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Accuracy of FDG PET/CT in the evaluation of solitary pulmonary lesions — own experience

Użyteczność metody FDG PET-CT w ocenie pojedynczych zmian ogniskowych w płucach — doświadczenia własne

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Abstract

Introduction: In recent years, positron emission tomography (PET) has been increasingly applied in the diagnosis of neoplastic lung diseases. In contrast to conventional imaging studies, PET-CT enables the visualisation of not only the morphology of the suspicious lesion, but also its metabolism. The aim of the present study was to investigate the role of PET-CT in the initial assessment of patients with indeterminate solitary pulmonary lesions.

Material and methods: The study was conducted on a group of 82 patients with indeterminate lung nodule diagnosed at the National Institute of Tuberculosis and Lung Diseases in the period from January 2008 to May 2011. CT and PET-CT were performed in all of the patients. Histological or cytological examination of the biopsy specimens obtained from bronchoscopy, mediastinoscopy and intraoperatively were the reference tests.

Results: Malignancy was documented in 40 patients (48.8%). Histopathological analysis of all tumours revealed 12 cases of squamous cell carcinoma, 18 cases of adenocarcinoma and 1 case of carcinoid, whereas in 9 patients the diagnosis of "non-small cell cancer not otherwise specified" was made. All lesions except one were of solid character on chest CT. SUV_{max} values exceeding 2.5 were found in 38 cancer patients (true positives, TP). The mean value of SUV_{max} was 9.1 (1–26.8).

Forty-two lesions were documented as benign (51.2%). SUV_{max} values equal to or less than 2.5 were found in 37 patients (true negatives, TN). The mean value of SUV_{max} in this group was 1.9 (0.5–8.6). The diagnostic value of PET-CT SUV_{max} exceeding 2.5 in the prediction of neoplastic origin of solitary pulmonary lesions was: sensitivity — 95% (95% CI 84–99%), specificity — 88% (95% CI 75–95%) and accuracy — 91.5% (95% CI 83–96%). Positive predictive value (PPV) was 88.4% (95% CI 76–95%), and negative predictive value (NPV) was 94.8% (95% CI 83–99%). False negative results concerned two patients, with final diagnosis of carcinoid and adenocarcinoma; false positive results were obtained in 5 patients with various inflammatory lesions.

Conclusions: In the present study, PET-CT appeared to have high sensitivity (95%), but lower specificity (88%) for predicting the malignant character of solitary pulmonary lesions. Overall diagnostic value of PET-CT $SUV_{max} > 2.5$ was high — PPV was 88.4%, NPV was 94.8%.

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In the authors' opinion, the PET-CT value may increase when clinical data as well as other radiological documentation (with retrospective assessment) are taken into consideration.

Key words: solitary pulmonary nodule, lung cancer, PET-CT, fluorodeoxyglucose

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Streszczenie

Wstęp: W ostatnich latach w diagnostyce raka płuca coraz szersze zastosowanie znajduje pozytonowa tomografia emisyjna (PET). W odróżnieniu od klasycznych metod obrazowania PET-CT daje możliwość uwidocznienia nie tylko morfologii, ale także metabolizmu podejrzanego ogniska. Celem pracy była ocena przydatności metody PET-CT w ocenie charakteru zmiany ogniskowej w płucu.

Materiał i metody: Badanie przeprowadzono w grupie 82 pacjentów diagnozowanych w Instytucie Gruźlicy i Chorób Płuc pod kątem oceny charakteru zmiany ogniskowej w płucu w okresie od stycznia 2008 roku do maja 2011 roku. U wszystkich chorych wykonywano badania CT i PET-CT. Testem referencyjnym było badanie histologiczne lub cytologiczne materiału uzyskanego z bronchoskopii, mediastinoskopii oraz śródoperacyjnie.

Wyniki: Obecność raka płuca potwierdzono u 40 pacjentów (48,8%). Wśród zmian złośliwych 12 miało charakter raka płaskonabłonkowego, 18 odpowiadało gruczolakorakowi, jedna zmiana okazała się rakowiakiem, a 9 z nich miało charakter raka niedrobnokomórkowego bez określenia podtypu. Wszystkie guzki, poza jednym miały charakter lity. U 38 chorych w tej grupie wartości SUV_{max} przekraczały 2,5 (wyniki prawdziwie pozytywne). Średnia wartość SUV_{max} wynosiła 9,1 (1–26,8).

