Review article

Molecular Imaging in Oncology Using Positron Emission Tomography

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Summary

Background: Anatomical and molecular data can be acquired simultaneously through the use of positron emission tomography (PET) in combination with computed tomography (CT) or magnetic resonance imaging (MRI) as a hybrid technique. A variety of radiopharmaceuticals can be used to characterize various metabolic processes or to visualize the expression of receptors, enzymes, and other molecular target structures.

Methods: This review is based on pertinent publications retrieved by a selective search in PubMed, as well as on guidelines from Germany and abroad and on systematic reviews and meta-analyses.

Results: Established radiopharmaceuticals for PET, such as 2-[1^{8}F]fluoro-2-deoxyglucose ([^{18}F]FDG), enable the visualization of physiological processes on the molecular level and can provide vital information for clinical decision-making. For example, PET can be used to evaluate pulmonary nodules for malignancy with 95% sensitivity and 82% specificity. It can be used both for initial staging and for the guidance of further treatment. Alongside the PET radiopharmaceuticals that have already been well studied and evaluated, newer ones are increasingly becoming available for the noninvasive phenotyping of tumor diseases, e.g., for analyzing the expression of prostate-specific membrane antigen (PSMA), of somatostatin receptors, or of chemokine receptors on tumor cells.

Conclusion: PET is an important component of diagnostic algorithms in oncology. It can help make diagnosis more precise and treatment more individualized. An increasing number of PET radiopharmaceuticals are now expanding the available options for imaging. Many radiopharmaceuticals can be used not only for non-invasive analysis of the expression of therapeutically relevant target structures, but also for the ensuing, target-directed treatment with radionuclides.

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Clinical molecular imaging permits the in vivo characterization of biological processes on a cellular and molecular level (1, 2, e1). To this end, molecular imaging in nuclear medicine uses the highly selective binding or metabolization of radioactively labeled molecules to, e.g., visualize the expression of surface receptors or cell metabolism. As part of this, only trace amounts of the substance are injected, meaning that pharmacological effects are unlikely and physiological metabolic processes are not affected.

Methods

Against the backdrop of the authors‘ many years of scientific and specialist clinical experience, this overview is based on a selective literature search in PubMed. The search terms included: “positron emission tomography + PET,” “radiopharmaceutical,” “radiotracer,” “fluorodeoxyglucose + FDG,” “prostate specific membrane antigen + PSMA,” “somatostatin receptor.” Randomized controlled trials in particular were taken into consideration, and current guidelines were also included.

PET in oncology

Positron emission tomography (PET) offers an imaging technique in nuclear medicine imaging that enables the visualization of (often functional) molecular information (3, e1). Today, PET is almost exclusively performed as a hybrid procedure in the context of multimodal imaging, either in combination with computed tomography (PET/CT) or magnetic resonance imaging (PET/MRI) (4). This procedure has become a central component of the diagnostic algorithms used in oncology *(Table)*.

Producing radiopharmaceuticals for PET is complex, in addition to which central distribution is limited due to the half-life of the respective nuclides. PET radiopharmaceuticals are primarily labeled with the positron emitters fluorine-18 (^{18}F) or gallium-68 (^{68}Ga). The positron is the antiparticle of the electron, from which it differs only in terms of the sign of the electric charge and the magnetic moment. If the positively charged positron and negatively charged electron meet in tissue, annihilation occurs, whereby the two particles are converted into two photons of 511 keV each. The angle between the two emission directions is approximately 180° (5). These two photons are ultimately detected in the ring of PET

