 16, 19, 20, 28, 30–32,

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35). Its anatomical accuracy is affected by differences in the position of the patient in the two scanners and by patient motion between the two examinations, e. g., arising from breathing.

The aim of this study was to evaluate the reproducibility and the anatomical accuracy of retrospective interactive rigid image registration between PET and CT. For this purpose, PET and CT data from 37 patients suffering from histologically confirmed malignancies were interactively registered using a commercially available software, the distances between the PET and CT representation of the whole 94 neoplastic lesions measured, and the intra- and interobserver reproducibility of the data match evaluated.

Patients, material, methods

Between 07/ 2002 and 05/ 2004 we examined 427 patients by whole-body FDG-PET at our institution. 37 patients fulfilled the following criteria:

- at least one clearly defined FDG-positive neoplastic lesion also visible on CT,
- CT imaging exactly 5 weeks before or after the PET scan,
- availability of the digital CT data (DICOM).

Bulky lesions were an exclusion criterion. 37 patients (27 men, 10 women), aged between 16 and 74 years (mean: 52 ± 14) entered the study. Further data are listed in table 1. The time between CT and PET scans was 5.5 ± 8 days, ranging from 0 to 35 days. 94 lesions, positive in PET and CT, were selected for further analysis. The number of the selected lesions per patient was 2.5 ± 1.9 (range: 1 – 9). Maximally, three lesions per anatomical segment (pelvis, upper abdomen, thorax) were chosen. The lesions were located in eleven anatomical regions and organs. CT scanning and FDG-PET was ordered primarily for diagnostic purposes.

CT and PET data acquisition

The patients received a CT-scan of thorax and abdomen. Either a 16-slice (Somatom Sensation 16) or a 10-slice (Somatom Sensation 10) CT-scanner (Siemens Medical Solutions, Erlangen, Germany) was used. The scans were performed according to routine protocols in maximum inspiration using intravenous as well as oral contrast material for abdominal scanning in a supine position with elevated arms in breath-hold inspiration.

For the CT images ranging from the lower neck to the groin, 120 ml contrast agent (Ultravist 300, Schering AG, Berlin, Germany) were injected with a start delay of 40 s (flow rate: 2.5 ml/s). Scan parameters: 120 kV, 160 mAs, rotation time 0.5 s, collimation 16 × (resp.10 ×) 0.75 mm; slice thickness: 5 mm using a 5 mm reconstruction increment; resolution: approximately 0.5 mm in X/Y-plane and 5 mm in Z-direction; matrix size: 512 × 512.

Patients were fasted at least 8 hours prior to PET imaging. Serum glucose concentration determined before starting PET examination was 89.1 ± 13.3 mg/dl. Whole-body PET scans from the vertex to the groin were performed using a partial-ring PET scanner (Ecat Emerge, Siemens Medical Solutions), a modification of the Ecat Art equipped with lutetium oxyorthosilicate detectors (LSO). The technical performance has been described recently (12). It has 47 image planes, 3375 mm apart; axial field-of-view: 16.2 cm. The Ecat Emerge allows data acquisition in 3D-mode. Emission data corrected for randoms, dead time and attenuation were reconstructed with an iterative reconstruction algorithm (OSEM – 2 iterations / 8 subsets). The number of projections and views was 192. The matrix size was 128 × 128 in plane with a pixel size of 0.515 cm and a reconstructed image resolution of approximately 6.5 mm. Transmission measurements were acquired with ^{137}Cs rod sources just before or after the emission scan at each bed position. The patient remained in a supine position with non-elevated arms near the body and normal breathing. To avoid further positional differences identical flat patient tables were used for PET and CT scans.

The PET scan was started 1 h after the i. v. injection of 7 MBq ^{18}F-FDG/kg body weight. The scanning time in each bed position was 8 min (5 min emission, 3 min transmission).

