Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

The impact of PET/CT scanning on the size of target volumes, radiation exposure of organs at risk, TCP and NTCP, in the radiotherapy planning of non-small cell lung cancer

Radovan Vojtíšek[a,*], *Jan Mužík*[a], *Pavel Šlampa*[b], *Marie Budíková*[c], *Jaroslav Hejsek*[a], *Petr Smolák*[a], *Jiří Ferda*[d], *Jindřich Fínek*[a]

[a] *Department of Oncology and Radiotherapy, University Hospital in Pilsen, alej Svobody 80, 304 60 Pilsen, Czech Republic*

[b] *Department of Radiation Oncology, Masaryk Memorial Cancer Institute in Brno, Žlutý kopec 543/7, 602 00 Brno, Czech Republic*

[c] *Department of Mathematics and Statistics, Faculty of Science, Masaryk University in Brno, Kotlářská 2, 611 37 Brno, Czech Republic*

[d] *Department of Imaging Methods, University Hospital in Pilsen, alej Svobody 80, 304 60 Pilsen, Czech Republic*

ARTICLE INFO

Article history:
Received 30 April 2013
Received in revised form
27 July 2013
Accepted 16 September 2013

Keywords:
Non-small cell lung cancer
PET/CT
Radiotherapy planning
TCP
NTCP

ABSTRACT

Aim: To compare radiotherapy plans made according to CT and PET/CT and to investigate the impact of changes in target volumes on tumour control probability (TCP), normal tissue complication probability (NTCP) and the impact of PET/CT on the staging and treatment strategy.

Background: Contemporary studies have proven that PET/CT attains higher sensitivity and specificity in the diagnosis of lung cancer and also leads to higher accuracy than CT alone in the process of target volume delineation in NSCLC.

Materials and methods: Between October 2009 and March 2012, 31 patients with locally advanced NSCLC, who had been referred to radical radiotherapy were involved in our study. They all underwent planning PET/CT examination. Then we carried out two separate delineations of target volumes and two radiotherapy plans and we compared the following parameters of those plans: staging, treatment purpose, the size of GTV and PTV and the exposure of organs at risk (OAR). TCP and NTCP were also compared.

Results: PET/CT information led to a significant decrease in the sizes of target volumes, which had the impact on the radiation exposure of OARs. The reduction of target volume sizes was not reflected in the significant increase of the TCP value. We found that there is a very strong direct linear relationship between all evaluated dosimetric parameters and NTCP values of all evaluated OARs.

* *Corresponding author*. Tel.: +420 377105605.
E-mail address: vojtisekr@fnplzen.cz (R. Vojtíšek).

http://dx.doi.org/10.1016/j.rpor.2013.09.006

Conclusions: Our study found that the use of planning PET/CT in the radiotherapy planning of NSCLC has a crucial impact on the precise determination of target volumes, more precise staging of the disease and thus also on possible changes of treatment strategy.

1. Background

In the current practice of radiotherapy planning and target volume determination in patients suffering from non-small cell lung cancer (NSCLC), a contrast-enhanced CT is usually used. Unfortunately, there are several clinical situations where we often encounter difficulties in contouring target volumes, as in the cases of tumour-related atelectasis, spiculated lesions and lesions close to the dystelectatic changes. Also, there are no adequate size-based criteria for nodal involvement assessment for these patients.[1]

Contemporary studies have proven that hybrid PET/CT examination has higher sensitivity and specificity in the diagnosis of lung cancer[2] and also leads to higher accuracy in the process of target volume delineation in NSCLC.

Although the prognosis of patients with NSCLC in stage III has become better in recent years, it is very difficult to improve the local control of the disease using conventional fractionation schedules and conventional doses (60 Gy).[3] This seems to be feasible by using accelerated hyperfractionated radiotherapy (HART,[4] CHARTWEL[5,6]), which increases toxicity, or by increasing the dose delivered to the target volumes, but it has been proven that the tolerance of surrounding organs at risk inhibits this effort.[7] On the other hand, reduction of the target volumes should lead to the possibility of delivering higher doses and thus to the increasing of tumour control probability (TCP) with acceptable normal tissue complication probability (NTCP). Nowadays, it seems that the way to reduce target volumes is to use the most precise imaging modality possible, optimally PET/CT.

Therefore, we proposed a representative study comparing radiotherapy plans made according to CT and PET/CT examinations in the same patient. For these comparative purposes we used different dose-volume parameters and sizes of target volumes. Furthermore, we investigated the impact of the changes in target volume sizes on TCP and NCTP and the impact of combined PET/CT examination on the staging of the disease and treatment strategy. According to our best knowledge, there has been no study published investigating the relationship between target volume changes that developed according to the use of PET/CT and NTCP values for all relevant organs at risk in the chest.

2. Patients and methods

2.1. Patients

Between October 2009 and March 2012, 31 patients (26 men and 5 women, with a median age of 68, see details in Table 1) suffering from histologically proven, inoperable, locally advanced NSCLC referred for radical radiotherapy – either as a single method or in combination with chemotherapy, sequential or concomitant – took part in our study.

Table 1 – Patients and disease characteristics.