TABLE

Selected clinical indications for positron emission tomography (PET) in oncology

Tumor entity	Indication	Radiopharmaceutical	Featured in guidelines	Selected publications
Lung cancer[*1]	Characterization of pulmonary nodules, particularly in patients at high risk for surgery	^{18}F-FDG	S3 guideline on lung cancer (12)	(6[*3], 13–15, e5[*3], e6[*3])
	Staging of primary non-small-cell and small-cell lung cancer			
	Recurrence diagnosis in primary non-small-cell and small-cell lung cancer			
Hodgkin's lymphoma[*1,*2]	Prior to treatment initiation, early treatment response; following treatment completion, recurrence diagnosis	^{18}F-FDG	S3 guideline on Hodgkin's lymphoma (e7)	(7[*3], 16, e8, e9)
Head and neck tumors[*1]	Decision on whether to perform neck dissection	^{18}F-FDG	S3 guideline on oral cancer (e10)	(17[*3], e11–e13)
Laryngeal cancer[*1]	Decision on whether to perform laryngoscopic biopsy in suspected persistent disease or recurrence following completion of treatment with curative intent	^{18}F-FDG	(no German S3 guidelines on laryngeal cancer currently available)	(e14[*3], e11)
Esophageal cancer[*1]	Detection of distant metastases	^{18}F-FDG	S3 guideline on esophageal cancer (e15)	(e16–e18)
Adenocarcinoma of the esophagogastric junction	Advanced staging following conventional staging	^{18}F-FDG	S3 guideline on gastric cancer (e19)	(e20, e21)
Colorectal cancer[*1]	Prior to resection of liver metastases with the aim of avoiding unnecessary laparotomy	^{18}F-FDG	S3 guideline on colorectal cancer (e22)	(e23[*3], e24[*3])
Cervical cancer	Specific investigations in the setting of recurrence, e.g., prior to salvage surgery	^{18}F-FDG	S3 guideline on cervical cancer (e25)	(e26[*3], e27)
Breast cancer	Diagnosis of metastasis in clinical abnormalities/equivocal findings with other imaging techniques	^{18}F-FDG	S3 guideline on breast cancer (e28)	(e29–e31)
Malignant ovarian cancer	Staging and diagnosis of recurrence	^{18}F-FDG	S3 guideline on malignant ovarian cancer (e32)	(e33–e35)
Melanoma	In suspected or proven stage IIC and III locoregional metastasis	^{18}F-FDG	S3 guideline on melanoma (e36)	(e37–e39)
Chronic lymphocytic leukemia	Selection of biopsy area in cases of Richter's transformation	^{18}F-FDG	S3 guideline on chronic lymphocytic leukemia (e40)	(e41, e42)
Prostate cancer	Diagnosis of recurrence following primary treatment	^{68}Ga/^{18}F--PSMA ligands	S3 guideline on prostate cancer (27)	(21, 22, 25, 28)
Gastroenteropancreatic neuroendocrine tumors	Localization, staging, and diagnosis of recurrence	^{68}Ga-DOTA-TATE/-TOC/-NOC	ENETS guidelines (33, e43)	(31, 32)

Possible indications for PET in oncological diseases are shown. Examples of tumor entities have been taken into consideration for which an S3 guideline is available in the oncology guideline program of the German Cancer Society/German Cancer Aid (*Deutsche Krebsgesellschaft/Deutsche Krebshilfe*), as well as laryngeal cancer and neuroendocrine tumors that are not currently accounted for in this program.

[*1] Featured in the guideline on methods of outpatient and inpatient treatment (lung cancer, Hodgkin's lymphoma, laryngeal cancer, head and neck tumors) or in specialized outpatient care (esophageal cancer and colorectal cancer)

[*2] Not all indications

[*3] Randomized controlled clinical trial

detectors in opposite scintillators and form the basis for the localization of the site of decay in the reconstructed PET image.

By imaging the individual molecular phenotype, PET makes it possible to investigate oncologically relevant questions—such as the differentiation between benign and malignant lesions, initial staging, primary tumor detection, early detection of recurrence, as well as treatment response assessment—quantitatively and, in particular, earlier and more precisely compared with other techniques. The technology behind PET makes the method more sensitive in the detection of even small tumors compared with other imaging methods and, since both molecular information and size are taken into account in lesion characterization, it is able to differentiate these more specifically. A number of radiopharmaceuticals are now available to this end. In particular, early stage diagnosis (e.g., lung cancer [6]) and the assessment of tumor response to treatment (e.g., lymphomas [7]) have been enhanced by this form of metabolic imaging.