Tab. 1 Clinical data of the 37 patients ([1] vertebral or pelvic)

malignant tumour	37 patients	lesion localization	number of patients	number of lesions	mean lesion volume (ml)
melanoma	24	inguinal region	3	5	24.9
non-Hodgkin-lymphoma	4	retroperitoneum	11	15	17.4
colonic cancer	2	mesenterium	4	4	3.6
sarcoma	2	mediastinum	9	13	12.5
breast carcinoma	1	gluteal region	4	5	4.5
pancreatic carcinoma	1	liver	9	10	84.4
carcinoma of the duodenum	1	spleen	3	3	22.8
oesophageal cancer	1	pancreas	4	4	12.2
Hodgkin's lymphoma	1	lung chest wall bone[1]	15 6 4	24 7 4	6.0 23.9 4.0

Image registration

CT and PET images were transferred in DICOM format to a viewing station (Syngo, Siemens Medical Solutions). The slice thickness of the CT images was 5 mm, since only these data were routinely available due to storage limitations. The CT scans were displayed at the soft tissue window settings (level 50 HU; width 350 HU). In addition, the thorax was evaluated at lung window settings (level, –600 HU; width, 1700 HU). The colour scale of the whole-body PET scans could be manipulated by the reader.

Subsequently, manual image registration was performed separately by two physicians experienced both in radiology and nuclear medicine (A.N., W.R.), using a commercially available 3D volume fusion tool (Syngo advanced Fusion VC20H, Siemens Medical Solutions) which allows sub-voxel 3-D rigid-body transformations with six degrees of freedom (three translations and three rotations) (26). Reading was done in 3D-mode with the ability to change the ratio of CT and PET in the fused images (%-scale). The software allows interactive manual image co-registration by visually detected landmarks. The observer can view the scan data simultaneously in three planes (axial, coronal, sagittal).

The registration was performed for three body segments with reference to physiological FDG uptake in the following specified organs:

- pelvis from the symphysis to the iliac crest with the main landmarks bottom of the bladder, bladder wall, and skin contour,
- upper abdomen from the diaphragm to the iliac crest including as main landmarks contours of liver and spleen and the upper poles of the kidneys,
- thorax using the contours of the lungs, the mediastinum and the diaphragm as landmarks.

The average time for registration was less than 6 min (range: 4–7 min). All registrations were performed by two physicians: A.N. repeated the procedure twice on two days (O1a and O1b, respectively); in addition, W.R. (O2) also fused the images independently from A.N.

The PET images were displayed using an SUV interval of 0–6 and the CT scans at soft tissue window settings (level 50 HU; width 350 HU). In addition, the thorax was evaluated at lung window settings in CT (level –600 HU; width 1700 HU). O1a, O1b, and O2 measured the so-called signed distances (29) between the representation of each of the 94 lesions on PET and CT in X-, Y-, and Z-direction with reference to a coordinate system centered in the CT representation of each lesion. These variables contained information on the absolute distance between the representation of the lesions as well as on the direction of the deviation with reference to the dimensions X, Y, and Z. The subsequent analysis used the signed distances as well as their absolute values (signed and absolute X-, Y-, Z-distances). The rationale for this is that an analysis of the signed distances averaged over different observers allow a comparative estimation of the bias of registration, whereas an analysis of the absolute distances permits to assess differences in the magnitude of average errors.

The CT volume of each lesion was approximated using the volume formula for ellipsoids (length × width × height × 0.5) and was 19.1 ± 43.7 ml (range 0.04-200 ml).

Furthermore, the distance of the center of each CT lesion to the border of the vertebral body or – in the five cases of inguinal localization – to the symphysis were determined on the axial CT slice best representing the lesion in question. This variable was mean 7.1 ± 4.3 cm, ranging from 0 to 18.9 cm (observer 1a).

To estimate the error, the absolute distances between the PET and CT lesion representation were determined by O1a in five patients twenty times each for one lesion, yielding a mean coefficient of variation (mean / standard deviation) of 0.062 for X, 0.065 for Y and 0.052 for Z-direction. This indicates a low measurement error with high reproducibility of the estimation of the lesion center and the measurement of the misregistration in X-, Y-, and Z-direction. Analogously, a low measurement error was determined for the distance of the lesions to the vertebral column with a coefficient of variation of 0.006.