Zmiany łagodne potwierdzono u 42 pacjentów (51,2%). U 37 chorych SUV_{max} był niższy lub równy 2,5. Średnia spośród podanych wartości SUV_{max} dla zmian łagodnych wynosiła 1,9 (0,5–8,6).

Wartość diagnostyczna SUV_{max} powyżej 2,5 w PET-CT dla oceny nowotworowego charakteru zmiany ogniskowej w badanej grupie chorych była następująca: czułość testu — 95% (95% CI 84–99%), swoistość — 88%, (95% CI 75–95%), dokładność — 91,5% (95% CI 83–96%). Wartość predykcyjna wyniku dodatniego (PPV) wynosiła 88,4% (95% CI 76–95%), wartość predykcyjna wyniku ujemnego (NPV) — 94,8% (95% CI 83–99%). U dwóch chorych z ostatecznym rozpoznaniem: rakowiaka oraz gruczolakoraka wykazano fałszywie ujemny wynik badania PET-CT ($SUV_{max} < 2,5$). U pięciu chorych z guzkami o etiologii zapalnej stwierdzono fałszywie dodatni wynik PET-CT.

Wnioski: W badanym materiale stwierdzono wysoką czułość (95%) i nieco niższą swoistość (88%) badania PET-CT w prognozowaniu nowotworowego charakteru pojedynczych zmian ogniskowych w płucu. Ogólna wartość diagnostyczna PET-CT w różnicowaniu zmian ogniskowych w płucach była wysoka: wartość predykcyjna wyniku dodatniego (PPV) wynosiła 88,4%, wartość predykcyjna wyniku ujemnego (NPV) — 94,8%. W opinii autorów, szczególnie istotne jest, aby przy analizie badania PET-CT brać pod uwagę w ocenie zmiany również dane kliniczne i wyniki różnych badań obrazowych (wraz z ich oceną retrospektywną).

Słowa kluczowe: pojedynczy guzek płuca, rak płuca, PET-CT, fluorodeoksyglukoza

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Introduction

Positron emission tomography has been used with increasing frequency in the diagnosis of lung cancer during recent years. It plays a crucial role in differentiating between benign and malignant pulmonary lesions. Contrary to classical methods of imaging, a PET-CT scan shows not only the morphology, but also the metabolism of the suspicious lesions. The pattern of accumulation of the marker in neoplastic lesions depends on various factors, such as the number of neoplastic cells, their metabolic activity and the size of the lesion. PET-CT examination enables the localisation of the foci of pathological uptake of 18-fluorodeoxyglucose (FDG) in the metabolic image of an organism (visual qualitative assessment), and the quantitative assessment of glucose uptake measured with SUV (standard uptake value). The value of SUV_{max} gives information about maximum FDG uptake in the tumour area. This parameter is the most frequently used in clinical interpretation. It is commonly assumed that $SUV_{max} > 2.5$ is a positive result that signifies malignancy.

However, many authors recommend, apart from assessment of SUV_{max}, visual assessment of lesions, particularly nodules of small diameter and those with suspected neoplastic aetiology, despite little marker uptake [1].

However, increased 18F-FDG uptake may also concern non-neoplastic inflammatory lesions, which is connected with excessive activity of macrophages and neutrophils in the tissues [2].

The objective of the study was to assess the usefulness of PET-CT in the evaluation of solitary pulmonary lesions.

Material and methods

Among the patients referred for the PET-CT examination from the National Institute of Tuberculosis and Lung Diseases in the period from

January 2008 to May 2011, two groups were distinguished: patients with confirmed lung cancer, examined due to staging procedures; and patients with pulmonary lesions of ambiguous nature. In the present paper, only the patients from the second group were analysed.

The study group included 82 patients: 51 men and 31 women, mean age 63.2 years (42–85 years).

In the case of malignant lesions, histological or cytological examinations of the material obtained from bronchoscopy, mediastinoscopy, transthoracic biopsy and/or intraoperatively were the reference tests.

In the case of benign lesions, negative results of histological and cytological examinations were the reference tests, or when biopsy was not performed, the results of long-term observation showing inflammatory character of lesions (in the case of their complete regression).

