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Assessment of recurrence of non-small cell lung cancer after therapy using CT and Integrated PET/CT

Ocena wznowy po leczeniu NDRP przy użyciu TK i PET/CT

The authors declare no financial support.

Abstract

Introduction: Non-small cell lung cancer (NSCLC) has become the leading cause of cancer-related deaths in Poland. Follow-up of patients with NSCLC is aimed at early detection of local recurrence, metastatic process, treatment-related complications or second primary lung cancer. We investigated the diagnostic accuracy of FDG-PET-CT in the detection of recurrence of NSCLC after treatment.
Material and methods: Seventy-two NSCLC patients (19 females, 56 males), stage I to IV, who had undergone surgery and/ /or radiation therapy, occasionally associated with chemotherapy, were retrospectively included in our study.
Chest radiographs and thoracic computed tomography (CT) were performed to localize the abnormality prior to PET-CT. All the patients underwent CT and PET-CT in the period from January 2008 until January 2012. All PET images were interpreted in conjunction with thoracic CT. PET-CT and CT diagnoses were correlated with pathological diagnoses.
Results: Forty-five patients had recurrent tumour. Tumour recurrence was observed more often in men than in women and also in case of neoplastic cell emboli in lymphatic or blood vessels. In three patients second primary lung cancer was diagnosed. False positive diagnosis of relapse based on PET-CT was obtained in 4 patients, mainly due to inflammatory lesions. The accuracy of PET-CT for diagnosis of recurrence was 94.4% (95% CI 91; 100).
Conclusions: FDG PET-CT was the best method to differentiate recurrent bronchogenic carcinoma from inflammatory lesions, especially at post-therapeutic sites. It has been shown that PET-CT is more accurate method than CT in recurrent NSCLC. PET-CT results had a further impact on the clinical management and treatment planning.

Key words: lung cancer, recurrent NSCLC, PET-CT

Pneumonol. Alergol. Pol. 2013; 81: 214–220

Streszczenie

Wstęp: Niedrobnokomórkowy rak płuca (NDRP) jest wiodącą przyczyną zgonów spowodowanych chorobami nowotworowymi w Polsce. Kontrola pacjentów po leczeniu raka płuca ma na celu wczesne wykrycie wznowy miejscowej, rozsiewu procesu nowotworowego, powikłań po leczeniu. Istotne jest też wczesne wykrycie kolejnego nowotworu.

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Praca wpłynęła do Redakcji: 29.05.2012 r.

ISSN 0867–7077

W pracy badano przydatność metody PET-CT w ocenie nawrotu NDRP po leczeniu.
Materiał i metody: Do badania włączono retrospektywnie 72 pacjentów (19 kobiet, 56 mężczyzn) z NDRP w stopniu zaawansowania I–IV poddanych leczeniu operacyjnemu i/lub radioterapii. Niektórzy z nich byli poddani chemioterapii. Radiogram klatki piersiowej i/lub badanie TK lokalizowały zmiany podejrzane o wznowę przed badaniem PET-CT. Wszyscy pacjenci mieli wykonane badanie TK i PET-CT pomiędzy styczniem 2008 roku a styczniem 2012 roku. Badania PET-CT interpretowano w zestawieniu z badaniami TK. Następnie wyniki zestawiono z badaniem histopatologicznym.
Wyniki: Wśród badanych pacjentów u 45 potwierdzono nawrót raka płuca, u 3 obecność drugiego raka płuca. Wznowa występowała częściej u mężczyzn niż u kobiet oraz u chorych, u których stwierdzono zatory z komórek nowotworowych w naczyniach guza. U 4 chorych rozpoznanie wznowy na podstawie PET-CT nie zostało potwierdzone podczas dalszej diagnostyki. Dotyczyło to przede wszystkim chorych, u których ostatecznie rozpoznano zmiany o etiologii zapalnej. Dokładność badania PET-CT u pacjentów badanych pod kątem nawrotu raka płuca wyniosła 94,4% (95% CI 91; 100).
Wnioski: FDG PET-CT pozwoliło u większości pacjentów odróżnić zmiany nowotworowe od zmian zapalnych po przebytym leczeniu. W pracy wykazano, że PET-CT jest bardziej dokładne od metody TK w ocenie nawrotu raka płuca. Badanie PET-CT ma istotne znaczenie w postępowaniu klinicznym i planowaniu leczenia.