Data analysis

In order to reduce the variables for the subsequent analysis and to increase the number of data points, the data from the pelvis and the upper abdomen were pooled.

The significance of differences in the absolute and signed distances between the three dimensions X, Y, and Z were tested using the Friedman's test. Furthermore, for the tree dimensions X, Y, and Z, we modelled the misregistration by means of a mixed effects model (22). When using this approach, the signed and absolute distances are modelled by a linear combination of the covariates where the independent measurement errors are assumed to follow a normal distribution. For each patient, multiple lesions have been measured and thus the independence assumption of the ordinary linear regression model is violated. For the mixed effects model some of the regression coefficients are assumed to be random in order to allow for subject specific effects. For our analyses we assumed that the misregistration was influenced by a random effect for each patient and lesion, thus accounting for varying effects among patients and lesions. The effects for lesion volume, distance to the vertebral collumn, location (thorax or abdomen), and observer were assumed to be fixed. P-values <0.05 were considered as significant.

Fisher's exact test was used to perform a test on independence in 2 × 2 contingency tables. In this paper all data are given as mean value ± standard deviation unless otherwise specified. Distributions are visualized by box plots, the computations were performed using the R-system for statistical computing (version 1.9.1, R Development Core Team, 2004) (33), using especially the lme4 package (2).

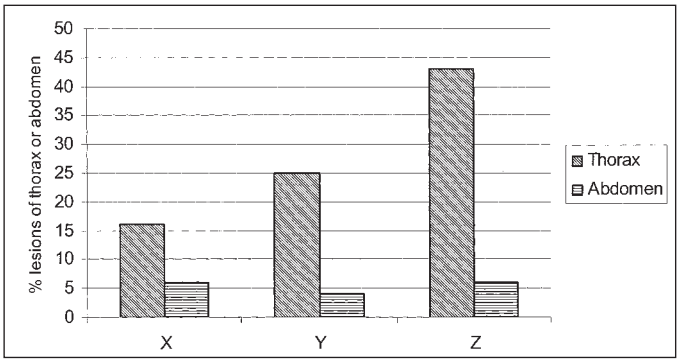

Fig. 1
Lesions misregistration by >1.5 cm (in % of total thoracic or abdominal lesions)

