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Follow-up with ^{18}FDG-PET–CT after radical radiotherapy with or without chemotherapy allows the detection of potentially curable progressive disease in non-small cell lung cancer patients: A prospective study

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ABSTRACT

Background: Follow-up of patients treated with curative intent for non-small cell lung cancer (NSCLC) with X-ray or CT-scans is of unproven value. Furthermore, most patients with progressive disease present with symptoms outside of follow-up visits. Because the accuracy of ^{18}FDG-PET–CT is superior to CT, we hypothesised that FDG-PET–CT scans 3 months post-treatment could lead to early detection of progressive disease (PD) amenable for radical treatment.

Patients and methods: Hundred patients with NSCLC, treated with curative intent with (chemo) radiation, were prospectively evaluated. All patients underwent a planned FDG-PET–CT scan 3 months after the start of radiotherapy.

Results: Twenty four patients had PD 3 months post-treatment. 16/24 patients were symptomatic. No curative treatment could be offered to any of these patients. In 3/8 asymptomatic patients progression, potentially amenable for radical therapy was found, which were all detected with PET, not with CT only.

Conclusions: PET-scanning after curative treatment for NSCLC led to the detection of progression potentially amenable for radical treatment in a small proportion (3%) of patients. Selectively offering a PET–CT scan to the patient group without symptoms could possibly lead to an effective follow-up method.

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1. Introduction

Lung cancer is the leading cause of cancer death, with an estimated 161,000 patients dying of this disease in the United States (US) in 2008.[1] The survival of non-metastatic non-small cell lung cancer (NSCLC) patients remains poor, with 5-year survival rates of about 50% in stages I–II and 20% in stage III disease.[2,3] This poor survival is due to a high amount of both locoregional and distant progressions.[4] Theoretically, early detection of progressive disease (PD) at a time when radical therapy is an option could improve the survival. In NSCLC, however, there are at present no convincing data supporting that early detection of progression improves survival.[5–8] Moreover, most patients who have PD present with symptoms outside of planned follow-up visits.[5,9] A recent study showed no significant improvement of survival with intensive follow-up by repeated CT-imaging compared to less intensive radiologic follow-up.[5] A major restriction of both conventional chest X-ray and CT after curative treatment for NSCLC is the poor discriminating capacity between residual or recurrent tumour and post-treatment changes.[7,10] Therefore, repeated imaging is often needed to confirm PD. This delay could lead to missing the chance for salvage treatment.

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) scanning, which allows imaging of glucose uptake of tissues, has shown to be superior to CT in the evaluation of lung lesions and mediastinal lymph nodes,[11–13] as well as in the detection of distant metastases in the primary staging of NSCLC.[14] Furthermore, FDG-uptake of the primary tumour before and during therapy, as well as 3 months after treatment is prognostic for outcome.[15–22] Finally, PET is more accurate than CT in the distinction of tumour from post-radiotherapy (RT) effects.[18,23,24] Based on these data, we hypothesised that the use of PET–CT in the follow-up of patients with NSCLC treated with curative intent would be superior to CT alone. The aim of our study was to evaluate the detection rate of PD amenable for salvage treatment using routine PET–CT in the follow-up of NSCLC patients treated with curative intent with (chemo) radiation. Therefore, we prospectively investigated the impact of follow-up with PET–CT 3 months after therapy on the outcome in 100 consecutive patients with NSCLC, who were treated with curative intent.

2. Materials and methods

2.1. Patient population and study design

Patients with stages I–III NSCLC, who were treated with curative intent with (chemo) radiotherapy at our institute from February 2005 until August 2007, consenting to an additional PET–CT in the follow-up, were prospectively evaluated. Patients with stage IV disease on the basis of a solitary brain metastasis, treated with curative intent, were also included. As part of the primary staging, all patients underwent a FDG-PET–CT and imaging of the brain (either MRI or CT) before the start of treatment. The follow-up consisted of a visit 3 weeks after the end of the treatment for the evaluation of acute side-effects. Thereafter, 3-monthly visits, comprising history taking and physical examination, were performed alternately by the pulmonologist and radiation oncologist for the first 2 years. Thereafter, 6-monthly visits were performed until 5 years post-treatment. A FDG-PET–CT scan was planned irrespective of the presence of symptoms at 3 months after the start of radiotherapy, with a minimum interval of 2 months (60 days) to account for persistent increased FDG-uptake immediately after therapy. Within 1 week following the PET–CT scan, a follow-up visit was planned. Request of other diagnostic imaging procedures was left at the decision of the physician, as indicated by the presence of symptoms.

