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Radiation treatment planning using positron emission tomography for patients with non-small cell lung cancer

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Aim. Positron emission tomography imaging significantly improves the accuracy of clinical staging in patients with non-small-cell lung cancer (NSCLC). The aim of the study was to evaluate the alterations in target volume (GTV) contouring based on computed tomography images and PET/CT fusion during radiotherapy planning in NSCLC patients.
Material and methods. We performed a retrospective study of 20 diagnostic FDG-PET/CT examinations performed in NSCLC patients between September 2003 and July 2005. FDG-PET studies were performed on an integrated Biograph SL (Siemens) PET/CT scanner to assess clinical staging additionally to conventional images. The first stage included spiral computed tomography, FDG-PET examination was performed as stage two, without repositioning the patient. In the course of the retrospective study the PET and CT data were sent to the Eclipse 7.1 radiotherapy planning system and registered using the same coordinate system (DICOM ORIGIN). First, the target volume (GTV) was contoured on the platform of the CT images. The GTV/CT volume included the primary tumor and mediastinal lymph nodes exceeding 10 mm in the maximal diameter.Then the GTV volume was contoured using PET/CT fusion images. The GTV/PET volume included foci of pathological FDG uptake and the, primary tumor mass with the involved mediastinal lymph nodes as seen on the CT with enlarged lymph nodes discerned independently of FDG uptake.
Results. The incorporation of PET/CT fusion images into target contouring volumes led to volume change in all study patients with GTV/PET volume reduction in 16 cases (group I) (caused by differentiating neoplastic lesions from atelectasis, fibrosis, pleural effusions and mediastinal organ displacement). Mean difference between GTV/CT and GTV/PET in this group was 53 cm³ (range: 0.3 cm³ to 148 cm³), i.e. 45% (3%-82%) of the primary GTV/CT volume. In this group, in 14 cases the changes exceeded 17% of the GTV/CT volume. In the remaining 4 cases the FDG/PET images caused an increase in the GTV/PET volume due to the incorporation of new groups of involved mediastinal lymph nodes. The mean difference between GTV/CT and GTV/PET was 18 cm³ (range: 9 cm³ to 35 cm³), i.e. 32% (10%-80%) of the primary GTV/CT volume.
Conclusions. Positron emission tomography cannot replace morphological imaging, yet it provides additional data concerning the pathological lesions. PET/CT fusion images used for radiotherapy planning in NSCLC patients significantly affect thee GTV target volume.

Key words: radiation treatment planning, positron emission tomography, non-small cell lung cancer

Isotope imaging of the metabolism of different anatomic structures has been applied as a diagnostic tool in oncology for a number of years. During the 1970' and the 1980's positron emission tomography (PET) was considered inferior to computed tomography (CT) and magnetic resonance imaging (MRI) due to its poor resolution and technical difficulties arising from short isotope half-life. The beginning of the 1990's saw the introduction of 18-F-fluorodeoxyglucose – a fluorine isotope-labeled glucose metabolite – which provided a breakthrough point for PET.

The value of FDG-PET in the diagnosis and staging of non-small cell lung cancer (NSCLC) has been the subject of numerous clinical trails since the mid-nineties. Its sensitivity and specificity for differentiating pulmonary lesions recognised in CT is 93-100% and 63-90%, respectively [1-3]. Such high sensitivity assures a very low probability of the presence of a malignant lesion within areas that are free of pathologic isotopic marker uptake. The reason for false positive results is usually the presence of specific or non-specific inflammatory infiltrations of the lungs. FDG-PET has also improved the diagnostics of NSCLC metastases to the mediastinal lymph nodes. Acc. to Vansteenkiste the sensitivity of PET and CT was 89% and 79 % respectively, while their specificity – 99% and 54%, respectively [4]. Pieterman reported similar results [5] – with the sensitivity of PET and CT reaching 91% and 75%, respectively and specificity – 86% and 66%,

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respectively. The results obtained in the course of PET and CT were, in the course of both these studies, confirmed pathologically while the differences achieved statistical significance. The additional value of PET lies in the possibility of performing whole body imaging, which in some 19 to 29% of patients allows discerning unsuspected metastatic lesions. [6,7]. Thus PET results may alter TNM grading based on conventional diagnostic methods in as many as 30-40% of cases [6, 7] and acc. to the results of the "Onco-PET III" trial – change the therapeutic strategy in 18% of patients.

Radiotherapy planning involving PET and CT image fusion has been applied in the course of treatment of head and neck cancers, rectal cancer and female genital cancers, however a majority of papers concerning this issue deal with NSCLC, due to the unquestionable value of FDG-PET in this particular malignancy.