PET-CT examinations were performed in two centres: Euromedic in Warsaw (A-aparat GE Discovery STE) and the Department of Nuclear Medicine of the Medical University of Warsaw (B- Siemens Biograph Truepoint64). In all PET-CT examinations, the radiopharmaceutical ^{18}FDG was used, which was administered intravenously. In the 18FDG PET-CT examination, SUV_{max} for tumours was assessed. As a limit value for lesions suspected of neoplastic nature, SUV_{max} higher than 2.5 was assumed.

All patients included in the study underwent single-phase helical computed tomography (CT) after contrast administration. Chest CT was performed at the National Institute of Tuberculosis and Lung Diseases, with the help of a Siemens SOMATOM Sensation 16 CT scanner. The size of the lesions was determined based on CT, relying on a larger measurement.

A diagnostic value of PET-CT $SUV_{max} > 2.5$ in the prognosis of malignant character of solitary pulmonary lesions was assessed. The results were expressed as follows: true positives (TP) — the number of patients with cancer and a positive result of the test, false positives (FP) — the number of patients without cancer and with a positive result of the test, false negatives (FN) — the number of patients with cancer and a negative result of the test, and true negatives (TN) — the number of patients without cancer and a negative result of the test. The test results were divided according to the parameters of a table including 4 fields: TP, TN, FP and FN. Then, in order to assess diagnostic efficacy, the following parameters were calculated: sensitivity (Se), specificity (Sp), accuracy (Acc), positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic odds ratio (DOR), with 95% of confidence intervals. In order to estimate differences in the diagnostic efficacy of the tests, the sign test was applied. To conduct statistical tests, the program Statistica for Windows 6.5 was used.

Results

Malignant lesions

The presence of lung cancer on PET-CT was confirmed in 40 patients (48.8%). The group included 30 men and 10 women; the mean age was 65.9 years (51–85 years). Malignant lesions included: 12 squamous cell carcinomas, 18 adenocarcinomas, 1 carcinoid and 9 non-small cell cancers (without precisely determined histological type).

The mean size of neoplastic lesions on chest CT was 27.9 (11–60 mm). All malignant lesions were of solid nature, apart from one that was not completely solid and turned out to be adenocarcinoma (lepidic type of adenocarcinoma).

In 38 patients from this group, SUV_{max} exceeded 2.5 (TP results). The mean value of SUV_{max} was 9.1 (1–26.8). A neoplastic lesion with high FDG PET-CT uptake is presented in Figure 1.

The mean value of SUV_{max} in patients with adenocarcinoma was 8.8 (2–26.8). The mean value of SUV_{max} in patients with squamous cell carcinoma was 9.3 (2.9–16.3). The difference was not significant.

Based on SUV_{max} lower than 2.5, in 2 patients benign lesions were suspected, despite their neoplastic nature (FN results). Finally, in one of these cases carcinoid was diagnosed, and in the second, adenocarcinoma. In this case, the low value of SUV_{max} could have resulted from the small size of the nodule (11 mm).

Benign lesions

Benign lesions were confirmed in 42 patients (51.2%): 21 men and 21 women. The mean age of patients in this group was 61 years (42-83 years). The size of lesions was determined based on chest CT in 29 patients. The mean size of lesions was 21.7 mm (10-66 mm).

Thirty-seven patients had SUV_{max} lower than or equal to 2.5. The SUV_{max} values were given in 22 reports; in the remaining patients, the lesions did not accumulate the marker. The mean value of SUV_{max} for benign lesions was 1.9 (0.5-8.6). A benign lesion with low FDG PET-CT uptake is presented in Figure 2.