	All patients ($n = 31$)
Sex	
Male	26 (83.9%)
Female	5 (16.1%)
Age at the time of diagnosis (median, range)	68 (56–80)
Side	
Right	21 (67.7%)
Left	10 (32.3%)
Histology	
Squamous cell carcinoma	24 (77.4%)
Adenocarcinoma	7 (22.6%)
Dose delivered (Gy; median; range)	66 (40.5–80)
Stage according to CT	
IA	0
IB	2 (6.4%)
IIA	1 (3.2%)
IIB	0
IIIA	18 (58.1%)
IIIB	6 (19.4%)
IV	4 (12.9%)
Stage according to PET/CT	
IA	0
IB	2 (6.4%)
IIA	0
IIB	3 (9.7%)
IIIA	17 (54.8%)
IIIB	6 (19.4%)
IV	3 (9.7%)
Radiotherapy purpose according to CT	
Radical	27 (87.1%)
Palliative	4 (12.9%)
Radiotherapy purpose according to PET/CT	
Radical	27 (87.1%)
Palliative	4 (12.9%)

2.2. Radiotherapy simulation and image acquisition

All patients underwent initial preparation at the Department of Oncology and Radiotherapy, University Hospital in Pilsen, according to our institutional standards, i.e. the choice of proper positioning and immobilization devices (we normally use WingBoard^R, MED-TEC, for immobilization of the upper arms when patients are in the supine position with both arms above the head), determination of the reference plane on X-ray simulator and drawing of the projection points of the simulated isocentre on the patient's skin. Planning PET/CT examination was carried out at the Department of Imaging

Methods at the same hospital and in the same way as routine diagnostic examinations with the exception that patients were positioned in radiotherapy positions with dedicated immobilization devices. The concavity of the examination table was compensated for with a radiolucent hand-made board. Patients were placed into the required position with the help of a laser positioning system, the projection points on the skin were marked with radiopaque marks.

PET scans were performed 60 min after the intravenous administration of ^{18}FDG (2-[^{18}F]fluor-2-deoxy-D-glucose) with a radioactivity level of about 400 MBq. 1000 ml of a 2.5% solution of mannitol was used as bowel preparation. CT scans were performed on a Biograph HiRez/16 slice (Siemens, Forcheim, Germany) after intravenous administration of 100 ml of a non-ionic iodine contrast agent between the base of the skull and the inguinal region. CT scans were performed during inhalation, during PET acquisition the patient was instructed to breathe slowly and shallowly. CT and PET scans were then exported to our treatment planning system PlanW 2000.

In this treatment planning system PET units are transferred to grey values (GVal) following the next formula (DispWindow = user-adjustable display window of PET units matrix; typical example: wide display window has DispWindow.LowLevel = 0 and DispWindow.HighLevel = 32,600): if PET units ≤ DispWindow.LowLevel, then GVal = 0; if PET units ≥ DispWindow.HighLevel, then GVal = 255; and if GVal = round (255 × (PET number − DispWindow.LowLevel)/(DispWindow.HighLevel − DispWindow.LowLevel)). Grey values (GVal) are transferred to red, green and blue (R, G, B) scheme following the next formula: if GVal ≥ 128, then TPS use R = 255, G = 2 × (GVal − 128) and B = 0; if GVal ≤ 128, then TPS use R = min (2 × GVal, 255), G = 0 and B = 0. Typical example: for wide display window (DispWindow.LowLevel = 0 and DispWindow.HighLevel = 32,600) the bright red colours start from PET units about 10,000 and bright yellow colours start from PET units about 23,000.

2.3. *Radiotherapy planning*

Contouring of all plans was carried out in two separate sessions by the same radiation oncologist (R.V.). First, we used only CT data for contouring (as we did not pay attention to results from PET scans) and we delineated target volumes GTV (Gross Tumour Volume), CTV (Clinical Target Volume), PTV (Planning Target Volume) and organs at risk according to the ICRU Report 50[8] and 62 recommendations.[9] Delineation was carried out using the lung (GTV-T) and the mediastinal windows (GTV-N). Subsequently, we merged the copied CT scans with PET scans and carried out a new delineation of target volumes according to the same recommendations. No mathematical algorithm for automatic contouring of GTV was used nor any threshold for SUV (standardized uptake value). It was an entirely subjective contouring based on detailed descriptions of pathological findings. We consulted a radiologist in case of doubts and used all accessible clinical information, as per the latest recommendations.[10] The margin between GTV and CTV was 5 mm and the margin between CTV and PTV was 10–15 mm depending on the breathing excursions found during the first X-ray simulation. Until November 2010, we were standardly using the "shrinking-field" technique with elective nodal irradiation (ipsilateral hilum and mediastinum or both hilar regions and mediastinum). In December 2010, we modified our own standard treatment protocol with respect to the results of numerous clinical studies[11–14] and the EORTC recommendations.[15,16] We also did not include elective nodal regions into target volumes anymore, but only involved nodal stations.

We also contoured all at-risk organs in the thorax according to our institutional protocol – the lungs (the volume of both lungs minus PTV), the oesophagus (from just below the larynx to the gastroesophageal junction), the spinal cord (defined by the inner margin of the bony spinal canal) and the heart (the cranial extent should include the infundibulum of the right ventricle and the apex of both atria while excluding the great vessels as much as possible, and the caudal border defined by the lowest part of the ventricle' inferior wall that is distinguishable from the liver).