Aim

The aim of the study was to present the differences in target volume (GTV) contouring based upon CT imaging and upon PET/CT image fusion in the course of radiotherapy planning in patients with NSCLC

Material and methods

We performed a retrospective analysis of PET/CT scan results obtained from 20 NSCLC patients (18 men, 2 women, mean age: 60 yrs.) between September 2003 and July 2005 at the Dept. of Nuclear Medicine of the Centre of Oncology in Bydgoszcz, Poland. The scans were performed to assess the clinical stage of the disease and were intended to complement conventional diagnostics – chest CT, bronchoscopy, abdominal ultrasound and laboratory tests. In all cases the results of the chest CT did not allow to assess local advancement. In all cases the diagnosis of cancer had been confirmed by pathological examination of bronchial tissue samples obtained in the course of bronchoscopy – 14/20 cases of *carcinoma planoepitheliale*, 4/20 – of *adenocarcinoma* and 2/20 – of NSCLC with no type. TNM staging was based on the results of conventional diagnostic methods (Table I).

10/20 patients underwent radical surgical treatment, (of whom 3 received preoperative chemotherapy). Radical radiotherapy was performed in 5/20cases (with 3 patients receiving radio-chemotherapy). The remaining 5/20 patients received palliative treatment only. In the case of 6 patients we performed PET/CT in order to assess the degree of remission after neoadjuvant chemotherapy, while in the case of another 2 patients – to investigate the possibility of failure 12 and 46 months, respectively, after surgical treatment.

The scans were performed using an integrated Biograph SL PET/CT scanner (Siemens). Before the scan the patients were administered 18-F-fluorodeoxyglucose i.v. (4.5-5 MBq/kg b.w.). In the first stage we performed spiral CT without contrast from the crown of the skull to the mid-femur. In the second stage PET scanning was performed over the same area without patient repositioning, using 4-5 different bed positions. After obtaining a fusion of the functional PET scans and morphological CT scans the results were analysed by nuclear medicine specialists.

For the purpose of further retrospective studies the PET and CT data was fed into the Eclipse 7.1 planning system using DICOM RT protocols and registered using the same coordinate system (DICOM ORIGIN). The first stage of the analysis consisted of contouring the target volume (GTV) on the platform of the CT images. The GTV/CT included the primary tumour and mediastinal lymph nodes exceeding 10 mm in diameter. In the course of the second stage of the analysis the GTV/PET volume was contoured using PET/CT image fusion. The GTV/PET volume included foci of pathological glucose uptake and corresponded to the CT image of the primary tumour mass, metastatic lymph nodes and all mediastinal lymph nodes fulfilling the criteria of metastatic involvement (i.e. exceeding 10 mm in the maximal axis) independently of the

Table I. Patient characteristics

Pts/Nr	Age/sex	H-P	TNM	Treatment before PET/CT
1	78/M	non-small	T4N2M0	none
2	69/M	non-small	T3N0M0	CHTHx6
3	55/F	adeno-ca	T2N2M1	lobectomy, RT50Gy, CHTHx6,relapse
4	51/M	squamous	T2N2M0	none
5	75/M	adeno-ca	T2N0M0	none
6	57/M	squamous	T4N2M0	none
7	63/M	squamous	T4N3M0	none
8	58/F	squamous	T2N0M0	lobectomy, relapse
9	57/M	squamous	T2N2M0	none
10	55/M	squamous	T2N2M0	none
11	46/M	adeno-ca	T2N2M0	CHTHx3
12	53/M	adeno-ca	T1N0M0	none
13	62/M	squamous	T4N1M0	none
14	64/M	squamous	T2N2M0	none
15	55/M	squamous	T1N2M0	CHTHx3
16	58/M	squamous	T3N2M0	CHTHx3
17	64/M	squamous	T3N2M0	none
18	58/M	squamous	T2N2M0	CHTHx4
19	66/M	squamous	T3N2M0	CHTHx3
20	50/M	squamous	T3N2M0	CHTHx6

FDG uptake. In both cases we additionally relied on clinical data and on the results of additional tests.

The Eclipse planning system was used to perform calculations of the GTV/CT and GTV/PET volumes and to calculate the differences between them. We also assessed their common volume i.e. the volume representing the overlapping of the GTV/CT and the modified volume calculated in the course of PET/CT image fusion.