Słowa kluczowe: rak płuca, nawrót raka płuca, PET-CT

Pneumonol. Alergol. Pol. 2013; 81: 215–220

Introduction

Non-small cell lung cancer (NSCLC) remains a major oncological challenge in most countries. Surgical treatment is combined with best prognosis and the possibility to cure of the disease; however, the tumour stage at diagnosis precludes resectability in most patients. These patients are submitted to chemotherapy, radiation therapy, or a combination of the two therapeutic modalities. Follow-up after treatment permits early detection of: disease relapse, another primary lung tumour, or treatment-related complications. Early and correct diagnosis of disease recurrence leads to appropriate therapy and gives a chance for longer survival. Detection of local relapse or the presence of single distant metastasis results in implementation of further therapeutic methods such as chemotherapy, radiotherapy, or a repeated surgical procedure.

We investigated the diagnostic accuracy of FDG-PET-CT in the detection of recurrence of NSCLC after treatment.

Material and methods

The study population included 72 patients with previously treated NSCLC, who were admitted to the National Tuberculosis and Lung Diseases Research Institute between January 2008 and January 2012 due to suspected disease recurrence (possibility of local recurrence or suspicion of distant metastases). Relapse of NSCLC was suspected based on clinical picture, results of bronchoscopic investigation, chest X-ray, and/ /or computed tomography. In 69 of 72 analysed patients, PET-CT was performed in radiological facilities of the Euromedic Company in Warsaw (centre A), using the GE Discovery STE device. In three patients, PET-CT scanning was performed at the Department of Nuclear Medicine of the Medical University of Warsaw, using a Siemens Biograph Truepoint64 device (centre B).

All patients were intravenously administered 18FDG radiopharmaceutical as a part of the PET-CT scanning procedure. The activity of the radiopharmaceutical applied in centre A was 320–400 MBq, and 250-450 MBq in centre B. Radiopharmaceutical was administered 45 minutes before PET-CT scanning in centre A and 60 minutes before PET-CT procedure in centre B.

Marker uptake was measured semiquantitatively and expressed as standardised uptake values (SUV), which represent corrected activity of the radio marker (mCi) per millilitre of tissue confined to the area of interest [mCi/ml] and/or expressed as the given activity of the radio marker (mCi) per lean body mass (g) in centre A or per total body mass (g) in centre B [mCi/g].

The adopted threshold SUV value for benign lesions was equal to or less than 2.5, as described in literature.

Chest CT scans were taken at the National Tuberculosis and Lung Diseases Research Institute using a Siemens 16-detector-row Somatom Sensation device. Spiral CT scanning was performed in all patients included in the study. Dimensions of recurring lung tumours were measured on CT scans along the longer axis of the lesion. Nodal recurrences were also evaluated on CT scans, using the dimension along the shorter axis, if two dimensions could be measured.

Average time interval between CT and PET-CT scanning was four weeks.

Histopathological diagnosis was made in majority of patients based on evaluation of surgical specimens and/or samples obtained through

transthoracic biopsy. In 5 patients the diagnosis was obtained from bronchial biopsy specimens, in two — from bronchoalveolar lavage cytology.

For tumour description and classification, 2004 WHO criteria were applied. Histological type, grading (degree of tumour differentiation, G feature), and completeness of resection (R feature) were assessed, alongside with investigation of the presence of tumour cell embolisation of lymphatic (L feature) or blood vessels (V feature) in selected cases.

Table 1. Clinical characteristics of 45 patients with recurrent NSCLC

Sex	Women	14
	Men	31
Age	Mean	66,5
	Range	48–86
Histological type	Adenocarcinoma	18
	Squamus	25
	Carcinoma pleomorphicum	1
	Carcinoma adenosquamosum	1
Extension of disease — 29 patients	I	2
	II	9
	III	15
	IV	3
G status — 42 patients	1	1
	2	30
	3	11
R status — 29 patients	R0	28
	R1	1
	R2	0
L status — 29 patients	L0	3
	L1	26
	L2	0
V status — 29 patients	V0	3
	V1	26
	V2	0
Therapy	Surgery	33
	Surgery and radiochemotherapy	10
	Radiation therapy and/or chemotherapy	2

Results

Patients with disease recurrence

PET-CT revealed disease recurrence in 49/72 patients, of which in 45/72 true lung cancer relapse was diagnosed (Tab. 1). Cancer recurrences were confirmed by histopathology and/or by clinical observation. The mean age of the patients who relapsed was 66.5 years (range 48–86 years), men constituted 70.5% of the subjects with disease recurrence (31/45).