2.2. Treatment characteristics

Patients were treated with radical radiotherapy (RT), either alone (medically inoperable stages I–II disease) or in combination with concurrent or sequential chemotherapy in stage III disease. For stages I and II NSCLC, radical RT was given in fractions of 1.8 Gy, twice daily, to a mean lung dose (MLD) of 19 Gy (maximum total tumour dose: 79.2 Gy).[25] Patients with stage III disease received induction chemotherapy with one cycle of carboplatin–gemcitabine (carboplatin (total dose: target AUC*(GFR+25) on day 1 – gemcitabine 1250 mg/m^2 on days 1 and 8). This was followed by concurrent chemo-radiotherapy. RT was given to a dose of 45 Gy in twice daily fractions of 1.5 Gy, followed by 2 Gy daily fractions to a MLD of 19 Gy (maximum total tumour dose: 69 Gy), concurrent with cisplatin 50 mg/m^2 and vinorelbine 20 mg/m^2 on days 1 and 8. Patients with stage III disease who were considered unable to undergo concurrent chemo-radiotherapy were treated either with radical RT alone, or with sequential chemo-radiotherapy, consisting of three cycles of induction chemotherapy (carboplatin–gemcitabine) followed by RT as described for stage I/II.

2.3. PET–CT imaging

A combined whole-body PET–CT scan was performed about 3 months (but at least 2 months) after the start of radiotherapy. Patients had to be fasting for at least 6 h before the examination. The injected total activity of FDG was calculated based on the weight of the patient: (weight * 4) + 20 MBq. After a rest period of 60 min (time needed for uptake of FDG), PET and CT images were acquired. A whole-body CT-scan was performed with intravenous contrast. The CT–PET and FDG-PET findings were first interpreted and reported independently by an experienced chest radiologist and nuclear medicine specialist, respectively. Tumour progression was defined according to the EORTC criteria for PET[26] and to the RECIST criteria for CT.[27] Thereafter, both specialists jointly evaluated the combined PET–CT images, from which a distinct report was written.

2.4. Data acquisition

For each patient, the following data were collected: patient demographics; initial tumour characteristics (stage according to the TNM-classification (UICC, 6th edition), location and histology) and treatment characteristics (dose, overall treatment time (OTT) of radiotherapy and treatment modality).

Results of the PET–CT scan were recorded as described in the diagnostic report of the radiologist and nuclear medicine specialist. Progressive disease was defined as locoregional when situated at or around the original tumour site or regional lymph nodes, and further specified as within or outside the RT-field. Progression was defined as distant when situated either in a different lobe as the primary tumour, or outside of the thorax. The site of distant relapse was recorded as well. If both locoregional and distant progression was detected, both were recorded. PD was judged as either diagnosed on basis of CT alone when it was described in the distinct report of the CT (PD according to the RECIST criteria), or diagnosed with PET when it was only described in the distinct report of the PET (PD according to the EORTC criteria) and/or the report of the combined PET–CT, with the report of the CT being either negative or inconclusive.

PD was defined as amenable for salvage treatment when it was either locoregional, or in case of oligometastasis, defined as 1 or 2 metastases, amenable for radical local treatment by either radiotherapy or surgery.[28] The distinction between locoregional progression and post-RT changes was recorded on the basis of the diagnostic report, and was made on a visual interpretation by the nuclear medicine physician. Because these radiation-induced changes can normally be readily distinguished from persistent or recurrent tumour by their FDG-uptake distribution, no quantitative threshold was used.[24,29]

The absence or presence of symptoms at the time of the PET–CT was noted. Furthermore, it was judged whether at least one of the symptoms was corresponding to the site (or one of the sites) of progression found on PET–CT. This was based on the following assumptions: pain was defined as corresponding to the site of progression when it was localised at the dermatome corresponding to the site. Pulmonary symptoms (cough, dyspnoea) were defined as corresponding when progression was either locoregional or metastases in the lung, and symptoms had increased over time after RT. Neurological symptoms were judged corresponding when either brain metastases were diagnosed, or symptoms were consistent with the site of metastasis in the central or peripheral nervous system.