Results

The inclusion of PET/CT image fusion results into GTV contouring resulted in GTV alteration in all the studied patients (Table II). GTV/PET was decresed in 16 patients (Group 1). This was caused by the possibility to differentiate between metabolically active tumour invasion and areas of fibrosis, atelectasis, effusion or displacement of mediastinal structures. The mean calculated difference in volume between GTV/CT and GTV/PET values was 53 cm^3 (range: 0.3-148 cm^3), i.e. 45% (3-28%) of the original GTV/CT volume. In 14/16 Group I patients the volume of the lesions exceeded 17% of the GTV/CT.

In the case of the remaining 4 patients the use of FDG/PET caused a GTV increase. GTV/PET was in these cases greater due to the diagnosis of additional groups of involved mediastinal nodes which could not be found in CT. The mean calculated difference in volume between GTV/CT and GTV/PET values was 18 cm^3 (range: 9-35 cm^3), i.e. 32% (10-80%) greater than the original GTV/CT volume. (Figure 1).

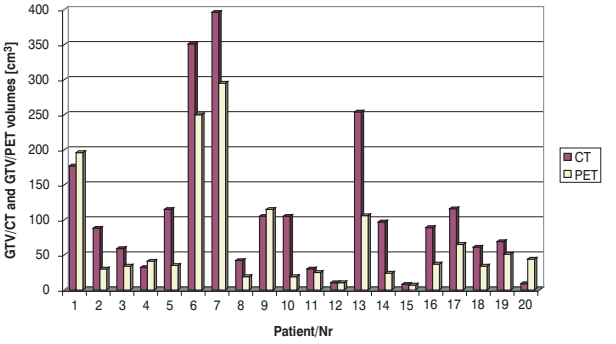

Figure 1. Comparison of target volumes GTV/CT and GTV/PET for indyvidual patients

In 6/20 cases the differences between GTV/CT and GTV/PET were the result of a calculation combining both a decrease in volume associated with differentiating adjacent benign masses and an increase caused by the discovery of involved mediastinal nodes. In 9 cases of CT-occult mediastinal nodal metastases the FDG/PET discerned pathological glucose uptake which would have remained outside the GTV/CT. Eclipse contouring

Table II Comparison of the target volumes contoured on the platform of computed tomography (GTV/CT) and positron emission tomography computed tomography (GTV/PET)

Pts Nr	GTV/CT cm^3	GTV/ PET cm^3	GTV difference cm^3 / %	Common target volumes cm^3 / %	Cause of GTV change
1	177	196	19 / 11Î	160 / 90	**Mediastinal lymph nodes**
2	88	30	58 / 66↓	28 / 93	Atelectasis, pleural effiusion
3	59	34	25 / 42↓	32 / 94	Relapse,fibrosis,mediastinal displacement
4	32	41	9 / 28Î	29 / 91	**Mediastinal lymph nodes**
5	115	35	80 / 70↓	32 / 91	Atelectasis
6	351	250	101 / 29↓	215 / 86	Mediastinal invasion
7	396	295	101 / 40↓	241 / 88	Atelectasis, **mediastinal lymph nodes**
8	42	19	23 / 55↓	16 / 84	Relapse, mediastinal displacement, fibrosis
9	105	115	10 / 10Î	97 / 92	**Mediastinal lymph nodes**
10	105	19	86 / 82↓	19 / 100	Atelectasis
11	30	25	5 / 17↓	20 / 80	Atelectasis, **mediastinal lymph nodes**
12	10.4	10.1	0.3 / 3↓	7 / 69	No changes
13	254	106	148 / 58↓	105 / 99	Atelectasis
14	97	24	73 / 75↓	19 / 79	Mediastinal invasion
15	8	7	1 / 13↓	4 / 57	No changes
16	89	37	52 / 58↓	37 / 100	Atelectasis, mediastinal invasion, media**stinal lymph nodes**
17	116	65	51 / 44↓	63 / 97	Mediastinal invasion
18	61	34	27 / 44↓	33 / 97	Fibrosis, **mediastinal lymph nodes**
19	69	51	18 / 26↓	35 / 69	Atelectasis, **mediastinal lymph nodes**
20	9	44	35 / 80Î	9 / 100	Fibrosis, **mediastinal lymph nodes**

Î – increase of GTV/PET volume to GTV/CT
↓ – decrease of GTV/PET volumesto GTV/CT