A number of radiopharmaceuticals can be labeled either with a diagnostic radionuclide such as gallium-68 or, alternatively, with a suitable therapeutic radionuclide such as the β-emitter lutetium-177 (^{177}Lu) (8, 9). This offers the possibility to noninvasively analyze expression of the target molecular structure using PET imaging, followed by targeted radionuclide therapy.

This article provides an overview of diagnostic radiopharmaceuticals frequently used in oncological PET investigations, illustrates examples of guideline-compliant clinical applications, and presents a selection of other radiopharmaceuticals.

Radiopharmaceuticals for PET

Glucose metabolism imaging

As a radiopharmaceutical that can be used universally, the glucose analog 2-^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) is the one most frequently used in clinical routine, since it is metabolized by numerous tumor entities as well as other cell types such as, e.g., macrophages. The hallmark of many malignant tumors is increased aerobic glycolysis, in the course of which glucose is metabolized to form adenosine-5‘ triphosphate (ATP). This characteristic property of tumor cells was first described by Otto Warburg in the 1920s (10). As part of this process, glucose is taken up by the insulin-independent glucose transporters 1 and 3 (GLUT1 and GLUT3), which are overexpressed in many tumor cells (11).

The main indications for ^{18}F-FDG PET in oncology include:

- Management of invasive diagnostic methods in localized cancer
- Differentiation between benign and malignant lesions
- Initial staging of malignant tumors
- Detection of unknown primary tumors
- Detection of recurrence
- Early response assessment and therapy surveillance.

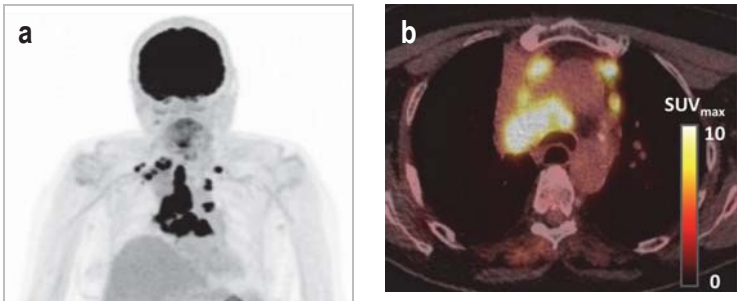

Figure 1: Molecular imaging of tumor metabolism
a) ^{18}F-FDG PET of metastatic lung cancer; physiological, intense visualization of the brain, kidneys, and urinary bladder
b) Fusion PET/CT showing multiple lymph node metastases in a right central primary tumor
CT, computed tomography; ^{18}F-FDG, 2–^{18}F-fluoro-2-deoxyglucose; PET, positron emission tomography

The use of ^{18}F-FDG PET can be illustrated using oncological lung investigations as an example. According to the current S3 guideline, solitary pulmonary nodules measuring >8–10 mm should be investigated using ^{18}F-FDG PET in patients at increased risk for surgery if diagnosis is not possible using invasive diagnostic methods (12). In a meta-analysis, ^{18}F-FDG PET showed a sensitivity of 0.95 and a specificity of 0.82 in the diagnosis of malignant nodules (13). This differentiation between benign and malignant findings makes it possible to avoid further invasive measures and their attendant morbidity and potential mortality. In the case of lung cancer with an indication for curative treatment, ^{18}F-FDG PET should be used for mediastinal and extrathoracic staging, since it currently represents the most sensitive and specific imaging-based staging technique (14). It has high sensitivity in the detection of locoregional and distant metastasis *(Figure 1)*, particularly due to the additional detection of metastases unsuspected in previous staging including contrast-enhanced CT of the chest and upper abdomen (15). The use of ^{18}F-FDG PET in lung cancer significantly reduces the rate of futile thoracotomies (e.g., recurrence, distant metastasis, or death within 12 months of surgery); the use of PET in the Dutch randomized controlled PLUS study made it possible to avoid futile thoracotomy in 20% of patients with non-small cell lung cancer (21% compared with 41% of patients in the group that did not undergo PET; relative risk reduction of 51%, p = 0.003) (6).