Subsequently, two plans were made with the same prescribed dose in the ICRU reference point, which differed from case to case according to the clinical situation and the relationship with the chemotherapy administration, and with the same dose-volume constraints of organs at risk. 30 patients were treated with 3D-CRT (3D conformal radiotherapy) and only 1 patient with IMRT (intensity modulated radiotherapy). Both plans had their own dose-volume histograms for target volumes and for organs at risk. These plans were mostly not identical in terms of fields arrangement, they were different, depending on the size and shape of the PTV. Eventually, we used a radiobiological modelling programme (BioGray v. 1.5) to obtain the parameters such as TCP (tumour control probability) and NTCP (normal tissue complication probability).

2.4. *Dose constraints, TCP, NTCP*

We use dose constraints in our department for organs at risk as follows: the lungs $V_{20} < 35\%$, MLD (mean lung dose) < 20 Gy, the spinal cord $D_{max} < 50$ Gy, the heart $V_{33} < 60\%$, $D_{mean} < 46$ Gy and the oesophagus $V_{50} < 30\%$, $V_{55} < 28\%$, $V_{35} < 65\%$, $D_{max} < 70$ Gy.[16,17]

TCP (tumour control probability) and NTCP (normal tissue complication probability) reflect the effectiveness or toxicity of radiotherapy schemes. Generally, the TCP value should be as high as possible (100% being unattainable). The NTCP shows the probability of occurrence of early or late toxicity in organs (tissue) as a result of radiotherapy. Especially the manifestations of late toxicity can severely decrease the quality of life or endanger the viable tissues (paralysis, blinding, etc.).

In an effort to obtain these parameters, we used the BioGray v. 1.5 programme, which is a comprehensive programme dedicated to modelling and predicting radiobiological late or early effects in radiotherapy as well as the probability of tumour control. The programme is based on a linear-quadratic model (LQM) using the concept of a biological effective dose (BED) created by Barendsen[18] and the 4-component Lyman model for calculating NTCP and TCP. The programme works using a method of simultaneous simulation of effects on selected tissues. It calculates the radiobiological status after every fraction of therapy for each tissue, namely the cumulative applied dose, BED, TCP and NTCP. The results of these calculations may be displayed either as a function of time or applied

physical (cumulative) dose.[19] The programme contains a library of predefined items representing critical structures and tumour types with entered parameters that correspond to a radiobiological model and its characteristics. According to DVH of a structure (and target volume), the maximum dose and percentage partial volume is determined and these values are used to adjust the actual structure irradiation.

2.5. *Compared parameters*

We compared the following parameters: staging, aim of treatment, the size of GTV and PTV (or PTV reduced in situations when patients were treated with the "shrinking-field" technique in two phases), the exposure of organs at risk – the lungs V_{13}, V_{20}, MLD; the spinal cord D_{max}; the heart V_{33}, D_{mean} and the oesophagus V_{50}, TCP and NTCP of all organs at risk.

2.6. *Ethics*

As this was a planning/modelling study, patients were diagnosed and treated according to standard guidelines at our institute.

2.7. *Statistics*

The following methods were used for statistical analyses of the data file:

Frequency tables of absolute and relative frequencies and the contingency tables of simultaneous absolute and relative frequencies.

Descriptive statistics of observed variables, i.e. the mean, the median, the range and the standard deviation.

Paired tests comparing the mean values or the medians of two variables surveyed on the same object, either the paired *t*-test (in case the variables are normally distributed) or the paired Wilcoxon test (in case the variables are not normally distributed).

Tests of the independence of two variables: the asymptotic χ^2-test of the independence for the nominal variables; a test of the serial independence with the use of Spearman correlation coefficient for the ordinal variables or the continuous variables that are not bivariate normally distributed; a test of the stochastic independence with the use of correlation coefficient for the continuous variables, that are bivariate normally distributed.

For descriptive statistics, the means are given ± standard deviation (SD) or the medians are given ± interquartile range (IQR).

3. Results

3.1. *Change of staging and its influence on the treatment strategy*

The findings obtained from PET/CT examination led in 9 patients (29%) to upstaging of the disease evaluated according to separate CT examination, in 10 patients (32.3%) to downstaging and in 12 patients (38.7%) no change was observed between the stages evaluated according to CT and PET/CT.

When the CT findings underestimated the extent of the disease, new findings (metastatic disease) led to changes in treatment strategy in 3 patients (9.7%), namely to palliative radiotherapy (2 patients, 6.5%) and palliative chemotherapy (1 patient, 3.2%). When the CT findings overvaluated the extent of the disease, radical treatment was started in 3 patients (9.7%), although it would be not indicated based on a CT scan alone.

Change in the sizes of target volumes GTV (gross tumour volume) and PTV (planning target volume).

Incorporating PET/CT scan information in target-volume contouring led to a significant decrease of the sizes of target volumes unlike the contouring using separate CT scan information: the median $GTV_{CT} = 61\ cm^3 \pm 92.6$ (range 19.4–431.7 cm^3), median $GTV_{PET/CT} = 52.5\ cm^3 \pm 70.3$ (range 15.7–399 cm^3); $p = 0.001$. Median $PTV_{CT} = 320\ cm^3 \pm 212.4$ (range 151.2–1204 cm^3). Median $PTV_{PET/CT} = 262.7\ cm^3 \pm 169.5$ (range 107.9–1147 cm^3); $p < 0.001$ (see Table 2).

