ANTICANCER RESEARCH *30*: 1741-1746 (2010)

Usefulness of Combined FDG-PET with CT or Tumour Markers in Lung Cancer Diagnosis

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Abstract. *Background: The synergy between in vitro and in vivo imaging was investigated in this study. Patients and Methods: Comparison of fluorodeoxyglucose positron-emission tomography (FDG-PET) and computerised tomography (CT) included 62 patients (group 1), while that for comparison of FDG-PET and serum tumour markers included 26 patients (group 2). Results: In group1, FDG-PET had positive and negative predictive values of 81% and 80% respectively, compared to 73.7% and 71.4% for CT, respectively. Combined imaging showed 100% sensitivity and 100% specificity. In group 2, FDG-PET and CEA were both positive in 42.9%, and only CEA was falsely negative in all other cases. FDG-PET and TPA were both positive in 47.6%, and in 52.4% only FDG- PET was positive. NSE and SCC had 100% specificity; their sensitivity was 38% and 25%, respectively. Conclusion: FDG-PET diagnosis was improved by CT. Because the serum tumour markers were falsely negative in more than 50% and there were no falsely negative results for FDG-PET, combined imaging may allow reduction of cut-off values for conventional serum tumour markers.*

According to the report of the European Society for Medical Oncology (ESMO) the incidence of lung cancer in Europe is 52 cases in 100,000 diseases per year (1). The mortality rate is approximately 50 per 100,000 diseases per year, of which 80% are non-small cell lung tumours. The remaining cases are mainly small cell cancer and rarely appearing tumour entities such as carcinoids or large cell carcinomas. The mortality rate amounts to 90% for men and to 80% for women, which can be attributed to smoking behaviour in many cases (1).

With respect to the ESMO recommendation, diagnosis is carried out primarily by a pathologist using bioptic tissue from surgical resection during bronchoscopy, direct surgical operation, or by fine-needle biopsy obtained from the primary tumour, lymph node or distant metastases (1, 2).

In cases of small cell lung cancer, a single 2-fold staging has been developed by the Veterans' Administration Lung Cancer Study Group, which is used for limited or extensive disease (1). In such cases, the recommended method of primary diagnosis is X-ray of the thorax, computed tomography (CT) of the thorax and abdomen and in case of neurological symptoms, magnetic resonance imaging (MRI) CT of the brain (1).

In cases of non-small cell lung cancer, staging is made according to the TNM classification, which includes CT of the thorax and upper abdomen, and possibly of the brain in case of neurological deviations (2). In addition, EMSO already recommends the indication of a positron-emission tomography (PET)-CT scan, allowing a better M and N staging compared to the CT scans (2). Bone scintigraphy is recommended if FDG-PET is not available for clinical stage III patients planned for definitive local treatment (2).

However, bone scintigraphy does not differentiate between metastatic and benign processes in the bones. Recent investigations give evidence that PET-CT scanning seems to be superior to bone scintigraphy for detection of bone metastases (3, 4).

FDG-PET is based on increased glucose uptake and metabolism in lung cancer cells compared to the surrounding cancer-free tissue. Meta-analyses for single nodules report a sensitivity and specificity of 96% and 78%, respectively. The sensitivity and specificity in the mediastinal area is 83% and 92%, respectively (5). The main limitations of a PET investigation, however, are for small lung nodules below 1 cm, because breathing artifacts may confound the diagnostic reliability and there may also be partial volume effects. Nevertheless, some reports state that a diagnosis is possible, even under these circumstances (5-7). A pitfall in FDG-PET investigations is physiological trapping in the gastrointestinal tract, in brown fatty tissue and in arteriosclerotic plaques, which may lead to incorrectly tumour staging and to a false patient management. This is why expert anamnestic interview is mandatory, especially with respect to pulmonary

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Key Words: Serum tumour markers, FDG uptake, PET, CT, diagnosis, lung cancer.

Table I. *Diagnostic values of combined FDG-PET and CT results in patients with pulmonary nodules of primary lung cancer (non-small cell).*

PET	CT			
	TP	TN	FP	FN
TP	64.7%	0	0	11.8%
TN	0	17.6%	0	0
FP	0	0	0	0
FN	5.9%	0	0	0

TP, True-positive; TN, true-negative; FP, false-positive; FN, false-negative.

Table II. *Diagnostic values of combined FDG-PET and CT results in patients with pulmonary nodules from metastases of extrathoracic primary non-lung cancer.*

PET	CT			
	TP	TN	FP	FN
TP	42.4%	0	0	3.4%
TN	0	27.1%	3.4%	0
FP	0	10.2%	0	0
FN	13.5%	0	0	0

TP, True-positive; TN, true-negative; FP, false-positive; FN, false-negative.

disease and inflammation, before the patient is assigned to an FDG-PET investigation. Further artifacts may occur due to inflammatory changes (*e.g.* during the course of tuberculosis, sarcoidosis, or granuloma) or well-differentiated lung tumours, (*e.g.* bronchoalveolar carcinoma, carcinoids or giant clear cell carcinoma) (8, 9). Various groups have attempted to improve PET results by employing other tracers such as fluoro- or carbonate-labelled thymidine, methionine or choline (10-12). Recently, gallium 68 DOTATOC was investigated as an analogue of somatostatin receptor scintigraphy. However, no significant improvements were obtained compared to FDG-PET (13). The aim of this investigation was to explore whether there is synergy between FDG-PET, CT and serum tumour markers in lung cancer patients. To the best of the Authors' knowledge, there has been no equivalent report in the current literature.