As a parameter of vitality, ^{18}F-FDG PET has become firmly established in the staging, treatment response assessment, and therapy surveillance of

Hodgkin's and non-Hodgkin's lymphoma (16). For example, the HD15 study conducted by the German Hodgkin Study Group (GHSG) investigated whether radiotherapy could be restricted to patients with PET-positive residual findings following the completion of chemotherapy. Even without subsequent radiotherapy, patients with PET-negative residual lymphomas had a similar prognosis to patients that achieved complete remission on CT. In that particular study, PET had a negative predictive value (NPV) of 94% and contributed to a de-escalation of chemotherapy (7). ^{18}F-FDG PET is also well-established in the therapy surveillance of solid tumors and, thus, in the individualization of treatment. For example, neck dissection can be dispensed with in patients with locally advanced head and neck tumors in whom a PET yields negative cervical lymph node findings following chemoradiotherapy; this resulted in a 76% reduction in the number of surgical procedures required in the PET surveillance group (54 compared to 221 neck dissections in the group without PET surveillance) (17). The 2-year overall survival rate in the PET surveillance group in the PET-NECK trial was 84.9% compared with 81.5% in the planned neck dissection group (17).

In summary, ^{18}F-FDG represents a radiopharmaceutical that can be used in numerous entities and which, in addition to its use in sensitive initial staging, is increasingly becoming a standard of care in therapy surveillance *(Table)*; as such, PET plays a crucial role in personalized medicine.

Prostate-specific membrane antigen imaging

Prostate-specific membrane antigen (PSMA) is a transmembrane protein expressed, e.g., in benign and malignant prostate tissue. It functions as an enzyme; however, its actual role in the prostate epithelium is not yet fully understood (18). High PSMA expression is associated with an unfavorable tumor phenotype (higher initial T-stage, higher initial prostate-specific antigen [PSA], and higher Gleason score) and a higher rate of biochemical recurrence (19). The introduction of small-molecule inhibitors—based on a robust PSMA-binding glutamate-urea-lysine scaffold—has been rapidly translated into clinical application due to their excellent imaging properties and high sensitivity in the detection of PSMA-expressing metastases, particularly in prostate cancer (20).

Indications for diagnostic investigations using PSMA ligands include, e.g.:

- Diagnosis of biochemical recurrence following primary prostate cancer treatment
- Evaluation of PSMA expression prior to radioligand therapy in advanced castration-resistant metastatic prostate cancer.

A number of ^{68}Ga- or ^{18}F-labeled PSMA ligands are now available for use in clinical routine (21–24). In the case of biochemical recurrence of prostate cancer, PSMA ligand PET/CT yields high detection rates even in very small metastases or low PSA levels. For example, it was still possible to detect metastases in 39%–46% of cases at PSA levels of ≤ 0.2 ng/ml (21, 22). As such, PSMA imaging *(Figure 2)* is more sensitive than are methods such as bone scintigraphy or CT (25, 26). Therefore, according to the current S3 guideline, PET hybrid imaging with radiolabeled PSMA ligands can be performed in a first step in the context of recurrence diagnosis to assess tumor spread, assuming findings give rise to therapeutic consequences (27). However, the significance of detection of early recurrence is controversial, since these are often asymptomatic biochemical recurrences whose treatment can lead to a reduction in patient quality of life. Simultaneous ^{68}Ga-PSMA ligand PET/MRI appears to be superior to multiparametric MRI for the localization of primary tumors (98% sensitivity compared with 66%) (28). ^{68}Ga-PSMA ligand PET shows higher sensitivity and specificity for the detection of lymph node metastases in the primary staging of high-risk cancer compared with other methods, although metastases from PSMA-negative primary tumors and micrometastases may evade detection (25).

