Positron emission tomography (PET) in clinical routine

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Background. *Positron emission tomography (PET) is a non-invasive imaging technique that utilizes positron emitting isotopes of biological elements in order to assess metabolism in vivo. The most commonly used tracer is the F-18-labelled glucose analogue called fluorine-18-fluorodeoxyglucose (F-18-FDG). Due to increased restrictions in the national health system and marked expenses for PET studies indications have to be defined thoroughly. Therefore, in the last years several round table expert meetings have been held in order to clearly define the clinical impact of PET in various diseases, e.g. neurological, oncological, and cardiovascular disorders resulting in well-defined indication lists.*

Conclusions. *The indication lists for PET may help both the referring clinician as well as the nuclear medicine physician to optimize cost- effectiveness. Moreover, national health services increasingly utilize these indication lists to decide on reimbursement regarding PET studies in the individual patient.*

Key words: tomography, emission-computed; positron emission tomography, F-18-FDG; utilization, cardiology, neurology, oncology; economics, cost-effectiveness

Introduction

Positron emission tomography is a non-invasive imaging technique that utilizes positron emitting isotopes of biological elements. Thus, PET allows both an assessment and quantification of metabolism *in vivo*. During the last two decades PET has become a part of clinical routine due to both technical advances and an increasing availability of positron emitting isotopes.

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The most commonly used tracer is a F-18-labelled glucose analogue called fluorine-18-fluorodeoxyglucose (F-18-FDG). FDG is taken up by cells and converted to F-18-FDG-6-phosphate in the same manner as conventional glucose. However, in contrast to physiological glucose-6-phosphate, F-18-FDG-6-phosphate can not be utilized and therefore, accumulates within the cell. Thus, distribution of F-18-FDG reflects glucose metabolism *in vivo*. This was first used in the assessment of neurological and cardiovascular disorders. However, since cancer cells have an increased rate of anaerobe glycolysis as compared to non-malignant transformed cells, PET allows a selective visualization of vital tumor tissue. Due to the intracellular accumulation of F-18-

FDG-6-phosphate the contrast between malignant and non-malignant transformed cells is increased, thereby providing the high sensitivity of PET in the detection of vital tumor tissue. Thus, PET plays a more and more important role in diagnosis of oncological disorders.

The high costs for a PET study as well as the growing public focus on health care expenses are the main reasons for the necessity of clearly defined indications for PET imaging. Therefore, in the last years several round table expert meetings have been held [1-4] in order to clearly define the clinical impact of PET in various diseases, e.g. neurological, oncological and cardiovascular disorders resulting in well-defined indication lists. These indication lists may help both the referring clinician as well as the nuclear medicine physician to optimize cost-effectiveness. Moreover, national health services increasingly utilize these indication lists to decide on reimbursement regarding PET studies in the individual patient.

Table 1. Classification of indications for PET studies

Indications PET is...	
Ia	usually appropriate and considered useful
Ib	acceptable but usefulness less well-established
IIa	helpful
IIb	evaluation not possible at that time
III	generally not appropriate

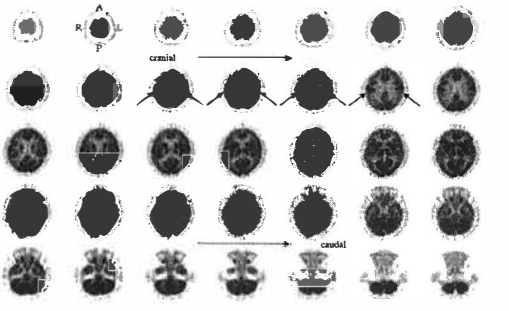

Figure 1. 60-year-old patient with progressive loss of memory and concentration. PET was appropriate (Ia) in order to establish differential diagnosis of dementia. Transversal slices show a global decreased tracer accumulation of the cortex when compared to the basal ganglia. Note, physiological glucose metabolism in area close to the central sulcus as well as in the area of the visual cortex. Typical findings of a progressive Alzheimer's disease.