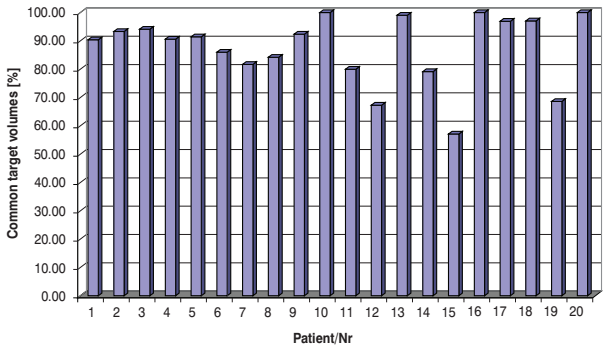

Figure 2. Common target volumes for GTV/CT and GTV/PET for indyvidual patients

allowed to contour a common volume for GTV/CT and GTV/PET. In patients from group 1 (i.e. with decreased GTV) the mean common volume was 57 cm^3 (range: 4-241 cm^3), i.e. 88% of the GTV/PET value. In group 2 (i.e. with increases GTV) the mean common volume was 74 cm^3 (range: 9-160 cm^3). (Figure 2).

Discussion

Precise staging of the disease is one of the basic conditions of correct treatment planning in the course of radical radiotherapy for NSCLC. The reasons for the inclusion of PET/CT image fusion into treatment planning include the identification of patients who are ineligible because of disseminated disease and the precise imaging of the range of malignant lesions within the thorax, thus reducing normal tissue irradiation, limiting the risk of committing a geographic mistake and escalating the total delivered dose. PET/CT is especially valuable in advanced cases of NSCLC, as a means for radical radiotherapy qualification. In case of conventional staging the frequency of finding unsuspected distant metastases in PET scans is significantly higher in stage II patients than in stage I and II patients and reaches 24% [7].

We have presented a comparison of GTVs contoured conventionally according to the results of CT scans with GTVs contoured according to PET and CT image fusion. Scanning was performed with an integrated PET/CT scanner which performs CT and PET in the course of the same session, in a short time, without patient repositioning. Such apparatus minimalises errors which may occur during image fusion and increases the diagnostic accuracy through the localisation of areas of pathologic glucose uptake within the anatomical structures [9].

Radiotherapy planning with the aid of a CT/PET scanner does not differ from typical CT-based treatment planning. The modification of the shapes and sizes of GTVs was brought on by the recognition of additional nodal groups which could not be found in CT scans and by the possibility of differentiating benign lesions in the direct vicinity of malignant masses.

The number of literature reports concerning PET/CT image fusion in radiotherapy treatment planning increases as PET becomes more available. Studies presenting the comparisons of the volumes and shapes of GTV and PTVs contoured according to CT and PET/CT image fusion were performed on various types of apparatus with various resolution (PET scanners or gamma-cameras). Although the study designs differed as to the methods of CT and PET image fusion, patient positioning and result analysis, yet in all cases the authors have reported that PET/CT image fusion causes significant modifications of the GTVs in as many as 40% to 100% of patients [10-17].

In the course of an analysis of 73 patients with N2 tumours confirmed in CT and/or PET Vanuytsel observed significant GTV changes associated with PET/CT image fusion in 45 cases (62%), with an increase in 16 cases (22%) and a decrease in 29 cases (40%). The mean value of PTV volume reduction assessed in the first 10 patients from this group was 29±18%, range: 12-66% [10].

Bradley reported similar results of a prospective study, where a significant change in GTV was observed in 14/24 patients (58%) [11]. In the remaining 10 patients the differences ranged from 1 cm^3 to 56 cm^3 and referred to as minimal, yet GTV corrections enforced by PET/CT image fusion were performed in all the patients. Giroud