Before onset of therapy, clinical staging (cTNM classification) was performed in 64.4% of the patients (29/45), revealing stage I disease in 2/45 patients, stage II — in 9/45, stage III — in 15/45, and stage IV in 3/45 patients.

Adenocarcinoma was identified in 40% of patients (18/45), squamous cell carcinoma in 56% (25/45), pleomorphic carcinoma in 2% (1/45), and adenosquamous carcinoma in 2% (1/45). Completeness of resection and angioinvasion criteria (RLV features) were evaluated in 64.4% of patients (29/45). Complete resection was confirmed in 28/29 patients. Signs of invasion of lymphatic vessels were found in 26/29. Invasion of blood vessels was observed in 26/29 patients. Degree of tumour differentiation was assessed in 42/45 patients, including 1/42 case of well-differentiated carcinoma (G1), 30/42 cases of moderately differentiated carcinoma (G2), and 11/42 cases of poorly differentiated tumour (G3).

The average dimension of a recurrent lung tumour was 31 mm. Pulmonary recurrences were identified in 35 patients, of which one case turned out to be a false positive finding. In 10 patients, recurrences were found among post-radiation lesions; differential diagnostics in these cases concerned treatment-related changes and focal disease relapse. Post-radiation lesion was described as tumour relapse in one patient (false positive result). Mean SUV for pulmonary recurrence was 6.9 (1.9–28.5).

Disease relapse in lymph nodes was found in 19 patients, of which three cases turned out to be false positive findings. Recurrent tumour foci were found in normally sized lymph nodes in two patients. Mean SUV for nodal recurrence was 6.0 (2.0–22.3).

Extrathoracic metastases were found in six patients. These included metastases to the skeletal system, adrenal glands, liver, and spleen.

In four of the analysed patients, PET-CT examination permitted precise delineation of tumour recurrence among the surrounding structures.

In some patients surgical resection of recurrent tumours could be performed, whereas others were irradiated or received chemotherapy.

Patients with identified second primary tumour

Histopathological examination confirmed the presence of another primary lung cancer in three of the 72 analysed patients. Two of them were diagnosed with squamous cell carcinoma, and the second primary tumour was of adenocarcinoma type. In another patient, the first diagnosed tumour showed signs of glandular differentiation (adenocarcinoma), whereas the second one turned out to be squamous cell carcinoma.

Patients with no signs of cancer recurrence

No signs of recurrence were found in 33.3% of patients (24/72) in the studied population (Tab. 2). The mean age in this group was 64.7 years (37–82 years), and 79.2% of them were women (19/24). In 66.6% of these subjects (16/24) cTNM was assessed before therapy onset. There were no cases of stage I or stage IV disease, 10/16 patients were diagnosed stage II, and 6/16 patients — stage III.

Histopathological assessment of tumours revealed 25% of cases of adenocarcinoma (6/24), 41.6% of cases of squamous cell carcinoma (10/24), 4% of large cell carcinoma (1/24), and 12.5 % of cases of neuroendocrine tumours (3/24); the latter group included large cell neuroendocrine carcinoma in two patients, and multiple foci of typical and atypical carcinoid as well as the so-called tumorlets. In 12.5% of cases (3/24) the tumour was described as non-small cell cancer, not otherwise specified (NSCLC, NOS), and in 4% of cases (1/24) the diagnosis of pleomorphic carcinoma with no further specification was made. The RLV features were assessed in 62.5% of cases (15/24). Complete resection was confirmed in 14/15 patients. Invasion of lymphatic vessels was found in 7/15 cases. Involvement of blood vessels was identified in 9/15 patients. Assessment of tumour differentiation grade was performed in 21/24 patients, revealing moderately differentiated tumours (G2) in 10/21 subjects, and poorly differentiated cancer (G3) in 11/21persons. There were no cases of well-differentiated carcinoma (G1).