No distinction was made between the detection of a second primary or PD. Because of the short interval between the primary treatment and the PET–CT scan 3 months after therapy, a second tumour in the same lobe was considered as PD, while a second tumour in another lobe was considered a distant relapse rather than a second primary. Survival data were obtained by consultation of the Dutch Communal Data (GBA) register. Follow-up time was defined as the time from the end of radiotherapy until death or the last time of follow-up. At the time of analysis, 51 patients had died. For 3 patients, survival data could not be retrieved.

2.5. Statistical analysis

We estimated that 25% of the patients would have detectable PD at the time of the post-treatment FDG-PET–CT scan,[30,31] with an estimated 25% of them being eligible for salvage treatment. In order to detect this proportion (6%) with a 95% confidence interval (CI) of 1–11%, at least 85 patients evaluable 3 months post-treatment would be needed. To account for possible dropouts, 100 patients were included.

Statistical calculations were performed using SPSS (Version 15.0 for Windows). Results were described as either median or mean ± one standard deviation (SD) when the results were normally distributed. When there was no normal distribution, results were described as either median or mean with the range. For the calculation of 95% confidence intervals (95% CI) for proportions, the Wilson score interval was used.[32] *P*-values were calculated with the Chi-square test for proportions.

2.6. Ethics

The trial was performed according to the required Dutch laws and regulations. All patients gave informed consent for the study, which was part of two study protocols, NCT00573040 and NCT00572325.

3. Results

3.1. Patient and treatment characteristics

From February 2005 until August 2007, 100 NSCLC patients, stages I–III, treated with curative intent, were included. Patient, tumour and treatment characteristics are listed in Table 1. The mean follow-up of all patients was 55.9 ± 29.2 weeks, ranging from 13 to 182 weeks. Seventy males and 30 females were included, with a mean age of 66.0 ± 9.7 years (range: 44–86). The median radiation dose delivered was 63.5 Gy, ranging from 50.4 to 79.2 Gy. Most (86/100) patients had stage III disease at time of presentation. 84% of patients received chemotherapy, either sequential to or concurrent with radiotherapy. One patient had stage IV disease. This patient had a solitary brain metastasis, which was treated with stereotactic radiotherapy before radical treatment of the lung tumour.

3.2. Results of PET–CT scanning 3 months after treatment

The mean time interval from the start of RT until planned surveillance PET–CT scan was 16 ± 3.1 weeks (range: 9–27 weeks). All patients underwent the scan more than 2 months after the start of RT, and 75% underwent the scan within 4 months after start of RT. Twenty four patients had PD, of which 7 had locoregional progression only, 7 distant only and 10 had both locoregional and distant progression. The primary stage and treatment of the patients with progression are described in Table 2. Of the 24 patients with progression, 17 (71%, 95% CI: 51–85%) were detected with CT only, while for 7 patients, the PET-scan was necessary for the detection of the progression, with CT being either negative or inconclusive (Fig. 1). Of the 8 patients, who were symptomatic at the time of progression, PET was required for the detection in 4/8 patients (50%, 95% CI: 22–78%), while for the symptomatic patients, PET was required in 3/16 patients (19%, 95% CI: 6–43%).

In 36 patients (36%, 95% CI: 27–46%), the PET-scan showed findings that were defined in the diagnostic report as post-RT effects. In all patients, these findings could easily be distinguished from PD on the basis of the combined PET–CT images.

Table 1 – Patient, tumour and treatment characteristics.

	N ± SD (%)
Mean age (years)	66.0 ± 9.7
Range	44–86
Gender	
Male	70 (70)
Female	30 (30)
Stage	
IA	4 (4)
IB	6 (6)
IIA	0 (0)
IIB	3 (3)
IIIA	25 (25)
IIIB	61 (61)
IV	1 (1)
Histology	
Adenocarcinoma	15 (15)
Large cell carcinoma	30 (30)
Squamous cell carcinoma	18 (18)
Bronchioloalveolar cell carcinoma	1 (1)
NSCLC, NOS	36 (36)
Treatment	
Radical RT only	16 (16)
Sequential ChemoRT	65 (65)
Concurrent ChemoRT	19 (19)
Median dose (Gy)	63.5
Range	50.4–79.2
Median time interval[a]	16 ± 3.1
Range	9–27
Mean follow-up[b]	55.9 ± 29.2
Range	13–182

N = number of patients; SD = standard deviation; and NOS = not otherwise specified.
a Weeks from the start of radiotherapy to the date of PET–CT.
b Weeks from the end of radiotherapy until the death or lost to follow-up.