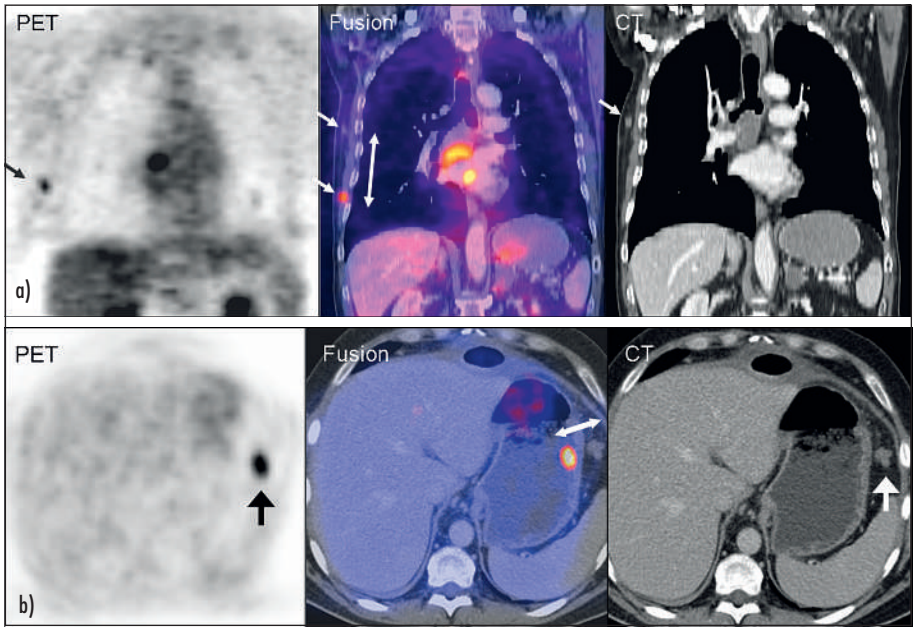

Fig. 2 Misregistration of metastasis of
a) malignant melanoma in the right chest wall due to inspiration and elevated arms in CT with marked caudal deviation of the PET lesion as compared to CT
b) rectal carcinoma concerning a lymph node in the epigastric fatty tissue due to different gastric filling between PET and CT.

Results

When averaging the absolute distances measured by O1a, O1b, and O2, the percentage of lesions misregistered by <1.5 cm was 91% for the X-, 88% for the Y-, and 77% for the Z-direction. The number of lesions misregistered by >1.5 cm was significantly bigger in the thorax than in the abdomen (Fig. 1) and in Z-direction than in X/Y-plane ($p < 0.001$ and $p < 0.02$). An analysis of these lesions disclosed systematic misalignments due to non-rigid body transformation caused by respiration and extension of the arms (Fig. 2A), or by bowel movements between CT and PET (Fig. 2B).

The absolute distances ranged between 0.57 ± 0.58 cm for O1a (X-direction) and 1.12 ± 1.28 cm for O2 (Z-direction) (Fig. 3A). The differences between these variables in the dimensions X, Y, and Z did not prove to be significant for any of the observers ($p > 0.05$ determined by Friedman's test).

Table 2a gives the results of the mixed effect analysis for the absolute distances. There were no significant differences for the observers O1a, O1b and O2 in any of the dimensions. The absolute Z-distance was significantly influenced by the distance of the lesion to the vertebral column, greater distances leading to greater errors of fusion. Furthermore, the anatomical inaccuracy of the match was significantly greater in the thorax than in the abdomen, comprising the results of fusion for the pelvis and the upper abdomen.

The signed distances were between 0.01 ± 0.81 cm for O1a (X-direction) and -0.6 ± 1.79 cm for O1b (Z-direction) (Fig. 3B). For O1a and O1b the signed Z-distance was significantly smaller than the X- and Y-misregistration, this difference just failed to reach significance for O2 ($p = 0.17$ determined by Friedman's test).

Table 2b gives the results of the mixed effect analysis for the signed distances. These variables allow the evaluation of the direction of misregistration between both examinations. Thus, they offer information not contained in the absolute values of the distances between the PET and CT representation of each lesion. There was only one significant difference of this variable between the three observers, namely between O2 and O1a in Y-direction. However, this effect was only minor, amounting to a difference in means of 3 mm, thus translating into a systematic tendency of O1b to register the PET image a little more ventrally in Y-direction on the CT scan compared to O2.

The signed Y- and the Z-distances were significantly influenced from the distance of the lesion to the vertebral column, larger distances leading to bigger errors of fusion. Furthermore, also for the signed distances, the anatomical inaccuracy of the match was significantly greater in the thorax than in the abdomen, comprising the results of fusion for the pelvis and the upper abdomen. The lesion volume did not influence the absolute or signed distances of misregistration (Table 1, 2).

Discussion

Several studies have demonstrated that retrospective interactive registration between CT and FDG-PET may improve diagnostic accuracy in the thorax and abdomen (5, 6, 13, 18). However, the reproducibility and the anatomical accuracy of this approach were questioned (13, 15).

To the best of our knowledge, its reproducibility has not been studied before. Surprisingly, the intraobserver reproducibility of retrospective image fusion was quite high: We did not find significant differences of absolute or signed distances between the two readings of one observer, i.e., between O1a and O1b. No significant differences of absolute distances were detected between O1a and O1b on the one hand and O2 on the other. This did not apply for the signed distances since a significant difference between O1b and O2 was found for this variable in Y-direction. However, this effect was only minor, amounting to a difference in means of 3 mm, thus translating into a systematic tendency of O1b to register the PET image a little more ventrally in Y-direction on the CT scan compared to O2.