Evaluation of PET

In several round table meetings[1-4] the value of PET studies has been defined in various diseases, and indications for PET studies were assigned according to three classes as described in detail in Tables 1 and 2 based on the results of clinical research and published studies. If a PET study was shown to be "usually appropriate and considered useful" or "acceptable but usefulness was less well established" PET was assigned to classes Ia and Ib, respectively. If a PET study was shown to be "helpful" or due to lack of experience there is "no evaluation possible at that time" the indications for PET studies were assigned to classes IIa or IIb, respectively. If a PET study is "generally not appropriate" it was assigned to class III. However, one should be aware that a class Ia indication does not imply that a PET study has to be performed necessarily. On the other hand, a class III indication does not automatically exclude a PET study from clinical patient work-up. In general, the indication for a PET study has to be thoroughly checked in the individual patient.

PET in Neurology

For early diagnosis of Huntington's disease, which is based on an atrophia of the caudate and the lentiforme nucleus, PET was classified appropriate (Ia). Moreover, PET was shown to be of high clinical impact in the localization of an epileptic focus. For detection of temporal lobe epilepsy PET was classified appropriate (Ia), whereas for detection of an epileptic focus located extratemporally

Table 2. Summary of indications for PET in clinical routine

Neurology			
Huntington's disease	early diagnosis		Ia
Dementia	early diagnosis		Ia
	differential diagnosis		Ib
Depression	cognitive alteration	differentiation from dementia	Ib
Epilepsy	temporal lobe epilepsy	preoperative localization of focus	Ia
	epilepsy located extratemporally	preoperative localization of focus	Ib
Cardiology			
Diagnosis of viable myocardium			Ia
Oncology			
Glioma	high-grade	diagnosis of relapse	Ia
	known relapse	suspected malignant de-differentiation	Ia
	suspected glioma	localization of biopsy site	Ia
	known glioma	determination of biological aggressiveness	Ib
Head and neck	search for primary tumor	histology positive, conventional imaging negative	Ia
	primary tumor	lymph node staging if primary tumor is resectable	Ib
	local relapse	more than 3 months after therapy	IIa
Differentiated thyroid cancer	I-131-scan negative	relapse of tumor or metastases suspected	Ia
	I-131-scan positive	search for further tumor manifestations if therapeutic regimen will be altered	Ib
Non-small-cell lung cancer	peripheral pulmonary nodule	high-risk patient	Ia
	lymph node staging		Ia
	suspected local relapse		Ia
	therapy monitoring		IIa
Breast cancer	primary tumor suspected		IIa
	local relapse suspected		IIa
	lymph node staging		IIa
	diagnosis of distant metastases	high-risk patient	IIa
	therapy monitoring		IIa
Pancreatic cancer	primary tumor suspected	differential diagnosis tumor tissue versus inflammatory tissue	Ia
	local relapse suspected	therapeutic option is considered	Ib
Colorectal cancer	relapse suspected	elevation of tumor markers and unclear findings of conventional imaging	Ia
	after chemotherapy	therapy monitoring	Ib
Cancer of the bladder	lymph node staging		IIa
Ovarian cancer	relapse		IIa
	re-staging		IIa
Germ cell tumor	non-seminomateous	therapy monitoring (not for differentiated teratoma)	Ib
		lymph node staging	IIa
		re-staging	IIa
Malignant lymphoma	primary staging		Ib
	after therapy	diagnosis of tumor remnants	Ib
	re-staging		IIa
	diagnosis of tumor relapse		IIa
Malignant melanoma	grade II and III	lymph node staging	Ia
		assessment of distant metastases	Ia

PET was defined acceptable (Ib). In case of early diagnosis of dementia PET was determined to be appropriate (Ia). Moreover, in differential diagnosis of dementia PET was classified acceptable (Ib) as shown in Figure 1.

PET in Cardiology

A PET-study has definitely been shown appropriate (Ia) in the diagnosis of myocardial viability (Figure 2). In combination with a