Patients and Methods

A retrospective evaluation was made of data of patients of the PET center in the Department of Nuclear Medicine at the University of Bonn, Germany. Two independent studies were performed.

In the first study, in order to compare FDG-PET and CT, patients with pulmonary nodules were investigated. Diagnostics included 90 FDG-PET scans (37 males, 53 females), with 82 corresponding CT scans and 63 X-ray scans of the thorax . Conventional diagnosis was based on histological procedures, bronchoscopy or results from follow-up in an interval of at least one year.

Table III. *Evaluation of sensitivity, PPV and NPV for NSE, SCC, CEA, and TPA serum determinations and FDG-PET imaging in patients with pulmonary nodules of primary lung cancer (NSCLC) on the basis of specificity derived from lung cancer patients with full remission.*

NSCLC n=31	NSE	SCC	CEA	TPA*	FDG-PET
Cut-off value	12 μg/ml	2 ng/ml	4 ng/ml	95 U/ml	Visual detection
Sensitivity (%)	38	25	48	48	100
Specificity (%)	100	100	88	88	88
PPV (%)	100	100	92	91	96
NPV (%)	38	33	37	39	100

*The TPA cut-off value was set to a higher unit/ml from 72 to 95 in order to decrease its specificity from 95% to 88%. This condition allowed a direct comparison of the arising TPA sensitivity to the already determined sensitivity of FDG-PET at the identical specificity of 88%.

The relationship between FDG-PET and the serum tumour markers CEA, TPA, NSE and SCC was investigated in a collective of 28 patients with lung cancer (26 non-small cell, 2 small cell). Twenty-three patients had proven active lung cancer, 8 were in full remission and were taken as the control group for specificity. *In vitro* tumour marker determinations were always made on the day when the patient underwent imaging by FDG-PET. Test kits for *in vitro* serum tumour marker determination of CEA and SCC were purchased from Abbott Diagnostics, Wiesbaden Delkenheim, Germany, and those for TPA and NSE from AB Sangtec Medical, Bromma, Sweden. Specificity of tumour markers was determined according to the cut-off levels provided by the manufacturers of the tumour marker test kits. In case of TPA, an additional cut-off value was calculated for gaining 88% specificity according to the specificity of FDG-PET (88%), for direct comparison of their sensitivities.

Results

Investigation of nodules in patients with primary lung cancer by either FDG-PET or CT imaging resulted in a positive and a negative predictive value (PPV and NPV, respectively) of 81% and 80%, respectively for FDG-PET, compared to 73.7% and 71.4%, respectively for CT. The corresponding values for patients with lung metastases from extrathoracic primary cancer were 77.4% and 56%, respectively for FDG-PET compared to 96.7% and 76.9%, respectively for CT.

Diagnostic values of sensitivity for single and combined FDG-PET and CT imaging in patients with pulmonary nodules of primary lung cancer (non-small cell) are shown in Table I, and the corresponding results for patients with lung metastases from extrathoracic primary tumours are shown in Table II. For patients with primary lung cancer

Table IV. *Comparison of diagnostic results from FDG-PET imaging and from TPA or CEA serum determinations and evaluation of results from combined FDG-PET imaging and both TPA/CEA serum determinations in patients with known viable lung cancer. Specificity for FDG-PET and CEA was 88%, while for TPA it was 95%.*

Patients with known viable lung cancer n=21		CEA cut-off value 4 ng/ml		TPA cut-off value 72 U/ml	
FDG-PET results	CEA/TPA results	Cases	%	Cases	%
False-negative	False negative	0	0	0	0
False-negative	True positive	0	0	0	0
True-positive	False negative	12	57.1	11	52.4
True-positive	True positive	9	42.9	10	47.6
Total		21	100	21	100

(Table I), there was a 64.7% rate of true positive results from the combined diagnosis using FDG-PET and CT, as well as a low rate for true-negative cases (17.6%). The rate of false-negative cases with CT is twice as high compared to results with FDG-PET (11.8% *vs.* 5.9%, respectively), favouring FDG-PET as a single procedure in this diagnostic approach. For patients with lung metastases originating from primary non-lung tumours (Table II), contrary to the results for primary lung cancer, the false-positive and false-negative cases are the highest in FDG-PET, favouring CT for this diagnostic approach. On the other hand, the combined use of both imaging techniques is superior again and results in the highest rate of true-positive cases (42.4%) and the second highest rate of true-negative cases (27.1%). Neither primary lung tumours nor metastases of extrathoracic tumours were misdiagnosed when both FDG-PET and CT were used as a diagnostic tool (zero rate of false positives and false negatives in Tables I and II), leading to 100% sensitivity and 100% specificity.