The mean absolute distance between CT and FDG-PET ranged from approximately 0.6 to 1.2 cm. Furthermore, roughly 85% of the CT representation of the neoplastic foci were found within a distance of 1.5 cm of the PET lesion and thus within three voxels of the emission tomographic image cor-

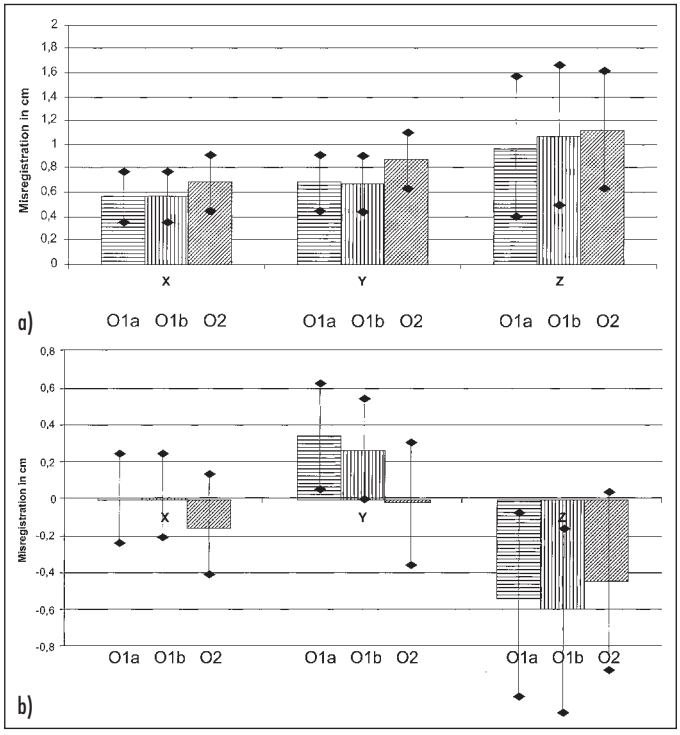

Fig. 3 Absolute (a) and signed (b) distances in X-, Y-, and Z-direction for observers O1a,b and O2 error bars: one standard deviation (SD)
+/-: direction of misregistration between PET and CT

a)

absolute distances	X		Y		Z	
	X Est.	p	Y Est.	p	Z Est.	p
intercept term (syst. error)[1]	0.46	0.34	0.61	0.07	-0.57	0.33
distance to vertebral column	0.00	0.95	-0.01	0.75	0.12	*0.02**
lesion volume (CT)	0.00	0.58	0.00	0.53	0.00	0.8
location (thorax or abdomen)	0.11	0.80	0.39	0.17	1.4	*0.01**
O1b – O1a[2]	0.01	0.93	-0.01	0.92	0.09	0.52
O2 – O1a[3]	0.14	0.35	0.2	0.17	0.14	0.35

b)

signed distances	X		Y		Z	
	X Est.	p	Y Est.	p	Z Est.	p
intercept term (syst. error)[1]	-0.04	0.95	0.85	*0.02**	1.11	0.11
distance to vertebral column	0.02	0.70	-0.06	0.07	-0.11	*0.03**
lesion volume (CT)	0.00	0.60	0.00	0.34	-0.00	0.56
location (thorax or abdomen)	-0.09	0.87	0.13	0.69	-1.39	*0.01**
O1b – O1a[2]	0.01	0.97	-0.08	0.59	-0.06	0.67
O2 – O1a[3]	-0.16	0.27	-0.36	*0.01**	0.11	0.47

Tab. 2 Mixed effects analysis of the influence of variables on absolute (a) and signed (b) distances; Est: estimated; * $p < 0.05$ considered as significant
[1]term to evaluate systematic errors; differences to evaluate the [2]intraobserver and [3]inter-observer reproducibility

responding to approximately twice its spatial resolution.