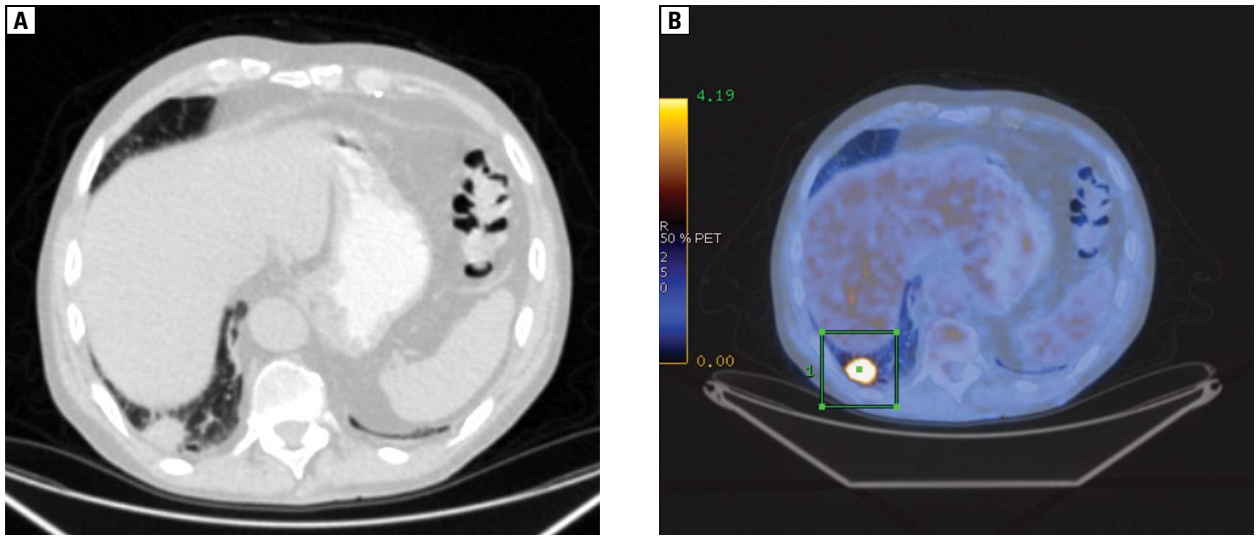

Figure 1. Malignant mass localised in the right lung shows high 18F-FDG uptake on PET-CT image

Rycina 1. Zmiana ogniskowa w płucu prawym o charakterze złośliwym i wysokim gromadzeniu znacznika w PET-CT

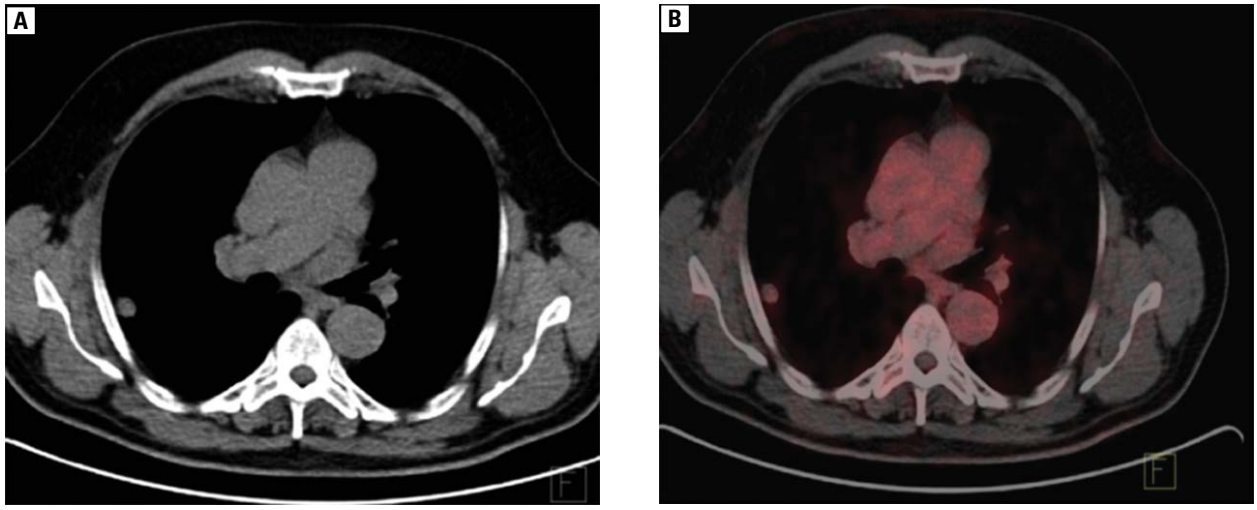

Figure 2. Benign mass localised in the right lung shows little 18F-FDG uptake on PET-CT image

Rycina 2. Zmiana ogniskowa w płucu prawym o charakterze łagodnym i słabym gromadzeniu znacznika w PET-CT

In four patients examined at the centre of the Medical University of Warsaw, SUV_{max} was measured additionally in the delayed phase. In the first phase, the mean value of SUV_{max} was 2.2 (1–5.6). The second phase showed a slight increase in SUV_{max} in two patients, in one patient the value did not change, and in the last one SUV_{max} significantly decreased. In two patients in whom the SUV_{max} values increased in the second phase, inflammatory aetiology of lesions was confirmed.