3.2. *Radiation exposure of healthy lung tissue and NTCP*

Comparing PET/CT planning with CT planning only, we found that radiation exposure of healthy lung tissue decreased insignificantly: the mean V_{13} from 39.8% ± 20.6 (range 9–81%) to 38.7% ± 20.9 (range 8–82%), $p = 0.176$; the mean V_{20} from 30.4% ± 16.4 (range 7–73%) to 30.2% ± 17.1 (range 6–73%), $p = 0.428$; and the mean of mean lung dose (MLD) from 16.2 Gy ± 6.8 (range 4–29.6 Gy) to 16 Gy ± 7.0 (range 3.6–29.8 Gy), $p = 0.328$.

Identified NTCP values did not differ between different means of radiotherapy planning: the median $NTCP_{CT} = 14.8\% \pm 16.6$ (range 4–50%) and the median $NTCP_{PET/CT} = 13.7\% \pm 19.4$ (range 4–54%), $p = 0.355$.

3.3. *Radiation exposure of the oesophagus and NTCP*

The use of PET/CT led to a significant decrease in radiation exposure of the oesophagus analyzed according to the value V_{50}: the median decreased from 16% ± 42 (range 0–72%) to 11% ± 37 (range 0–70%); $p = 0.0033$.

The median of NTCP has decreased from 30.8% ± 39.8 (range 0–76%) to 25.7% ± 45.2 (range 0–75%); $p < 0.001$.

3.4. *Radiation exposure of the spinal cord and NTCP*

Also, radiation exposure of the spinal cord with the use of PET/CT planning was lower: the median D_{max} decreased from 43.6 Gy ± 10.5 (range 14.9–51.9 Gy) to 40 Gy ± 17.9 (range 3.2–49.9 Gy); $p = 0.0065$.

The change of NTCP values was not statistically evaluable, because we had a very low number of nonzero values.

3.5. *Radiation exposure of the heart and NTCP*

The same results were found in evaluation of radiation exposure of the heart, incorporating the PET/CT to the planning led to a decrease in all analyzed dosimetric parameters: the median V_{33} decreased from 18% ± 22.5 (range

Table 2 – Changes of target volumes sizes and TCP with the use of PET/CT.

Target volume	The size of target volume (median, IQR, range)			TCP (median, IQR, range), in %		
	CT	PET/CT	*p*-Value	CT	PET/CT	*p*-Value
GTV (cm^3)	61 ± 92.6 (19.4–431.7)	52.5 ± 70.3 (15.7–399)	0.001	68.1 ± 34.8(4.4–88)	69.1 ± 32.5 (4.2–88)	0.857
PTV (cm^3)	320 ± 212.4 (151.2–1204)	262.7 ± 169.5 (107.9–1147)	$p < 0.001$			

Abbreviations: GTV, gross tumour volume; PTV, planning target volume; IQR, interquartile range; TCP, tumour control probability.

Table 3 – Dosimetric parameters of organs at risk and subsequent NTCP values of all eligible patients ($n = 29$).

Parameter	Radiation exposure (median,[a] IQR,[a] range)			NTCP (median,[a] IQR,[a] range)		
	CT	PET/CT	*p*-Value	CT	PET/CT	*p*-Value
Lung (%)				14.8 ± 16.67 (4–50)	13.7 ± 19.46 (4–54)	0.355
V_{13} (%)	39.8 ± 20.6 (9–81)	38.7 ± 20.9 (8–82)	0.176			
V_{20} (%)	30.4 ± 16.4 (7–73)	30.2 ± 17.1 (6–73)	0.428			
Mean lung dose (Gy)	16.2 ± 6.8 (4–29.6)	16 ± 7 (3.6–29.8)	0.328			
Oesophagus (%)				30.8 ± 39.8 (0–76)	25.7 ± 45.2 (0–75)	<0.001
V_{50} (%)	16 ± 42 (0–72)	11 ± 37 (0–70)	0.0033			
Spinal cord (%)				0 ± 0.5 (0–2)	0 ± 0.5 (0–2)	NE
Maximal dose	43.6 ± 10.5 (14.9–51.9)	40 ± 17.9 (3.2–49.9)	0.0065			
Heart (%)				0.5 ± 5 (0–44)	0 ± 4.8 (0–44)	0.0116
V_{33} (%)	18 ± 22.5 (0–47)	16 ± 24 (0–51)	0.007			
Mean heart dose (Gy)	17.2 ± 17.5 (1.6–31.8)	14.4 ± 17.8 (0–31.8)	0.0017			

Abbreviations: V_x, volume of organ receiving at least *x* Gy; IQR, interquartile range; NTCP, normal tissue complication probability; SD, standard deviation; NE, not evaluable.
[a] Except lung parameters, those are expressed as the mean and SD.

0–47%) to 16% ± 24 (range 0–51%), $p = 0.007$; and the median D_{mean} from 17.2 Gy ± 17.5 (range 1.6–31.8 Gy) to 14.4 Gy ± 17.8 (range 0–31.8 Gy), $p = 0.0017$.The median of NTCP decreased from 0.5% ± 0.5 (range 0–44%) to 0% ± 4.8 (range 0 44); $p = 0.0116$.