Up to now, only few studies have reported the anatomical accuracy of lesion localization with interactive image fusion: Inagaki et al. (14) investigated the accuracy of interactive fusion of three dimensional images of upper abdominal CT and PET without external body surface markers. The average errors of translation were 3.43 mm in X, 4.7 mm in Y, and 9.23 mm in Z-direction, comparable to our results of misregistration in the abdomen.

Several other publications used different approaches to register CT and FDG-PET images. They include in particular automated or semi-automated methods:

- the surface-based chamfer matching method (4),
- lung segmentation (1, 36) and
- free form deformations/mutual information (MI)(19) or
- combined methods (31).

The anatomical accuracy of registration ranged from approximately 2-5 mm in X/Y-plane to 3-6 mm in Z-direction. Cai et al. (4), for example, studied the accuracy of PET-CT image fusion in the thorax for radiotherapy treatment planning, using the chamfer-matching method with automated segmentation of the lung surface contours by thresholding. The registration error was 2-3 mm in the transverse plane and 3-4 mm in the longitudinal direction. Mattes et al. (19) introduced an algorithm for three-dimensional positron emission tomography transmission to computed tomography registration in the chest, using mutual information as a similarity measure. The visually reported errors ranged from 0 to 6 mm.

Thus, automated registration seems to be more accurate than interactive fusion. However, the results from different studies are difficult to compare since major differences with regard to the soft- and hardware used as well as with respect to scanning conditions exist. For example, Slomka et al. (31) employed a non-linear algorithm with automated three dimensional registration and adjustment of normal breathing PET to inspiration CT and reported good matching quality. However, in this study PET and CT scanning were performed with elevated arms so that their results cannot be compared to ours since our data were obtained for different arm positioning in PET and CT (Fig. 2A). Studies directly comparing the accuracy of techniques have not yet been published.

In our study, 9% (X), 12% (Y), and 23% (Z), respectively, of the neoplastic lesions were misregistered by more than 1.5 cm. The majority of these were located in the thorax (Fig. 1). Correspondingly, multivariate analyses of our data disclosed a significantly higher misregistration for lesions located in the thorax as compared with abdominal foci. Furthermore, we observed a significant correlation of misregistration with the distance of the lesion to the vertebral column and significantly higher misregistrations in Z-direction than in X/Y-plane.

The axial slice of the CTs used was with 5 mm thicker than axial image resolution since we had to recur to data stored in this format due to storage limitations. However,

this situation represents daily routine. Therefore, the latter observation may also be due to the enhanced axial slice thickness of the CTs. Nevertheless, the majority of the described findings may be explained by non-rigid body transformations caused by respiration and by differences in the position of the arms between the PET and CT examination, leading to a strong thorax deformation resulting in systematic errors.

This effect is well described: Goerres et al. (10, 11) investigated the misregistration of pulmonary lesions with a combined PET/CT system at different respiration levels. They found mismatches between PET and CT to be greatest when CT was performed during maximal inspiration of the patient, then ranging from 5 to 33 mm. The best and second best matches were found for CT obtained during normal expiration (0–14 mm) and free breathing (0–31 mm). In our study, CTs were obtained at maximal inspiration: the major misregistration error is in Z-direction, with the PET lesion registered caudally to the CT lesion. This is due to the descent of the diaphragm caused by inspiration in CT since we used the diaphragm as one main reference surface for fusion.

The positioning of the arms still remains a considerable problem: PET scan performed with elevated arms would improve the matching quality of PET and CT, due to reduced deformation of the thorax (31). However, most tumour patients undergoing PET examinations are unable to hold their arms elevated during 30 to 45 min. On the other side, performing CT with the patient's arms positioned beside the body results in streak artifacts, predominantly in the upper abdomen with reduced diagnostic quality of the CT scan (25). To manage the problem caused by respiration it has been recommended for example to perform the CT scan with non-elevated arms and in normal expiration or free breathing to improve coregistration, with minimizing image misregistration to dimensions comparable to the spatial resolution of modern PET scanners, independent of whether combined PET/CT systems or stand-alone systems were used (10, 11). However, performing the CT scan in expiration or free breathing reduces the diagnostic quality drastically, due to partially collapsed lung segments, especially in the lower parts of the lung.