Five patients with benign lesions had SUV_{max} higher than 2.5 (FP result). In three patients, inflammatory aetiology was confirmed histologically (in two cases intraoperatively). The final diagnosis was: sarcoidosis, granulomatosis with polyangiitis (GPA) and benign inflammatory lesion.

The diagnostic value of SUV_{max} greater than 2.5 on PET-CT was assessed for the evaluation of the nature of the lesion (Figure 3). Test sensitivity was 95% (95% CI 84–99%), specifity — 88% (95% CI 75–95%), accuracy — 91.5% (95% CI 83–96%).

Positive predictive value (PPV) was 88.4%; thus the likelihood that the patient with the focus of increased 18F-FDG uptake had lung cancer was 88.4% (95% CI 76–95%). Negative predictive value (NPV) was 94.8%. Therefore, the likelihood

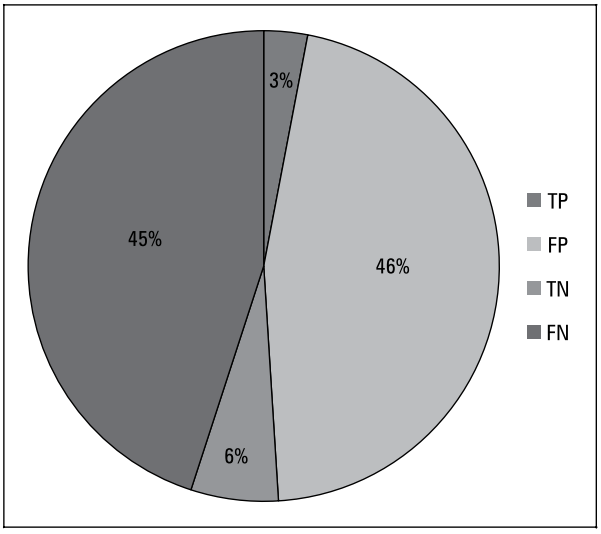

Figure 3. The diagnostic value of PET-CT SUV_{max} > 2.5 in the recognition of malignant lung lesion (true positives — TP, true negatives — TN, false positives — FP, false negatives — FN)

Rycina 3. Wartość diagnostyczna SUV_{max} > 2.5 w badaniu PET-CT w prognozowaniu nowotworowego charakteru zmiany ogniskowej (wyniki prawdziwie dodatnie — TP, prawdziwie ujemne — TN, fałszywie dodatnie — FP, fałszywie ujemne — FN)

that lung cancer did not occur in the patient without excessive 18F-FDG uptake was 94.8% (95% CI 83–99%).

Discussion

In the study group of 82 patients with solitary pulmonary lesions, a high sensitivity of PET-CT for predicting neoplastic character of lesion was found (95%), with a relatively lower specifity (88%). Among the studies that evaluate the value of PET-CT in diagnosis of pulmonary lesions, the most interesting are the meta-analysis by Gould et al. [3] and the study by Imdahl et al. [4]. The authors of the first publication proved that PET-CT has a high sensitivity, with a relatively lower specifity for the evaluation of pulmonary lesions larger than 10 mm; however, its diagnostic value for lesions smaller than 10 mm is limited. Similarly, the authors of the second publication showed a greater role of PET-CT in diagnosis of lesions larger than 10 mm, but also a greater role of PET-CT in the evaluation of neoplastic foci of low grade. In the present study, the diameter of the smallest lesion was 11 mm, and the average diameter of benign and malignant lesions exceeded 20 mm.

The differences in the diagnostic value of PET-CT described in various research projects may depend on the type of benign lesions examined at PET-CT. The lower specificity of PET-CT in the study by Deppen et al. (sensitivity 89%, specificity 40%) was caused by the fact that many examined patients had pulmonary granulomas, which increased the number of false positive results [5]. Nomori et al. showed lower sensitivity of PET-CT (38%) because their study also concerned ground-glass opacity lesions (established on computed tomography), which corresponded to neoplastic foci with little marker uptake [6]. In the study group, only one lesion was not completely solid (it turned out to be a well differentiated adenocarcinoma) and it showed a low (although exceeding the cut off point of 2.5) SUV_{max} value.

Many studies concern the methodology of the evaluation of lesions in PET-CT. Lowe et al. found that SUV values and visual evaluation of the lesion are comparably precise in differentiating between a benign and malignant lesion [7].