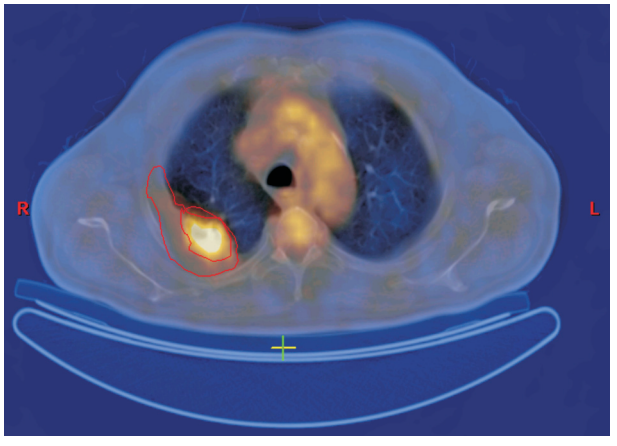

Figure3a

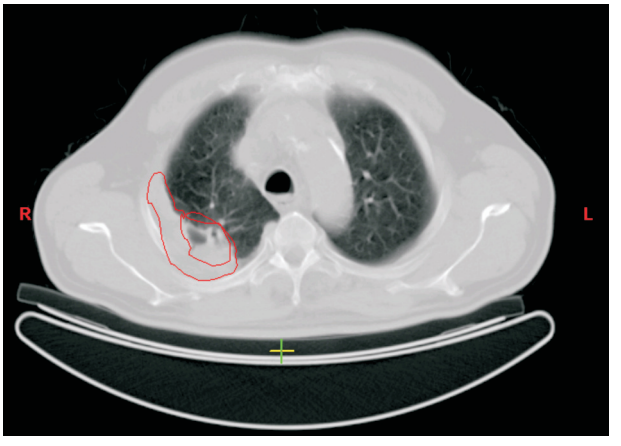

Figure 3b

Figures 3A and 3B. Neoplastic lesion with pathological FDG uptake in the FDG-PET study is included in the GTV target volume defined on the platform of CT

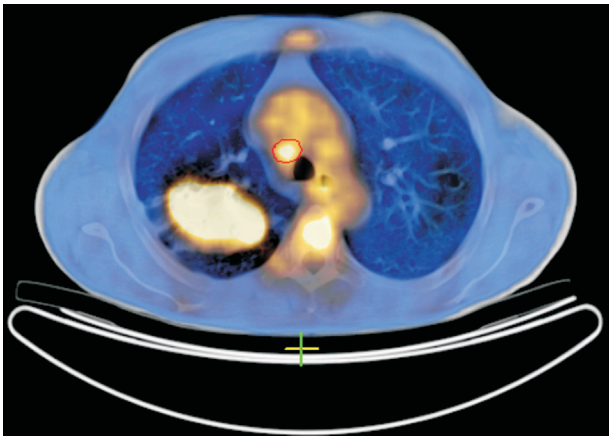

Figure 4. Fusion of FDG-PET and CT images shows mediastinal lymph node metastases undiscerned in computed tomography

reported significant GTV changes in 5/12 patients (41%) [12]. A decrease in GTV observed I 3 cases and presented as V95 was 59% on average.

In her prospective study Mah has documented that the application of PET for treatment planning has significantly altered treatment strategy in 12/30 patients (40%) [13]. 7 patients were referred for palliative treatment, instead of the originally prescribed radical treatment, due to up-staging after FDG-PET imaging. The PTV size defined using PET/CT image fusion did not match the PTV/CT-associated size in 17-29% of the patients, these variations arising from the different interpretations supplied by three independent oncologists employed I the course of the trial.

Treatment planning using the integrated PET/CT scanner does not require patient repositioning during the PET and CT scans and allows minimalising the errors occurring during image fusion [14]. IN the course of our study these conditions were similar. Ciernik conducted a study using an integrated PET/CT scanner on 31 patients, 6 of whom had NSCLC. Mean GTV/CT and GTV/PET values were 36.1 and 27.8%, respectively. PET/CT image fusion allowed to reduce the GTV in 4 patients as it had allowed differentiating between neoplastic infiltration and atelectasis. In the case of one patient mediastinal metastatic nodes were found with PET, thus allowing avoiding a geographic error.

The number of patients with altered (increased or decreased) GTVs after PET/CT image fusion contouring differs in the reports of different authors due to the fact that the patient groups were heterogeneous as to the stage of clinical advancement. In our patient material diagnostic PET was performed in patients in case of whom we suffered doubt as to the extent of disease invasion within the thorax. In all cases the malignant masses neighboured benign lesions – atelectasis, fibrosis, effusion or mediastinal dislocation rendering image interpretation difficult. What is more, the method of data analysis applied in a number of cases omitted minor corrections of the GTV values which have been included I this analysis. This explains our high ratio of patients with GTV/PET correction (100%), as compared to that reported by other authors (40-100%). Among the 16 patients with GTV/PET decrease in as many as 14 cases the reduction exceeded 17% of the original GTV/CT. Among the other 4 patients the alterations were caused by the recognition of additional nodal groups and their inclusion into the theoretic high-dose field. In 5 cases the final target volume and shape (GTV/PET) was extrapolated from a decrease caused by the differentiation of benign lesions and an increase brought on by the recognition of involved mediastinal nods. All in all without the PET/CT image fusion involved nodal masses would have remained outside the target area in as many as 9 cases.

The parameter of GTV/CT and GTV/PET common volume, which describes the degree of shape modification of the final target volume, has not been discussed in any previous studies. In our material in group 1 (16 pts) the common volume was 88% of the modified GVT/PET, while in group 2 (4 pts.) it accounted for 91%.

Conclusions

Positron emission tomography cannot take the place of morphologic imaging but it provides additional data concerning the character of observed pathologies. The application of PET/CT image fusion for radiotherapy treatment planning in patients with NSCLC has a significant impact on the GTVs.

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