3.3. *Sites of progression*

An overview of the sites of progression at the time of the PET–CT scan is shown in Table 2. Seventeen patients had locoregional PD. In 10 patients, the progression was located inside the RT-field, in 6 patients outside the RT-field and in 1 patient both inside and outside the RT-field. Six of 17 patients with distant metastases had metastases at more than one site.

3.4. *Correlation of PET–CT findings with symptoms*

The presence and distribution of symptoms are described in Table 3. Forty five patients (45%, 95% CI: 36–55%) had symptoms at the time of the PET–CT scan. Sixteen of them (36%, 95% CI: 23–50%) had PD on PET–CT. The sensitivity and specificity of symptoms for the presence of progression were 67% (95% CI: 47–82%) and 62% (95% CI: 51–72%), respectively. In 13/16 (81%, 95% CI: 57–93%) patients, the symptoms were in agreement with the site of progression. In the whole group, cough was the most common symptom, followed by pain. In the subgroup of patients with progression, pain was by far the most common symptom.

Table 2 – Characteristics of progressive disease.

	N (%)
Primary stage	
I	2 (8)
II	0 (0)
III	21 (88)
IV	1 (4)
Primary treatment	
Radical RT	2 (8)
Sequential ChemoRT	16 (67)
Concurrent ChemoRT	6 (25)
Site of progression	
Locoregional	17
Inside RT-field	10 (59)
Outside RT-field	6 (35)
Both inside and outside	1 (6)
Distant	17
Bone	9 (38)
Brain	4 (17)
Liver	2 (8)
Muscle	1 (4)
Adrenal gland	4 (17)
Lung	4 (17)
Axilla	1 (4)

N = number of patients.

3.5. *Treatment at the time of progression*

The type of treatment of the patients after detection of PD is described in Fig. 1. Of the 24 patients, 18 (75%, 95 CI: 55–88%) underwent treatment directly after the detection of PD.

PD amenable for salvage treatment was detected in 3/100 (3%, 95% CI: 1–8%) patients (Table 4), of which two eventually received a radical treatment. All 3 were detected by PET, and none of the 3 patients had symptoms at the time of detection of PD. The first patient finally underwent palliative chemotherapy because her lung function did not allow a pneumonectomy. The second patient had regional progression in the left hilus, which was treated with radical RT, and was alive without evidence of disease 1 year after the diagnosis of PD. The third patient was diagnosed with bilateral adrenal metastases (Fig. 2), for which he underwent a bilateral extirpation of the adrenal glands. Pathological examination confirmed the presence of adrenal metastases. He was alive without evidence of disease 1.5 years after diagnosis of the distant metastases.

4. Discussion

At present, no data from randomised trials are available concerning the optimal follow-up in NSCLC, while other available data show inconsistent results.[33] Guidelines from different cancer associations differ widely in their recommendations concerning chest imaging, from either no routine imaging to surveillance chest CT-scanning. No evidence exists that extensive follow-up with surveillance chest CT-imaging is superior to routine follow-up with physical examination and a chest X-ray. A major disadvantage of CT-scanning is the poor sensitivity and specificity for distinguishing post-