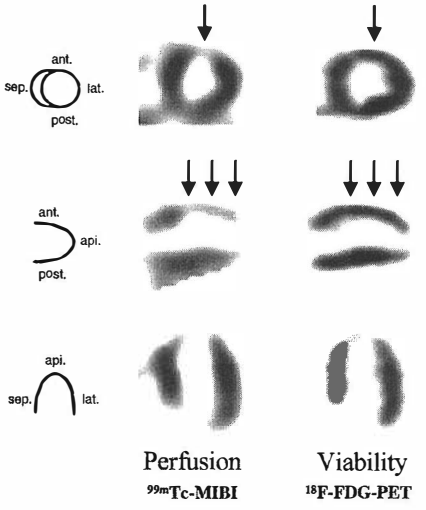

Figure 2. 74-year-old patient with a known stenosis of the left anterior descending artery. PET was appropriate (Ia) in order to establish viability prior to surgical revascularization. Myocardial perfusion scintigraphy (left) exhibited a deficiency of perfusion in the anterior wall and the apex corresponding to rest ischemia. PET study (right) shows a focal lack of glucose uptake in the apex (so called match) indicating scar tissue. In contrast, PET revealed significant FDG-uptake in the anterior wall (so called mis-match) indicating hibernating myocardium. Thus, recanalization probably may improve contractility of the anterior wall in this patient.

rest myocardial perfusion study using Tc-99m-MIBI PET allows a visualization of hibernating myocardium, i.e. myocardium which shows markedly diminished perfusion but is still vital. Thus, in assessing myocardial viability PET helps the clinician to choose the appropriate therapeutic approach in the individual patient.

PET in Oncology

During the last years several studies have been published evaluating the impact of PET in oncological diseases. These studies were focused on following main topics:

1. Differentiation of primary tumor tissue or relapse of tumor versus soft tissue or scar.
2. Lymph node staging and identification of distant metastases.
3. Therapy monitoring.

In diagnosis of *malignant melanoma* (Grade II and III) lymph node staging and detection of distant metastases by PET were shown to be appropriate (Ia).

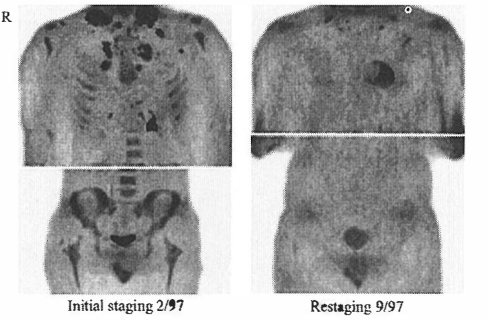

Figure 3. 24-year-old patient with Hodgkin's disease. PET was acceptable (Ib) for primary staging (left) as well as e-s restaging (right). Images are given as maximum intensity projections. Primary staging showed multiple focal accumulations of FDG indicating vital tumor tissue located at both sides of the neck, the mediastinum, the left axillary region, left and right supraclavicular region, behind the sternum, and around the coeliac truncus. Note, bone marrow infiltration as documented by homogenous tracer accumulation of the bone marrow. Initially, according to PET findings Hodgkin's disease was classified as grade IV. Re-staging seven months later showed no evidence of vital tumor tissue documenting complete remission.

In *malignant lymphoma* primary staging (Figure 3, left) and diagnosis of tumor remnants after therapy (Figure 3, right) were assigned as acceptable (Ib). Moreover, PET was classified as "acceptable" (Ib) in re-staging and in detection of relapse of malignant lymphoma.

In *non-seminomateous germ cell tumors* therapy monitoring of non-differentiated teratoma was defined as acceptable (Ib).

Moreover, PET was shown to be helpful (IIa) both in re-staging as well as in lymph node staging of non-seminomateous germ cell tumors.

PET was shown to be helpful (IIa) in several clinical settings in gynecology concerning *ovarian and breast cancer.* In ovarian cancer these included diagnosis of relapse and re-staging. In breast cancer PET was assigned as helpful (IIa) in diagnosis of the primary tumor, exclusion of local relapse, in lymph node staging, in therapy monitoring, and in diagnosis of distant metastases.

In lymph node staging of patients with *cancer of the bladder* a PET study was determined as helpful (IIa). In *pancreatic cancer* functional imaging using PET was assigned as "appropriate" (Ia) in differentiation between tumor tissue and inflammatory tissue. Moreover, PET was defined as acceptable (Ib) for an exclusion of local relapse of pancreatic cancer if these findings provided a therapeutic option.

In *colorectal cancer* PET was defined as appropriate (Ia) for re-staging, i.e. assessment of local relapse, staging of lymph nodes, and detection of distant metastases, in patients who present with unresolved elevated tumor markers or in patients in whom conventional imaging revealed suspicious findings. For therapy monitoring after chemotherapy and after radiotherapy PET was defined acceptable (Ib) and helpful (IIa), respectively.