Standardised uptake values (SUV) were positive (>2.5) in 12.5% of patients (3/24); Mean SUV was 7.9. All of them had false positive results of PET-CT investigation, i.e. disease relapse was finally not confirmed in these subjects. For the remaining patients, the lesions were described as showing no marker uptake.

In one of the patients, the SUV for a relapse -suspected lesion was 15.0, and increased to 17.5 min in the delayed phase investigation. Following PET-CT investigation, cancer recurrence was diagnosed, which, however, was not confirmed in a sample obtained through transthoracic biopsy. Follow-up CT performed three months after PET-CT

Table 2. Clinical characteristics of 24 patients with did not confirm recurrent NSCLC

Sex	Women	19
	Men	5
Age	Mean	64,7
	Range	37–82
Histological type	Adenocarcinoma	6
	Squamus	10
	Large cell carcinoma	1
	Neuroendocrine tumor	3
	Carcinoma pleomorphicum	1
	Non-small carcinoma	3
Extension of disease — 16 patients	I	0
	II	10
	III	6
	IV	0
G status — 24 patients	1	0
	2	10
	3	14
R status — 15 patients	R0	14
	R1	1
	R2	0
L status — 15 patients	L0	8
	L1	7
	L2	0
V status — 15 patients	V0	6
	V1	9
	V2	0

R0 — no residual tumor; R1 — microscopic residual tumor; R2 — macroscopic residual tumor; L0 — no lymphatic vessel invasion; L1 — microscopic lymphatic vessel invasion; L2 — macroscopic lymphatic vessel invasion; V0 — no venous invasion; V1 — microscopic venous invasion; V2 — macroscopic venous invasion

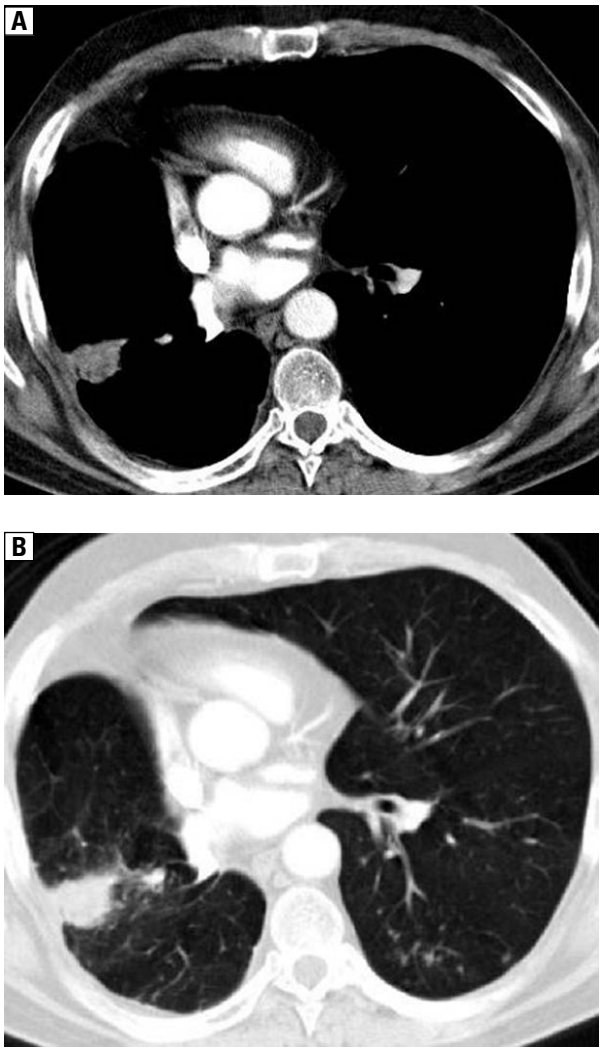

Figure 1. 58-year-old man with advanced carcinoma after radiation therapy. Abnormal area of consolidation. Suspected recurrent tumor. CT obtained 8 months after completion of radiation therapy