A number of PSMA ligands, such as PSMA-617 and PSMA I&T, can also be labeled with β^--emitters, such as ^{177}Lu, which, in early non-randomized observational studies, has opened up the promising option of molecular targeted treatment of advanced castration-resistant metastatic prostate cancer that progresses following guideline-compliant systemic therapy (29). Prior diagnostic PSMA ligand PET is helpful to evaluate suitability for PSMA ligand therapy.

Somatostatin receptor imaging

The majority of neuroendocrine tumors (NET) express somatostatin receptors, which can be investigated using molecular imaging. The importance of radiolabeled somatostatin analogs in the diagnosis of NET is established (30), and a number of different ligands are clinically available for PET, e.g., ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTATOC (e2). The ligands bind with varying affinity to the somatostatin receptor subtype 2, as well as in part to other receptors (e2).

The main indications for somatostatin analog PET in oncology include:

- Initial localization and staging of endocrine tumors
- Detection of unknown primary tumors
- Restaging during treatment
- Evaluation of somatostatin receptor expression prior to peptide receptor radionuclide therapy (PPRT) or somatostatin analog therapy (to estimate probability of response).

A recently published meta-analysis showed a high sensitivity of 90.9% and specificity of 90.6% for ^{68}Ga-DOTATATE PET in the staging of pulmonary and gastrointestinal NET (31). A meta-analysis including 14 studies on 1561 patients showed that, following the use of somatostatin receptor PET,

management changed in 44% of cases due to improved staging (32). Thus, somatostatin receptor PET represents an integral part of NET staging in the guidelines of the European Neuroendocrine Tumor Society (ENETS) and is, e.g., the method of choice for the localization and staging of pancreatic NET (33).

Radiolabed ^{177}Lu-DOTATATE (34) for targeted radionuclide therapy achieved an estimated progression-free survival of 65.2% after 20 months in the NETTER study on advanced gastroenteropancreatic NET compared with 10.8% under high-dose long-acting octreotide therapy in the control group; the objective response rate was also significantly higher under ^{177}Lu-DOTATATE (18% vs. 3%, $p < 0.001$) (8). Furthermore, the risk of death was 60% lower in the ^{177}Lu-DOTATATE group (hazard ratio of death in the ^{177}Lu-DOTATATE group 0.40, $p = 0.004$) (8). A number of other tumors, such as meningiomas, pheochromocytomas, and Merkel cell carcinomas, also express high levels of somatostatin receptors and, as such, are amenable to diagnostic investigation and, in some cases, also treatment.

Other radiopharmaceuticals

The use of radiopharmaceuticals, some of which have only recently become available, offers a multitude of other imaging options, particularly in clinical research. Radiopharmaceuticals for the imaging of amino acid transport and metabolism, such as O-(2-^{18}F-fluoroethyl)-L-tyrosine (^{18}F-FET) or ^{11}C-methionine, are primarily used in the diagnosis of brain tumors. Radiolabeled amino acids are absorbed to only a small extent in normal brain tissue. Therefore, they can be used in the differential diagnosis of gliomas and non-neoplastic lesions, in biopsy planning for the detection of highly malignant areas, in the definition of tumor extent, and in the assessment of treatment response (e.g., recurrence vs. pseudoprogression, pseudoresponse) (35). Expression of the CXC chemokine receptor 4 (CXCR4) can be measured using ^{68}Ga-Pentixafor. CXCR4 is physiologically expressed, e.g., on stem and progenitor cells and plays a major role in mobilization and targeted cell migration. However, CXCR4 is also expressed in many hemato-oncological as well as solid neoplasia and is often associated with a tendency to metastasize and an unfavorable prognosis (36). Following ^{177}Lu labeling, targeted endoradiotherapy of CXCR4-expressing cells can be performed (37).