Kawaharada et al. (16) developed a software-based fusion technique for PET and CT of the thorax by analyzing respiratory movements of the chest using CT and MRI and implementing the MRI information on these movements into the procedure of registration. With this procedure only minor misregistration was detected in any of the directions. For the lung hilus, the misregistration was by 3.6 mm dorsoventrally and by 6.1 mm in the craniocaudal direction.

Non-systematic coregistration errors may also occur because of different filling of the stomach and the gut between CT and PET (Fig. 2B), leading in particular to difficulties in registration of mesenteric lesions. Even with a combined PET/CT-scanner, misregistration is not totally avoidable, especially in the thorax. When using PET/CT hybrid systems misregistrations for thoracic lesions have been reported to range between 0.3 and 0.4 cm (5): The misregistrations were
In this study, both scans were performed in quiet tidal breathing (5). Similarly, Nakamoto et al. (20) described minor mismatches in location and organ size, using a combined PET/CT, due to physiological motion during patient breathing.

Taking together our data with those cited, we believe that retrospective interactive registration between CT and FDG-PET yields an anatomical accuracy sufficient for many diagnostic purposes, and in particular for localizing abdominal neoplastic lesions. Even if this method may not be accurate enough to help in the planning of radiation therapy at least in those cases where target structures are located closely to radiation-sensitive organs. The latter applies in particular to modalities of radiation therapy where sharply defined radiation fields are used such as in intensity-modulated radiation therapy. Interactive retrospective image registration may also have shortcomings for targeting biopsies from anatomically altered tissues potentially harbouring foci of vital tumour cells highlighted by PET. It is obvious that PET/CT hybrid cameras would be superior for these purposes.

Limitations

Our study has several limitations: Possibly, better results of registration would have been feasible by PET scanners with higher spatial resolution. For the majority of our patients, the mean time intervall between PET and CT examination was 5.5 days. One patient underwent CT 35 days after the PET examination, so this time intervall might influence the misregistration error, especially in case of tumour progress.

Furthermore, the analysis was not blinded: Although the observers' registered the images only with reference to the contours of normal organs, the neoplastic foci were also clearly visible throughout this process. On the other hand, eliminating the voxels representing the lesions beforehand would have been difficult and even better results would be expected if the rationale of the fusion had been to match the CT and PET representation of the neoplastic lesions as accurately as possible.

Interactive image fusion depends entirely on the subjective visual impression of the observer. To our knowledge, there is no commonly accepted method for quality control, but the low inter- and intra-observer variation in our study indicates an acceptable and reliable quality of this procedure. This is underlined by the good fit between the predicted and measured data by the statistical model used in this study.

Another shortcoming of our study is a possible imprecision of the manual localization of the lesion center, since no automated procedure was used for this purpose. However, the error of measuring misregistration was in the range of only 0.5 to 1mm so that these inaccuracies should have had only a limited influence on our data.

We hope that the data reported her define a starting point for future development of software for image registration. The limitation to rigid transforms for registration is the source for inaccuracies in image registration. Thus, the modelling of nonlinear deformations and the usage of non-rigid transforms for image registration are major tasks that will eliminate the weaknesses of the registration methods considered in this study. The interaction with the physician is required to restrict the degrees of freedom

for deformations. Future algorithms will have to consider boundary conditions like corresponding point features or contours.

Conclusion

Retrospective interactive registration of PET and CT images does not provide a perfect data match. The anatomical inaccuracy of retrospective interactive rigid image registration can be expected to be <1.5 cm for the majority of neoplastic foci. Errors of alignment are higher in the thorax and in Z-direction, due to non-rigid body transformations causes (e. g. breathing or arm position). Our data represent reference values as basis for possible improvements of the quality of CT/PET fusion by non-rigid methods of image registration.

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