However, other researchers showed that having an SUV value of 2.5 assumed as the cut off value gives lower sensitivity than visual evaluation [8].

The SUV values depend on many factors, e.g. body mass (including fat tissue content, which accumulates less marker) [9, 10], blood glucose level (hyperglycaemia may cause increased marker uptake and may lead to unreliable results) [11, 12], the time of the examination in relation to administration of the marker [13, 14] and the size of lesion [15, 16]. Due to the presented limitations, while describing the lesion it is important to take into consideration both visual evaluation and SUV_{max} on PET-CT, and the morphology of the lesion on computed tomography.

In the study group, in 5 cases, high 18F-FDG uptake was found in patients with non-neoplastic lesions in the course of sarcoidosis, GPA and unspecific inflammatory lesions.

Non-neoplastic lesions that show excessive 18F-FDG uptake are lesions with a great amount of macrophages and lymphocytes, such as tuberculosis, other granulomas (sarcoidosis), pneumoconiosis, lung abscess and mycotic infections (with a lack of uptake in their necrotic part). Increased marker uptake may also occur in rare benign lesions, such as calcified haematoma, leiomyoma or inflammatory pseudotumour [2].

Patients with an inflammatory process in the lungs, who are frequently encountered in everyday practice, require special attention. One female patient from the study group had a pulmonary lesion which enlarged in follow-up examination after 6 months. It showed excessive 18F-FDG uptake on PET-CT (SUV_{max} 5.3). During intraoperative examination, an inflammatory nature of the lesion was found (Fig. 4).