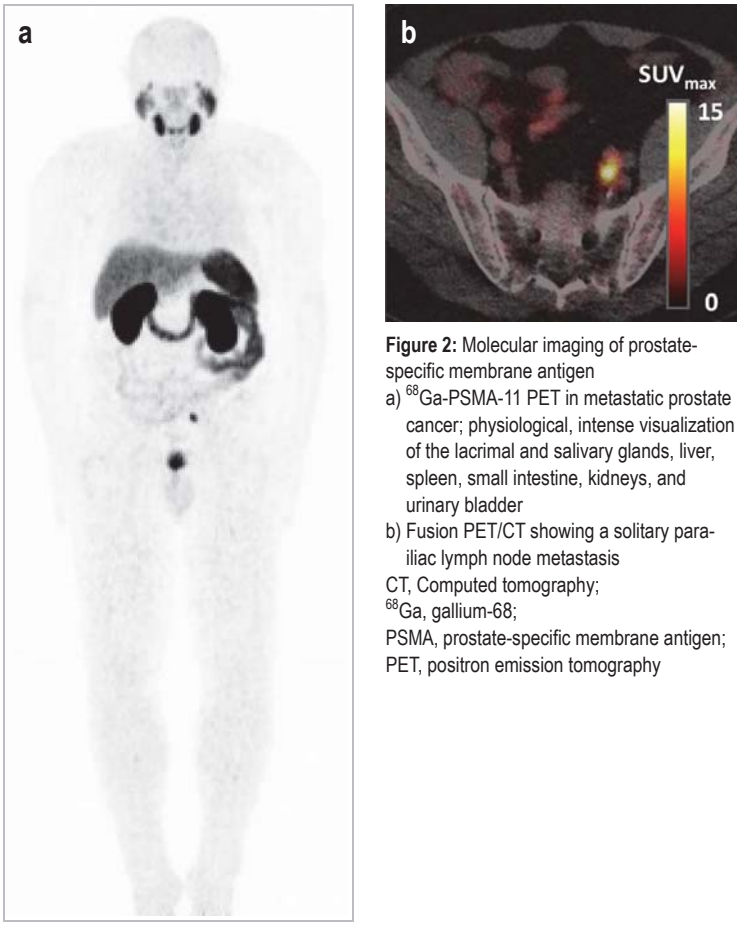

Figure 2: Molecular imaging of prostate-specific membrane antigen
a) ^{68}Ga-PSMA-11 PET in metastatic prostate cancer; physiological, intense visualization of the lacrimal and salivary glands, liver, spleen, small intestine, kidneys, and urinary bladder
b) Fusion PET/CT showing a solitary parailiac lymph node metastasis
CT, Computed tomography; ^{68}Ga, gallium-68; PSMA, prostate-specific membrane antigen; PET, positron emission tomography