In *non-small-cell lung cancer* PET was shown appropriate (Ia) in differentiating benign from malignant disease in solitary pulmonary nodules. Moreover, PET was assigned appropriate (Ia) in lymph node staging (Figure 4) as well as in exclusion of a local relapse in these patients. In order to assess treatment response PET was defined as helpful (IIa).

PET was described to be valuable in therapy monitoring of patients with *differentiated thyroid cancer.* In these patients presenting with elevated thyroglobulin levels but negative whole-body I-131 scintigraphy PET was

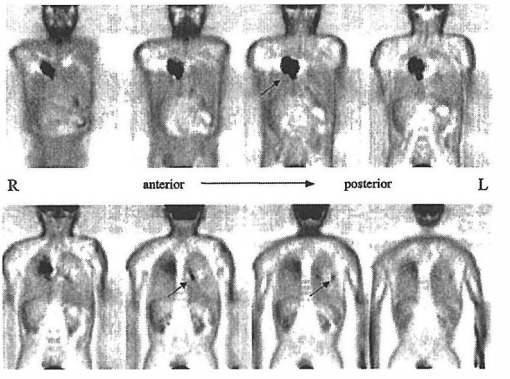

Figure 4. 61-year-old patient with suspected lung cancer of the right superior lobe. PET was appropriate (Ia) in order to determine dignity of the pulmonary mass. Coronal slices show massive tracer accumulation in the right superior lobe indicating vital tumor tissue. In addition, PET showed two pulmonary foci contralaterally (arrows). Thus, curative surgery was abandonned in this patient.

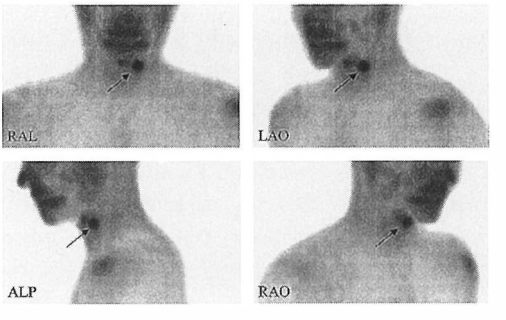

Figure 5. 39-year-old patient with differentiated thyroid cancer after total thyreoidectomy and radioiodine treatment presented with elevated thyroglobulin levels. Since whole-body I-131 scintigraphy was normal PET was appropriate (Ia) in order to detect metastases. Focal FDG uptake in the left paramedian neck corresponding to vital tumor tissue yielded to subsequent surgery.

shown to be appropriate (Ia) for identification of tumor relapse or distant metastases (Figure 5). Moreover, PET was assigned as acceptable (Ib) in patients presenting with positive I-131 whole-body scintigraphy in order to identify additional sites of metastases which may significantly alter treatment regimen.

In patients with *cancer of unknown origin in the head and neck region* PET was defined as appropriate (Ia) if a positive histology of

lymph node metastasis is not accompanied by tumor localization using conventional imaging technique. Moreover, in patients with a potentially resectable primary tumor lymph node staging by PET was assigned as acceptable (Ib).

Potential impact of PET was assigned appropriate (Ia) in patients with *brain tumors* in several clinical settings, i.e. for diagnosis of tumor relapse in patients with high-grade glioma, for the detection of a malignant dedifferentiation, and for localization of the biopsy site in suspected glioma. Furthermore, PET was assigned to be acceptable (Ib) for determination of the biological aggressiveness of a known glioma.

Cost-effectiveness

Most studies dealing with cost-effectiveness of PET studies are based on analysis of the American health system. PET has been shown helpful in cost reduction in certain indications as compared to other diagnostic procedures.[5-21] PET was shown to be both a more sensitive and more cost-effective strategy for differential diagnosis of pulmonary nodules when compared to fine-needle biopsy.[22] Thus, especially in differentiation benign from malignant masses PET helps to avoid more expensive strategies like biopsy or surgery.

Conclusion

PET provides additional information to conventional morphologically orientated imaging in numerous clinical settings. Whereas PET was first used in assessment of neurological and cardiovascular disorders, today, PET plays an increasing role in diagnosis and therapy monitoring in oncology. Due to growing restriction in the reimbursement policy of the national health system clearly defined indication lists have been established in several round table expert meetings. Thus, both performance of PET studies and cost-effectiveness may be improved.

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