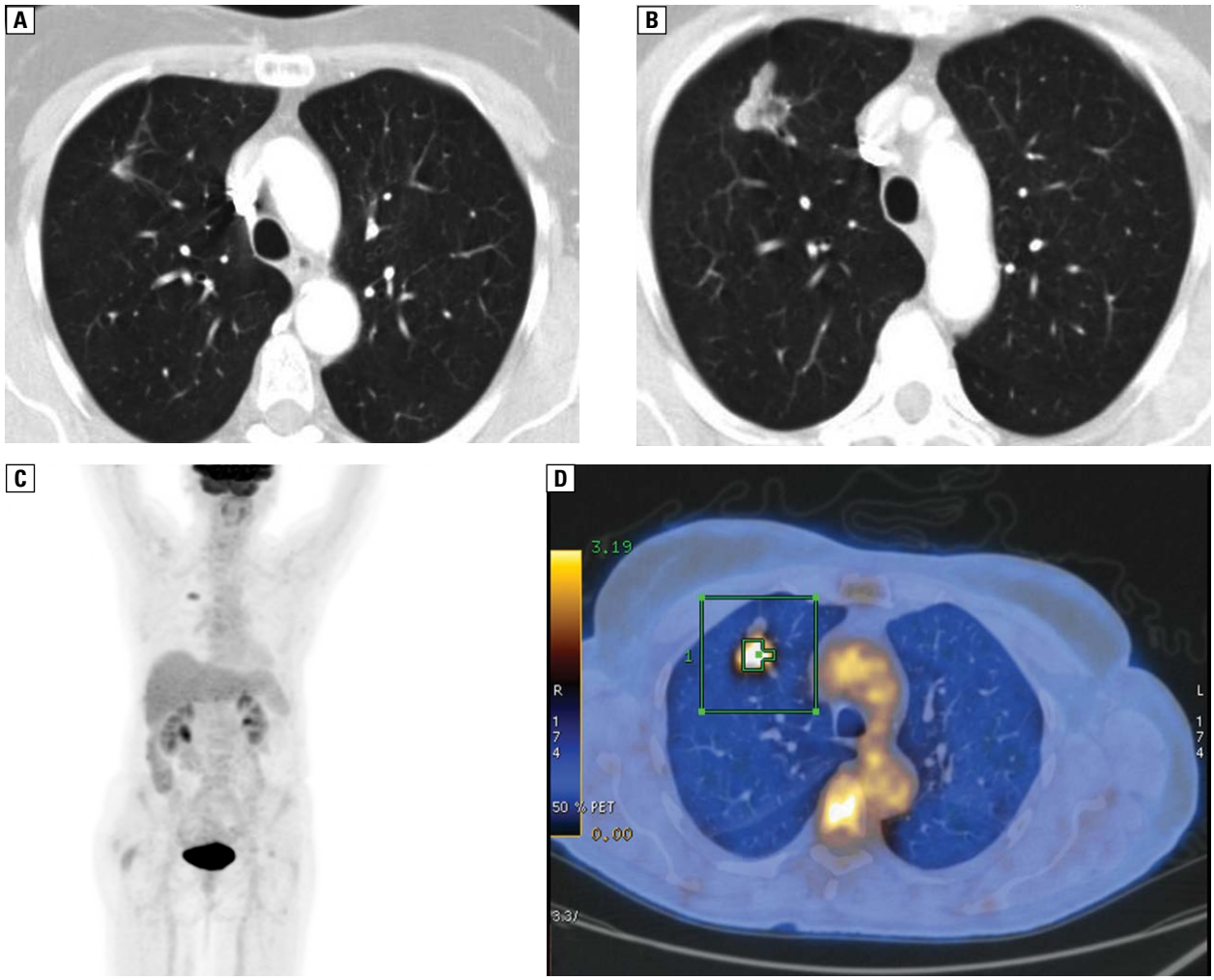

Figure 4. Inflammatory pseudotumour. **A** — pulmonary window, axial image of CT scan shows nodule localised in the right upper lobe; **B** — after 6 months, the nodule in the right upper lobe enlarged; **C**, **D** — increased 18F-FDG uptake is seen on PET-CT, suggesting neoplastic origin. Lesion was resected and pathology revealed an inflammatory pseudotumour

Rycina 4. Pseudoguz zapalny. **A** — okna płucne, przekrój osiowy, tomografia komputerowa uwidaczniają zmianę ogniskową w płacie górnym prawym; **B** — po 6 miesiącach zmiana ogniskowa w płacie górnym prawym powiększyła się; **C**, **D** — wzmożone gromadzenie znacznika w obrębie zmiany ogniskowej w płucu sugeruje jej nowotworowy charakter. Zmiana została usunięta, rozpoznano pseudoguz zapalny

The patients who underwent delayed phase of PET-CT require a separate discussion. In two out of four patients an increase of 18F-FDG uptake was found in the delayed phase. Finally, the lesions were classified as benign. This does not confirm findings from the literature, i.e. that in the delayed phase, in proliferative lesions, increased marker uptake is noted.

In two patients with nodules of neoplastic nature, false negative result of PET-CT (SUV_{max} < 2.5) was revealed. In one case, adenocarcinoma of 11 mm in diameter was finally diagnosed, and in another one — carcinoid.

In the literature there are reports on negative results of PET-CT in the case of lesions located in the lumen of the bronchus, or ground-glass opacities or not completely solid lesions. PET-CT may be particularly unreliable in the case of well differentiated adenocarcinomas of small size. The lowest 18F-FDG uptake is observed in adenocarcinomas with lepidic growth [17]. It is an invasive lung adenocarcinoma which accounts for 3% of all lung cancers. In the majority of patients, radiological changes are discovered accidentally. On CT scans this type of tumour is often described as a ground-glass opacity or as a disseminated form of lesion [18]. The sensitivity of PET-CT may be slightly higher in nodules with a diameter exceeding 8–9 mm and predominating solid component.

Another lung neoplasm which is difficult to diagnose on PET-CT is carcinoid. Due to high differentiation of cells, a typical carcinoid does not show excessive marker uptake [19]. Carcinoids