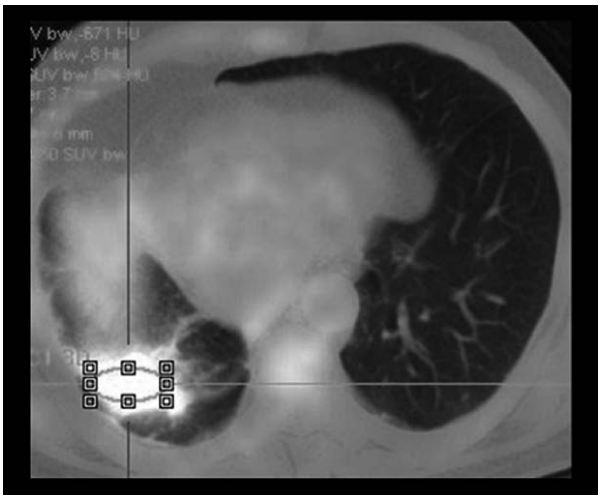

Figure 2. The same patient. PET-CT scan showed increased FDG uptake in the area of fibrosis. Transthoracic biopsy did not confirm reccurence

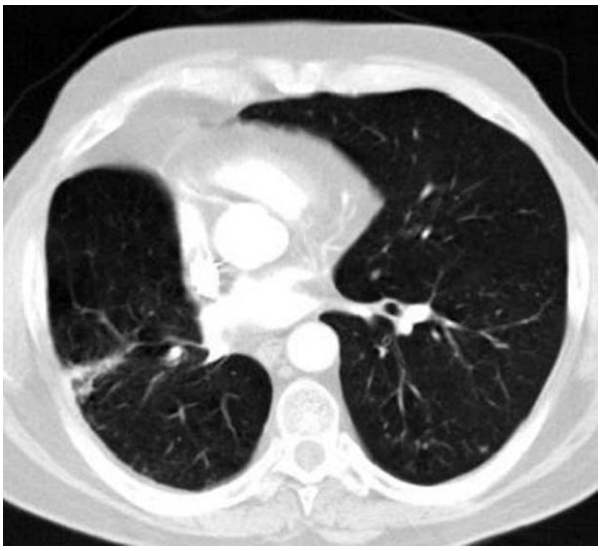

Figure 3. Follow up chest CT taken 3 months later. Abnormal area of consolidation got smaller

showed regression of lung consolidations, which were thus interpreted as inflammatory lesions (Fig. 1–3). In two other patients, disease recurrence was suspected based on positive PET-CT of enlarged lymph nodes, which then decreased in size in follow-up investigations.

Diagnostic accuracy for cancer recurrence detection was 94.4% in the analysed patient population (95% CI: 91–100). Identification of another primary lung cancer in 3/72 patients was also interpreted as a true positive result.

Discussion

Patients treated for NSCLC should be followed-up radiologically in order to detect potential signs of disease progression [1]. In the postoperative period chest X-ray is aimed at assessing pulmonary pathology secondary to operation. The persistence of fluid in the post-operation chamber for over 3–6 months in the patients treated with pneumonectomy suggests the presence of a bronchopleural fistula.

Disease recurrence may be local (i.e. in the area previously operated on), regional (in regional lymph nodes), or distant. Local or regional recurrences occur mainly in the bronchi and lymph nodes ipsilateral to the primary tumour; these sites also include supraclavicular lymph nodes [2]. Tumours remaining within the area of the surgical margins are described as local recurrences, whereas lesions located outside these margins

represent distant metastases. The risk of disease recurrence is multifactorial and remains not completely elucidated [3]. Recognised risk factors for lung cancer relapse include histological tumour type, disease stage at treatment onset, and surgery-related issues, such as completeness of resection, and involvement of lymphatic or blood vessels identified microscopically in surgical specimens. In the examined group of patients lung cancer relapse was observed more often in men than in women and in case of the presence of neoplastic cell emboli in lymphatic or blood vessels.

Planning of radiological follow-up depends on many issues, including tumor histopathology, concomitant diseases, reported symptoms of the disease, and patient's age. If clinical findings suggest the presence of extrathoracic metastases, the patient should be remitted for radiological assessment. An important piece of information, which should be emphasised in the referral formulary for radiological investigation, is whether the clinician requests a routine follow-up computed tomography scanning or if the investigation is carried on due to clinical suspicion of relapse or treatment related complications.