3.6. *Influence of size change in target volumes on TCP*

Although a significant reduction of the target-volume (GTV and PTV) sizes was found, it was not reflected in the significant increase of the TCP value: the median TCP_{CT} was 68.1% ± 34.8 (range 4.4–88%) and the median $TCP_{PET/CT}$ 69.1% ± 32.5 (range 4.2–88%); $p = 0.857$ (see Table 2).

The only findings made only showed a very weak, indirect, ordinal relationship between the size of GTV and the TCP value (Spearman' rank correlation coefficient was −0.167 and −0.282 with the use of CT and PET/CT, respectively).

3.7. *Influence of size change of radiation exposed organs at risk on NTCP*

Our results do conclude that there is a very strong direct linear relationship between all evaluated dosimetric parameters and NTCP values of all evaluated organs at risk (see Table 3).

4. Discussion

It has already been proven that a PET/CT imaging method is more precise than a CT scan alone in the assessment of lymph nodes status in lung cancer. Even PET/CT scanning is not the most precise method in predicting nodal involvement, as there is no doubt that currently the most precise method is a biopsy of suspected nodes. It has higher sensitivity and specificity as it has been proven in studies of Vanuytsel et al.[20] and Faria et al.[21]

PET/CT examination also helps to determine the primary tumour close to the atelectatic lung area. Doses between 60 and 70 Gy, which are commonly used in the treatment of locoregionally advanced lung cancer, are associated with frequent incidence of relapse and very dismal survival rates,[22] because it has been conclusively proven that there is a clear association between total dose, local control and overall survival of patients treated for NSCLC.[23,24] Currently, there is an effort to irradiate the smallest target volume with the highest dose possible while sparing the surrounding at-risk organs to the highest degree. To reach this aim, the latest imaging methods are used because they are able to precisely determine the target volume. This is especially true of PET/CT examination.

During contouring of GTV neither mathematical algorithm nor threshold for SUV (standardized uptake value) was used, it was entirely subjective contouring based on detailed descriptions of pathological finding and all accessible clinical information. The resolution of PET is low, average 4.5 mm, so the margins of the displayed tumour are somewhat blurred and human eye is not easily able to distinguish the borders of the target volume. This is also influenced by the software, the contrast between the tumour and the background and other artefacts.[25] There are several possibilities and ways how to define the borders of GTV on PET scans described in the literature. The first ever method described is the utilization of all accessible clinical information, knowledge and experience of a planning radiation oncologist, the method of visual assessment. It relies on a visual assessment of the PET image to identify and select areas of pathological uptake. These areas are then contoured by CT to take advantage of the greater spatial resolution of CT, which allows for a clear definition of the tumour border (unlike PET).[26] The second way, which was explored, is the use of mathematical automatic or semi-automatic models for the determining of the borders. For this purpose, some threshold cut-off values are used, either the percentage of the maximal SUV (40%,[27–29] 42%[30,31] and 50%[25,32,33]) or the absolute value of SUV (usually SUV 2,5[34]). Obtaining "the magical line" between malignant and normal tissue is as yet impossible.[35] According to the latest recommendations, the first method (visual assessment) should be used for contouring.[10]

In our study we found out that in radiotherapy planning there is a significant decrease of the target volumes with the use of PET/CT, which is mainly caused by omitting the uninvolved lymph node groups (better defined by PET/CT) and by more accurate definition of the primary tumour (differentiation from dystelectatic changes or atelectasis). The changes in target volume sizes often reflect the changed staging of the disease, particularly in terms of the changed assessment of the lymph node involvement. Changes in staging can also lead to a change in treatment strategy,[36] especially when distant metastases are found. We found that in 9 out of all 31 patients, PET/CT led to upstaging of the disease diagnosed by CT alone and in 10 patients PET/CT led to downstaging. Of the patients upstaged by PET/CT, in 6 cases the upstaging was caused by a change in the "N" category and in 3 patients distant metastases were found, leading to a change of the treatment strategy.

Our results are in accordance with published studies related to this topic. Erdi et al.[30] published their own study with a very modest number of 11 patients with NSCLC and they evaluated the impact of PET/CT performed subsequently after classical CT examination on the contouring of target volumes. An increase in target volumes was observed in 7 patients – especially influenced by newly diagnosed positive lymph node groups – and a decrease was observed in 4 patients, caused by omitting the atelectatic areas from the target volume. Brianzoni et al.[27] evaluated 28 patients who were investigated on an integrated PET/CT scanner. Generally, only 25 patients were evaluated, because in the remaining 3 patients the stage was modified and led to a change in treatment strategy. In 14 (56%) patients the information from PET did not lead to a significant change in target volumes, whereas in 11 (44%) patients that information led to a change in target volumes – in 5 of them it was decreased (2 patients had atelectasis and in 3 patients false positive lymph nodes on CT scan were observed) and in 6 of them increased (in 3 patients false negative lymph nodes on CT scan were observed and 3 patients had atelectasis). Ashamalla et al.[37] compared the contouring of GTV and PTV according to CT and PET/CT images created on an integrated scanner in 19 patients staged as II–IIIB NSCLC. A significant change in the size of GTV was found in 10 (52%) patients – in 5/10 patients the volume was increased and in the same number of patients it decreased. Changes in the size of PTV were observed in 8 (42%) patients. Bradley et al.[28] compared radiotherapy plans for 26 patients with I–III stage NSCLC. A change in TNM classification was observed in 8 (31%) patients. In 2 patients metastatic disease was found and, therefore, these patients were not further enrolled in the study. In 14/24 (58%) patients PET examination distinctly changed the sizes of target volumes. In 3 patients PET examination helped distinguish the primary tumour from a collapsed atelectatic lung (the decrease of the volume), unexpected nodal involvement was detected by PET in 10 patients and in 1 patient another tumour lesion in the same lobe was found (an increase in volume).