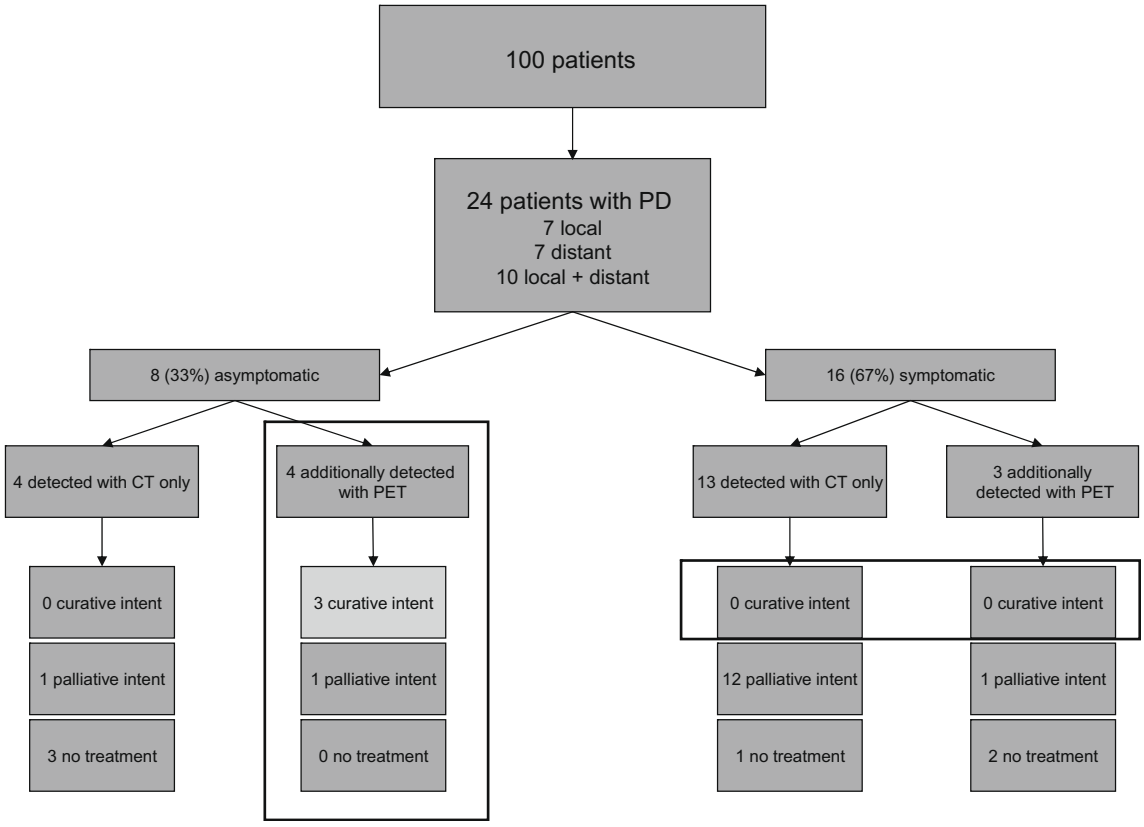

Fig. 1 – Disease progression: detection modality and treatment intent according to the presence of symptoms.

treatment changes from progressive disease, which is reflected in a high negative predictive value (99%) and a low positive predictive value (53%).[7,10] The accuracy of PET after treatment is assumed to be lower than that at initial staging because of inflammatory and perfusion changes due to therapy.[12] Nevertheless, PET has still shown to have a high accuracy in detecting recurrent lung cancer, with a sensitivity up to 98% and a specificity of 62–92%.[9,12,34] In this study, by using combined PET–CT scans, post-RT changes could be distinguished from PD in all patients.

Early detection of isolated locoregional progression or oligometastasis could allow a radical treatment, with long-term survival rates up to 30% and 22%, respectively.[28,35–37] In the present trial, PET–CT scanning 3 months after curative treatment for NSCLC led to the detection of PD potentially amenable for radical treatment in 3/100 (3%, 95% CI: 1–8%) patients. These 3 patients were all asymptomatic, and progression was only detected with PET, not with CT alone.

The most important question is whether an earlier detection of progression results in a longer overall survival. The improved overall survival reported in some retrospective studies could be attributable to lead time bias.[5,8,38] In the present study, we showed that none of the symptomatic patients with PD were amenable for radical treatment. Furthermore, none of the patients in whom progression was detected with CT only were amenable for radical treatment, while 3 of 8 patients with progression (all detected with PET) in asymptomatic patients were potentially amenable for radical treatment. The detection of PD with PET–CT in the 2 patients who finally received a radical treatment, being alive without evidence of disease 52 and 76 weeks after salvage therapy, has almost certainly led to a longer overall survival compared to a policy in which diagnostics were only performed at the time when symptoms developed. Of the 3 patients with PD potentially amenable for radical treatment, two had (either uni- or bilateral) adrenal metastases. Because radical treatment by adre-

Table 3 – Type and frequency of symptoms according to the presence or absence of progression.

Symptoms	All patients (%)	Pts without progression (%)	Pts with progression (%)	*P*-Value
Cough	18.0	19.7	12.5	0.42
Pain	15.0	5.3	45.8	<0.001
Dyspnea	14.0	14.5	12.5	0.81
Neurological	6.0	2.6	16.7	0.01
Dysphagia	3.0	2.6	4.2	0.70
Malaise	2.0	1.3	4.2	0.38
Palpable mass	1.0	0.0	4.2	0.07
Fatigue	1.0	1.3	0.0	0.57

Table 4 – Patients with progressive disease amenable for radical treatment.