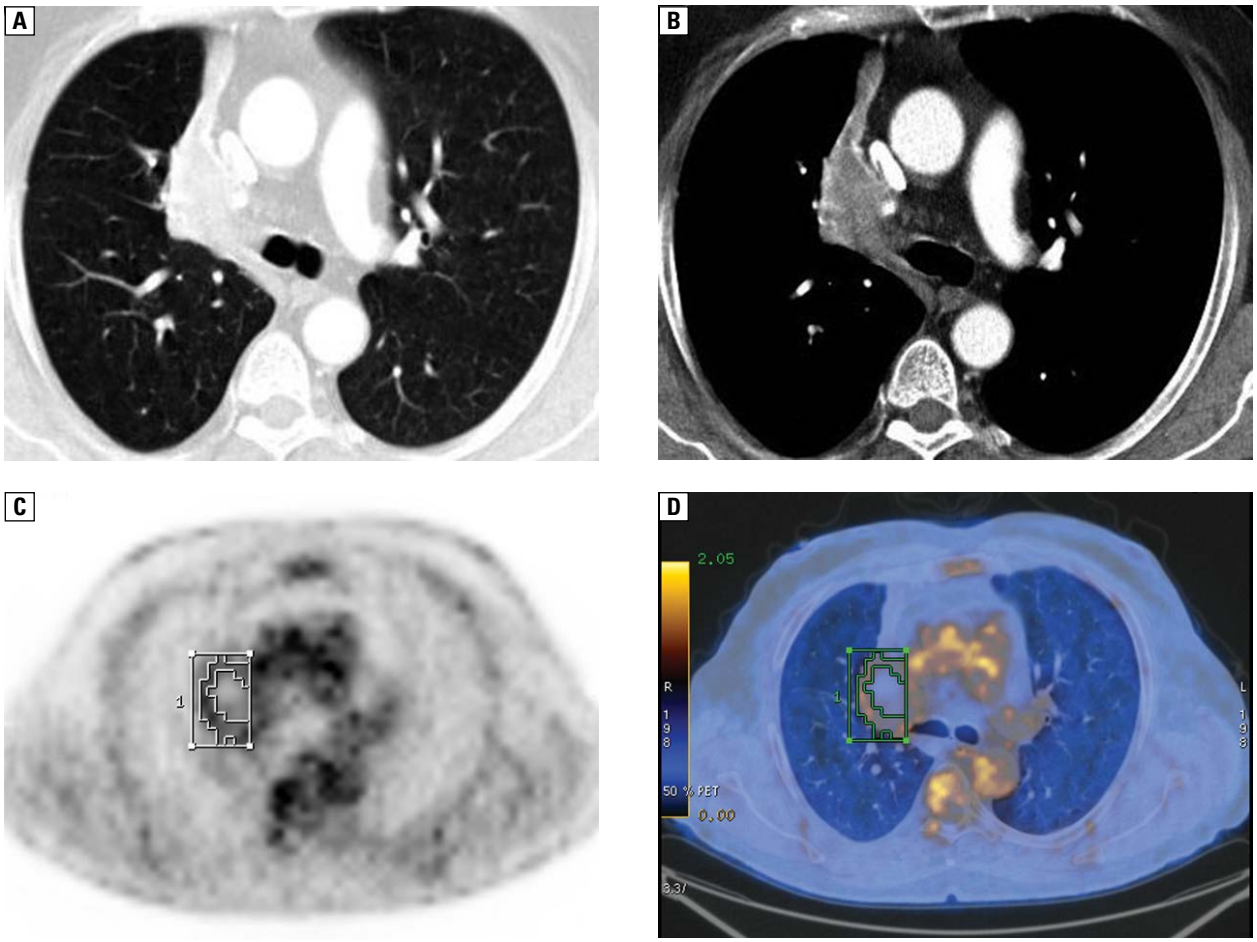

Figure 5. Carcinoid of the right upper bronchus. **A**, **B** — lung and mediastinal window of enhanced CT scan show a mass in the right upper lobe; **C**, **D** — mass shows little 18F-FDG uptake on PET-CT image

Rycina 5. Rakowiak wychodzący z oskrzela górnopłatowego prawego. **A**, **B** — okna płucne i śródpiersiowe uwidaczniają masę w płacie górnym prawym. **C**, **D** — niskie gromadzenie znacznika w masie guza w badaniu PET-CT

are distinguished by increased expression of somatostatin receptors; therefore, PET-CT that uses radiolabelled somatostatin analogues (68Ga-DO-TATOC, 68Ga-DOTATATE) has a significantly higher sensitivity and specificity. Carcinoid was confirmed in one patient from the study group. The lesion was closing the right upper bronchus, but it did not show excessive 18F-FDG uptake on PET-CT (Fig. 5).

Conclusions

In the examined material, high sensitivity (95%) and slightly lower specifity (88%) of PET-CT in diagnosis of the neoplastic nature of solitary pulmonary lesions was found. False negative results (2 cases) concerned patients with adenocarcinoma of small diameter (11 mm) and with carcinoid. False positive results (5 cases) concerned patients with sarcoidosis, granulomatosis with polyangiitis and benign inflammatory lesions. In the authors' opinion, while analysing the PET-CT examination, in the case of solitary lesions, it is vital to take into account numerous additional parameters: clinical data and the results of various imaging tests (with their retrospective evaluation).

Conflict of interest

The authors declare no conflict of interest.

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