Change in target volume sizes leads to a change in the irradiated volume of organs at risk. In this context, the differentiation of the atelectasis from the tumour is of the greatest importance, leading to a decrease in the probability of pneumonitis and oesophagitis.[28,38] In our study we observed that the change of target volume sizes has only a slight impact (statistically insignificant) on the radiation exposure of lung tissue, but there is a significant impact on the radiation exposure on oesophagus, heart and spinal cord. In our case the decrease of target volume sizes led to the decrease of dosimetric parameters of organs at risk, except the lung tissue. This could be due to the fact, that in the first half of our study we performed the elective nodal irradiation and thus a substantial part of healthy lung tissue was exposed regardless of the size of GTV. The decrease of dosimetric parameters was followed by a significant decrease of NTCP values. Similar Australian study[39] also did not reveal a significant change in MLD (mean lung dose) and V_{20} ($p = 0.801$ and 0.816, respectively) in radiotherapy plans made on the basis of CT and PET/CT in 10 patients with NSCLC, although in all cases a small part of $PTV_{PET/CT}$ (10–40%) was outside the PTV_{CT}; in 3 cases even the whole volume of $PTV_{PET/CT}$ was outside the PTV_{CT} (geographical miss). Five patients had atelectasis that was clearly distinguished by PET. In other study Ceresoli et al.[40] did not report significant changes regarding the irradiated

volumes of healthy lung tissue when PET/CT fusion was used for target volume contouring. But they found out the change in the maximum point dose to the spinal cord (D_{max}), which was significantly lower in PET/CT plans. Their results are in accordance with our findings. In their study with 21 enrolled patients a significant change in volume between GTV_{CT} and $GTV_{PET/CT}$ was also observed – $GTV_{PET/CT}$ was greater in 5 patients mainly due to the inclusion of pathological lymph nodes; $GTV_{PET/CT}$ was smaller in 2 patients due to the exclusion of enlarged lymph nodes and atelectatic area. In an extensive study comparing target-volume contouring on the basis of CT and PET/CT, Deniaud-Alexandre et al.[32] reported on the impact of changes in these volumes on the irradiation of organs at risk. They evaluated only radiation exposure of the lung (V_{20}) and the heart (V_{36}) in 92 patients. The volume of GTV decreased by PET/CT in 21 (23%) patients, the median of the change was 32.7% (range 2.5–143%) and in 24 (26%) patients the volume of GTV increased, the median of the change was 18.5% (range 1.5–77.5%). Of 81 patients receiving a total dose greater or equal to 60 Gy, the percentage of total lung volume receiving more than 20 Gy (V_{20}) increased in 15 patients (median 15.4%) and decreased in 22 patients (median 12.5%). The percentage of total heart volume receiving more than 36 Gy (V_{36}), predicting cardial toxicity, increased in 8 patients (median 53.5%) and decreased in 14 patients (median 65.5%).

When radiation exposure of organs at risk is decreased, the dose delivered to the target volume can be escalated and thus the probability of local control of the disease can be improved, expressed radiobiologically in numbers as TCP. We also compared TCP values of two treatment plans only according to the change of GTV and changed stage of the disease and we found that although significant decrease of GTV was reached, it was not reflected by increased median of TCP value. It was probably due to the same comparing doses, unlike in the below mentioned studies. The decrease of GTV itself (without increasing the delivered dose) could not lead to the increase of the TCP, but it has to be followed by the increase in the delivered dose if possible. Van Der Wel et al.[41] tried to find a maximum feasible dose delivered to target volume while respecting the tolerance doses in situations when the decreased radiation exposure of the oesophagus and the lung were observed from PET data. They evaluated 21 patients suffering from NSCLC with nodal stage N2–N3 according to CT. Radiation fields were reduced in 11 patients, enlarged in 3 patients and remained unchanged in 7 patients. Delivered dose could be escalated from 56 ± 5.4 Gy to 71 ± 13.7 Gy ($p = 0.038$), thereby TCP could be increased from $14.2 \pm 5.6\%$ to $22.8 \pm 7.1\%$ ($p = 0.026$). Dutch authors De Ruysscher et al.[7] approached this issue in a very similar way. They also evaluated the change of delivered doses to organs at risk and the influence on possible dose escalation leading consequently to the increase of the TCP value. 21 patients enrolled in their study suffered from locally or locoregionally advanced NSCLC, all of them had radiotherapy plan made according to CT and PET/CT. For assessment of radiation exposure of the oesophagus and the lung they used following parameters: MOD (mean oesophageal dose), V_{55} and MLD and V_{20}, respectively. PET/CT data led to a significant reduction of the dosimetric parameters of both, the oesophagus and the lung. Two-thirds of plans were changed with regard to PET data, in 2 patients the target volume was increased, in 12 patients decreased and remained unchanged in 7 patients. The above mentioned findings were the background for dose escalation modelling. Delivered dose was increased from 55.2 ± 2.0 Gy to 68.9 ± 3.3 Gy ($p = 0.002$) and as a consequence, the TCP value increased from $6.3 \pm 1.5\%$ to $24.0 \pm 5.6\%$ ($p = 0.01$).