Case	Primary stage	Follow-up[a]	Interval[a]	Results PET	Results CT	Therapy	Outome[b]
1	T4N0M0	22	12	Partial remission of primary tumour Hotspot left-adrenal gland	Volume reduction of primary tumour Nodus 1.8 cm left adrenal gland	Proposed for pneumonectomy and resection of adrenal metastasis No candidate for pneumonectomy → second line CTx	10 weeks: alive
2	T1N0M0	70	18	Hotspot left hilar node	Negative	Radical RT	52 weeks: alive; NED
3	T2N3M0	89	13	Pathological uptake in both adrenal glands	Slight increase in volume of both adrenal glands	Bilateral extirpation of adrenal glands	76 weeks: alive; NED

CTx = chemotherapy; RT = Radiotherapy; and NED = no evidence of disease.
a Weeks from start of radiotherapy.
b Weeks from diagnosis of progressive disease.

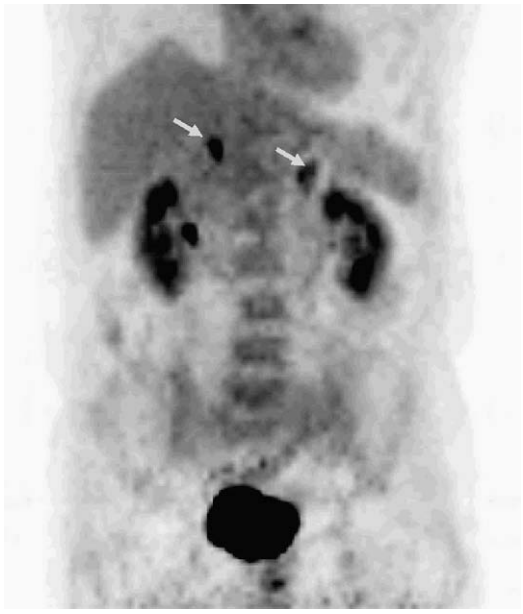

Fig. 2 – Case 3: bilateral adrenal metastases.

nalectomy may result in long-term survival rates of 25%,[39] we believe that there are good arguments to treat this patient group with radical intent.

No pathological confirmation was obtained in the patient with regional progression in the left hilus and in one of the patients with adrenal metastases on PET. As reported earlier, the accuracy of FDG-PET-scanning for the detection of a recurrence is high, with a specificity of 84%.[9] The accuracy of FDG-PET for the diagnosis of adrenal metastasis is reported to be 92–100%.[40–42]

Another important aspect is the timing of the PET–CT. It is recommended to perform a PET–CT scan not earlier than 3–6 months after the treatment to avoid false-positive results due to post-radiotherapy changes.[12,43] Hicks and colleagues found no confounding of the evaluation of tumour response by the presence of post-radiotherapy inflammatory changes in 73 patients, who underwent a PET–CT scan 70 days after radical radiotherapy.[44] Our data support those findings, as post-radiotherapy changes, being present in 36% of patients, did not influence the response evaluation. Furthermore, uptake associated with post-radiotherapy pneumonitis can last for 15 months after the end of radiotherapy.[45] Theoretically, performing a PET–CT scan earlier after therapy could result in the detection of more cases with potentially curable disease.

A potential drawback of PET–CT is that it is rather costly. An important topic for further research is, therefore, whether the effects of PET–CT are worth the extra costs and for which patient groups routine PET–CT imaging would be deemed cost-effective. As PD amenable for salvage treatment was only detected in asymptomatic patients, the added value of routine PET–CT imaging seems to be confined to this group (55% of the patients). In patients with symptoms 3 months after treatment, the type of symptoms could guide the choice for an additional investigation, and routine PET–CT imaging could possibly be reserved for the selection of patients without symptoms. Hereby, a potentially cost-effective follow-up method could be developed. The cost-effectiveness of PET–CT imaging in the follow-up will be examined in a separate study.

5. Conclusion

For all patients, PET–CT scanning after curative treatment for NSCLC led to the detection of progression amenable for salvage treatment in a small proportion, which is of questionable clinical value. The possible advantage seems to be confined to the patient group without symptoms. Selectively offering a PET–CT scan to this patient group could lead to an effective follow-up method. Further research is needed in this field.

Conflicts of interest statement

None declared.

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