Adenocarcinoma is the type of lung cancer with the greatest tendency for local recurrences or distant metastases [4]. Both squamous cell carcinoma and adenocarcinoma give more often distant metastases than locoregional recurrences [5]. Large cell carcinoma also has a strong tendency to recur, whereas well-differentiated adenocarcinoma with lepidic growth type very rarely recurs locally.

There are certain limitations to the utility of computed tomography in the assessment of cancer recurrence [6]. Nevertheless, many reports in literature suggest that even conventional radiological investigations can disclose the presence of cancer recurrences [7, 8]. The role of computed tomography remains controversial as this modality cannot differentiate between nonspecific lesions secondary to treatment and true cancer relapses [9]. Combined PET-CT is an important tool in the assessment of cancer recurrence [10, 11], due to its high sensitivity. The false positive rate reported by Shon et al. six months after completed oncological treatment, was only 8% [12]. The threshold of lesion size described on CT scans remains controversial since it is known that normally sized lymph nodes may contain cancer metastases, whereas enlarged nodes can be reactively changed [13].

Combined PET-CT analysis is used for precise determination of the area to be irradiated [14] as well as for the assessment of indications for chemotherapy in patients with multiregional disease relapse.

The probability of relapse is related to baseline disease stage, including T and N descriptors. Tumours larger than 5 cm in maximal dimension recur more often than lesions of 3–5 cm. Recurrence within thoracic wall is more often observed after treatment of large tumours. Higher T stage also correlates with more frequent nodal recurrences [4, 5].

Distant metastases are found more often than local recurrences of NSCLC. The coexistence of locoregional and distant recurrences can be identified in approximately 20% of patients [2]. The risk of recurrence depends also on the applied treatment modality. Cancer treated by radiotherapy can recur outside the irradiated area. A surgical approach limited to segmentectomy without lymphadenectomy bears a high risk of disease recurrence [15].

Differential diagnostics of treatment-related lesions (after surgery or radiotherapy) and true tumour recurrent foci are of the utmost importance. Post-radiation necrosis may present radiologically as a cavitated lesion, appearing in any lung area from one to seven years after treatment, and may raise a strong suspicion of metastasis [16]. False positive diagnosis of cancer relapse was diagnosed with PET -CT in one of our patients, who received radiotherapy.

Locoregional or distant recurrences are usually irradiated or treated with chemotherapy, and less often operated on, which depends on lung reserve among others [1]. Moreover, 1–4% of patients can also develop another primary lung cancer [17].

Radiological follow-up after lung cancer treatment is carried out in most cases for five years after therapy completion, as disease recurrence is most often observed during this period. Chest X-ray remains an important investigation; however, many cases of disease relapse occur outside of the thorax [1]. Chest X-ray is the basic follow-up investigation, and CT should be performed in case of chest X-ray pathology or clinical suspicion of relapse [6]. Some authors suggest that CT should be performed once a year, whereas in some centres chest X-ray is performed every four months during the first two years after treatment completion, complemented by CT once a year, in order to detect disease recurrence early [17]. Combined PET-CT permits differentiation between cancer recurrence and lesions secondary to surgery. This diagnostic modality is believed to be more sensitive than computed tomography alone (sensitivity 97–100%,

specificity 62–100%). False positive results of PET-CT investigation are related to the presence of inflammatory lesions, particularly in the irradiated area. Therefore, PET-CT scanning is recommended not earlier than 4–5 months after completion of radiotherapy.

Conclusions

1. In the presented study combined PET-CT was a diagnostic modality of high accuracy in recognizing NSCLC relapse. The correct diagnosis of relapse or second primary tumor was made in 45/49 patients. Increased radio-marker uptake in non-neoplastic tissue was observed in 4/49 patients only.
2. Preoperative clinical staging according to TNM revealed a predominance of stage III disease in patients with confirmed tumour recurrence after treatment, whereas stage II was diagnosed in most patients who did not develop recurrences.
3. Tumour recurrence was observed more often in men than in women.
4. Tumour cell emboli in lymphatic or blood vessels were found more often in surgical specimens of tumours that relapsed than in those that didn't.
5. Combined PET-CT scanning permitted precise delineation of tumour recurrence focus in relation to surrounding structures.

Conflict of interest

The authors declare no conflict of interest.

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