5. Conclusions

We found in our study that the use of PET/CT examination in planning of radiotherapy for non-small cell lung cancer has a crucial impact on the precise determination of target volumes, precise staging of the disease and thus also on possible change of treatment strategy. If the target volume size decreases, the dose delivered to this volume can be escalated and thus the TCP value can increase, meaning that the probability of local disease control can be increased while the toxicity of organs at risk remains acceptable. The probability of developing the toxicity of organs at risk is usually evaluated either according to dose-volume histograms or NTCP values, expressing the probability of damage of organs at risk. Further studies comparing TCP and NTCP values with clinical outcomes are warranted and we will continue our efforts in this area in our future studies.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Vojtisek R, Havranek K, Finek J. The use of PET/CT fusion in radiotherapy treatment planning of non-small-cell lung cancers. *Klin Onkol* 2011;**24**(1):23–34.
2. Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med* 2003;**348**(25):2500–7.
3. Sause W, Kolesar P, Taylor SIV, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest* 2000;**117**(February (2)):358–64.
4. Belani CP, Wang W, Johnson DH, et al. Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597): induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non-small-cell lung cancer. *J Clin Oncol* 2005;**23**(June (16)):3760–7.
5. Baumann M, Herrmann T, Koch R, et al. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). *Radiother Oncol* 2011;**100**(July (1)):76–85.
6. Soliman M, Yaromina A, Appold S, et al. GTV differentially impacts locoregional control of non-small cell lung cancer (NSCLC) after different fractionation schedules: subgroup