Comparisons of the diagnostic value of FDG-PET to that of the single serum tumour markers CEA, TPA, NSE and SCC are presented in Table III. All tumour markers showed lower sensitivity than FDG-PET. NSE and SCC had higher specificity than FDG-PET. The superior sensitivity of FDG-PET is further demonstrated in Table IV. In the case of true positive FDG-PET results, fewer than 50% of the CEA and TPA determinations confirmed the imaging results, while more than 50% were falsely negative. Since there were no false-negative results for FDG-PET, it was not necessary for the serum tumour markers to exclude false-negative FDG-PET results.

Discussion

Single and combined in vivo imaging by FDG-PET and CT. It is already evident from the literature that FDG-PET investigations hold an additional benefit over CT: Using FDG-PET, metastases are more often upstaged – corresponding to an average of 13% M-staging – relative to the diagnostic use of CT alone (14, 15). Combined FDG-PET and CT has been shown to be the best detection method, leading to upgrading especially in stages 1 or 2 in up to 50% of the cases and, consequently, causing changes in patient management and therapy (16). All these results show that a better diagnostic accuracy may be expected if integrated PET/CT scanners are used. Similar results have been reported for non-small cell lung cancer, which were published by Lardinois *et al.* (17). The authors reported a diagnostic accuracy of 81% for FDG- PET/CT for lymph node staging. In contrast, the visual and manual fusion of separately acquired PET and CT imaging data provided a diagnostic accuracy of merely 59%. The data reported from this investigation (Tables I and II) confirm the current findings and give evidence that FDG-PET imaging in lung cancer patients gives important additional diagnostic information. This is improved further when both FDG-PET and CT are used in a combined approach. According to these *in vivo* results for diagnosis of unknown pulmonary nodules, there is evidence that FDG-PET could even be regarded as a first choice compared to CT, because it had higher sensitivity and was able to detect unknown metastases of tumours from both primary and non-primary cancer.

FDG-PET imaging and various serum tumour marker determinations. Serum tumour markers are physiological markers having an advantage over CT, which is a structural marker for the early detection of tumour disease or its relapse, since these physiological markers are sensitive to functional changes appearing mostly in early stages of the disease. F-18 FDG uptake localization by PET scanning for *in vivo* tumour detection also applies a physiological marker (18). The difference between serum tumour markers and FDG-PET can be described as follows: serum tumour markers must be released from the tumour tissue to the circulating blood and this release has to overcome the clearance from the circulating blood in order to gain an elevated level compared to the normal level in blood (19).

This is why tumour marker determination in serum is an indirect and time-consuming method of detection, limited by necrotic events in the tumour tissue, diffusion from the tumour to blood circulation, and clearance from the blood (19, 20).

In contrast, F-18 FDG uptake detection in the tumour tissue provides a direct and not time-limited determination of the actual functional state of the immediate events in the vital tumour tissue itself. As a result, the immediate scanning of tumour function by FDG-PET may give the earliest information about vital tumour activity, leading to highest sensitivity and overall results compared to serum marker determinations (18). This is reflected by the results of this study. For true positive FDG-PET results, only fewer than 50% of the *in vitro* CEA and TPA determinations were able to confirm the detected tumours. FDG-PET imaging had better overall results compared to serum marker determinations. Because serum tumour marker determinations were not able to improve the specificity of FDG-PET (Table IV), it can be proposed that lowering the cut-off level for tumour markers, at a cost to their specificity, could at least help to increase their sensitivity. This would include patient follow-up at an individual patient level below the conventionally recommended cut-off values (which are in most cases established at a level referring to 90% to 95% specificity), in order to decide finally (exclude or include) on a suspected relapse by combined FDG-PET/CT imaging, when there are significantly rising serum marker levels.

Conclusion

All serum tumour markers and FDG-PET can be compared directly by their PPV and NPV. In this study, the PPV did not differ much, and was high in all cases. However, for exclusion of a tumour or for restaging, by the NPV, the difference was obvious and the best result were found by combined scanning using FDG-PET and CT. This, however, does not exclude the serum tumour markers from diagnosis. It has to be taken into account that combined FDG-PET and CT can lead to a high irradiation dose for the individual patient, which could be up to nearly 25 mSv per investigation, and that the cost for imaging is much higher than for the determination of serum tumour markers. Furthermore, a change of strategy using tumour markers can be delineated from the results shown here, leading to the following new approach. Due to the fact that combined FDG-PET and CT result in high sensitivity and specificity as well as high PPV and NPV, the level of tumour marker cut-off could be lowered, especially in clinical follow-up, to improve sensitivity. For *in vitro* serum elevations, the specific diagnosis could be confirmed by combined imaging, and, in case of positive localisation, it could give the earliest possible decisive information for a possible change in patient management. This new approach for combining tumour marker determination and *in vivo* scanning could improve diagnostics in lung cancer patients. However, due to the small number of cases in our investigation, it will be necessary to prove this hypothesis in a prospective study with a large collective of patients.

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Received August 19, 2009
Revised March 18, 2010
Accepted March 19, 2010