analysis of the prospective randomized CHARTWEL trial. *Radiother Oncol* 2013;**106**(March (3)):299–304.
7. De Ruysscher D, Wanders S, Minken A, et al. Effects of radiotherapy planning with a dedicated combined PET-CT-simulator of patients with non-small cell lung cancer on dose limiting normal tissues and radiation dose-escalation: a planning study. *Radiother Oncol* 2005;**77**(October (1)):5–10.
8. ICRU Report 50. *Prescribing, recording and reporting photon beam therapy*. Bethesda: International Commission for Radiation Units and Measurements; 1993. p. 71.
9. ICRU Report 62. *Prescribing, recording and reporting photon beam therapy (Suppl. to ICRU Report 50)*. Bethesda: International Commission for Radiation Units and Measurements; 1999. p. 52.
10. Biehl KJ, Kong FM, Dehdashti F, et al. 18F-FDG PET definition of gross tumor volume for radiotherapy of non-small cell lung cancer: is a single standardized uptake value threshold approach appropriate? *J Nucl Med* 2006;**47**(November (11)):1808–12.
11. Senan S, Burgers S, Samson MJ, et al. Can elective nodal irradiation be omitted in stage III non-small-cell lung cancer? Analysis of recurrences in a phase II study of induction chemotherapy and involved-field radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;**54**(November (4)):999–1006.
12. Klopp AH, Chang JY, Tucker SL, et al. Intrathoracic patterns of failure for non-small-cell lung cancer with positron-emission tomography/computed tomography-defined target delineation. *Int J Radiat Oncol Biol Phys* 2007;**69**(December (5)):1409–16.
13. Sura S, Greco C, Gelblum D, Yorke ED, Jackson A, Rosenzweig KE. (18)F-fluorodeoxyglucose positron emission tomography-based assessment of local failure patterns in non-small-cell lung cancer treated with definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;**70**(April (5)):1397–402.
14. De Ruysscher D, Wanders S, van Haren E, et al. Selective mediastinal node irradiation based on FDG-PET scan data in patients with non-small-cell lung cancer: a prospective clinical study. *Int J Radiat Oncol Biol Phys 2005* 2005;**62**(July (4)):988–94.
15. Senan S, De Ruysscher D, Giraud P, et al. Radiotherapy Group of European Organization for Research and Treatment of Cancer, Literature-based recommendations for treatment planning and execution in high-dose radiotherapy for lung cancer. *Radiother Oncol* 2004;**71**(2):139–46.
16. De Ruysscher D, Faivre-Finn C, Nestle U, et al. European Organisation for Research and Treatment of Cancer recommendations for planning and delivery of high-dose, high-precision radiotherapy for lung cancer. *J Clin Oncol* 2010;**28**(36):5301–10.
17. Milano MT, Constine LS, Okunieff P. Normal tissue tolerance dose metrics for radiation therapy of major organs. *Semin Radiat Oncol* 2007;**17**(April (2)):131–40.
18. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *Int J Radiat Oncol Biol Phys* 1982;**8**(November (11)):1981–97.
19. http://biogray.atlasweb.cz/
20. Vanuytsel LJ, Vansteenkiste JF, Stroobants SG, et al. The impact of (18)F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) lymph node staging on the radiation treatment volumes in patients with non-small cell lung cancer. *Radiother Oncol* 2000;**55**(June (3)):317–24.
21. Faria SL, Menard S, Devic S, et al. Impact of FDG-PET/CT on radiotherapy volume delineation in non-small-cell lung cancer and correlation of imaging stage with pathologic findings. *Int J Radiat Oncol Biol Phys* 2008;**4**: 035–38.
22. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiother Oncol* 1999;**52**:137–48.
23. Rengan R, Rosenzweig KE, Venkatraman E, et al. Improved local control with higher doses of radiation in large-volume stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;**60**:741–7.
24. Willner J, Baier K, Caragiani E, Tschammler A, Flentje M. Dose, volume, and tumor control prediction in primary radiotherapy of non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002;**52**:382–9.
25. Nestle U, Walter K, Schmidt S, et al. 18F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: high impact in patients with atelectasis. *Int J Radiat Oncol Biol Phys* 1999;**44**(June (3)):593–7.
26. Perea BC, Villegas AC, Delgado Rodríguez JM, et al. Recommendations of the Spanish Societies of Radiation Oncology (SEOR) Nuclear Medicine & Molecular Imaging (SEMNiM), and Medical Physics (SEFM) on ^{18}F-FDG PET-CT for radiotherapy treatment planning. *Rep Pract Onco Radiother* 2012;(November–December):298–318.
27. Brianzoni E, Rossi G, Ancidei S, et al. Radiotherapy planning: PET/CT scanner performances in the definition of gross tumour volume and clinical target volume. *Eur J Nucl Med Mol Imaging* 2005;**32**(12):1392–9.
28. Bradley J, Thorstad WL, Mutic S, et al. Impact of FDG-PET on radiation therapy volume delineation in non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;**59**(1):78–86.
29. Giraud P, Grahek D, Montravers F, et al. CT and (18)F-deoxyglucose (FDG) image fusion for optimization of conformal radiotherapy of lung cancers. *Int J Radiat Oncol Biol Phys* 2001;**49**(April (5)):1249–57.
30. Erdi YE, Rosenzweig K, Erdi AK, et al. Radiotherapy treatment planning for patients with non-small cell lung cancer using positron emission tomography (PET). *Radiother Oncol* 2002;**62**(1):51–60.
31. Fox JL, Rengan R, O'Meara W, et al. Does registration of PET and planning CT images decrease interobserver and intraobserver variation in delineating tumor volumes for non-small-cell lung cancer? *Int J Radiat Oncol Biol Phys* 2005;**62**(May (1)):70–5.
32. Deniaud-Alexandre E, Touboul E, Lerouge D, et al. Impact of computed tomography and 18F-deoxyglucose coincidence detection emission tomography image fusion for optimization of conformal radiotherapy in non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2005;**63**(December (5)):1432–41.
33. Mah K, Caldwell CB, Ung YC, et al. The impact of (18)FDG-PET on target and critical organs in CT-based treatment planning of patients with poorly defined non-small-cell lung carcinoma: a prospective study. *Int J Radiat Oncol Biol Phys* 2002;**52**(February (2)):339–50.
34. Videtic GM, Rice TW, Murthy S, et al. Utility of positron emission tomography compared with mediastinoscopy for delineating involved lymph nodes in stage III lung cancer: insights for radiotherapy planning from a surgical cohort. *Int J Radiat Oncol Biol Phys* 2008;**72**(November (3)):702–6.
35. Paulino AC, Johnstone PA. FDG-PET in radiotherapy treatment planning: Pandora's box? *Int J Radiat Oncol Biol Phys* 2004;**59**(May (1)):4–5.
36. Paulsen F, Scheiderbauer J, Eschmann SM, et al. First experiences of radiation treatment planning with PET/CT. *Strahlenther Onkol* 2006;**182**(July (7)):369–75.
37. Ashamalla H, Rafla S, Parikh K, et al. The contribution of integrated PET/CT to the evolving definition of treatment

volumes in radiation treatment planning in lung cancer. *Int J Radiat Oncol Biol Phys* 2005;**63**(November (4)):1016–23.
38. Singh AK, Lockett MA, Bradley JD. Predictors of radiation-induced esophageal toxicity in patients with non-small-cell lung cancer treated with three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;**55**(February (2)):337–41.
39. MacManus M, D'Costa I, Everitt S, et al. Comparison of CT and positron emission tomography/CT coregistered images in planning radical radiotherapy in patients with non-small-cell lung cancer. *Australas Radiol* 2007;**51**(August (4)):386–93.
40. Ceresoli GL, Cattaneo GM, Castellone P, et al. Role of computed tomography and [18F] fluorodeoxyglucose positron emission tomography image fusion in conformal radiotherapy of non-small cell lung cancer: a comparison with standard techniques with and without elective nodal irradiation. *Tumori* 2007;**93**(January–February (1)):88–96.
41. van Der Wel A, Nijsten S, Hochstenbag M, et al. Increased therapeutic ratio by 18FDG-PET CT planning in patients with clinical CT stage N2-N3M0 non-small-cell lung cancer: a modeling study. *Int J Radiat Oncol Biol Phys* 2005;**61**(March (3)):649–55.