Limitations of PET

Due to its use of radioactive tracers, PET is associated with radiation exposure to the patient; this depends on the activity applied—this being approximately 3.8 mSV (200 MBq ^{18}F-FDG) in the case of ^{18}F-FDG (e3), and lower in the case of somatostatin analogs and PSMA ligands (23)—and thus, if anything, in the lower range of radiation exposure of many diagnostic procedures. Added to this is the fact that, when performing PET/CT, CT causes additional radiation exposure, which is subject to significant variation depending on the scanning protocol used. However, oncological PET is a targeted indication and the benefit to the patient outweighs the theoretical risk of radiation exposure in the applications reported here. Since a definitive diagnosis of malignancy is not possible using non-tumor-selective radiopharmaceuticals such as ^{18}F-FDG—despite their higher specificity compared with other imaging methods—bioptic confirmation is sometimes required to establish therapeutic relevance (e.g., solitary distant metastasis in lung cancer). Furthermore, PET is relatively costly compared to other imaging methods. Given the important role assigned to PET in the guidelines, many oncological indications are reimbursable in the US and most European countries. In Germany, reference is still frequently made in many of these indications to the lack of randomized clinical trials with patient-relevant endpoints. However, this useful standard for the assessment and approval of new therapeutic agents cannot be readily extrapolated to the assessment of diagnostic procedures (38, 39). It is often impossible to translate the value of a diagnostic measure into endpoints such as survival time. For example, although the exclusion of a disease can represent a value that is neutral in terms of survival time, it is nevertheless relevant to the patient, particularly if unnecessary surgery can be avoided as a result.

Key messages

- Positron emission tomography (PET) is an important component of diagnostic algorithms in oncology.
- PET improves diagnostic accuracy particularly in localized disease (e.g., in lung cancer).
- PET is able to guide the extent of treatment and helps to individualize therapy.
- Numerous radiopharmaceuticals enable—depending on the radionuclide used—both diagnosis and targeted radionuclide tumor therapy.
- PSMA ligands and radiolabeled somatostatin analogs expand the oncological armamentarium for targeted tumor therapy.

To a certain extent, it is also not (or no longer) possible to randomize diagnostic investigations (e.g., if the procedure already corresponds to the established international standard and/or forms the basis for testing the treatment approach). Were this not the case, linking randomization of the diagnostic procedure with randomization of the subsequent therapeutic options would mean, e.g., also irradiating PET-negative target areas, which is impracticable for ethical reasons. A patient-relevant benefit can also be demonstrated beyond randomized clinical studies, e.g., in comparative accuracy studies or studies simultaneously evaluating a new biomarker and a new therapeutic agent (40, e4).

Conflict of interests

Prof. Dr. Derlin received travel expenses from ROTOP Pharmaka. He received lecture fees from Janssen-Cilag. He received royalties for publications relating to this subject from the publishers Thieme and Springer.

Prof. Westerholds holds shares in Scintomics. The German Research Foundation (*Deutsche Forschungsgemeinschaft*, DFG) provided him with support for studies (third-party funding) relating to this topic.

Prof. Steinbach declares that staff at his institute received study support (third-party funding) from the DFG for the development of PET radiopharmaceuticals.

Prof. Ross received travel expenses and lecture fees from ROTOP Pharmaka.

Prof. Grünwald declares that there are no conflicts of interest.

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Supplementary material
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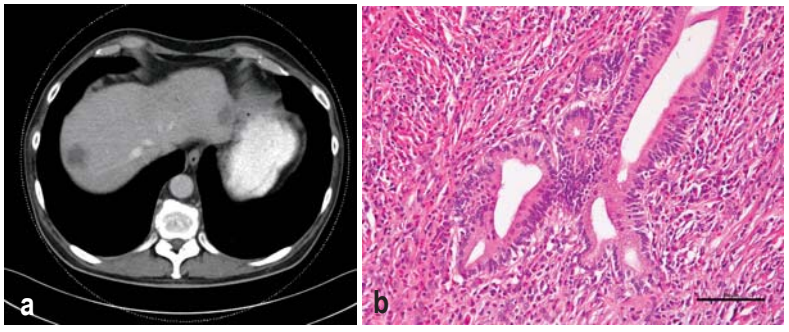
CLINICAL SNAPSHOT

IgG4-Associated Inflammatory Pseudotumor with Bilobar Hepatic Foci



a) Abdominal CT revealing bilobar hypodense hepatic lesions, compatible with lymphoma.
b) H & E stain of the hepatic lesions, showing inflammatory infiltrates and plasma cells.

A previously healthy 58-year-old man had elevated hepatic enzyme concentrations in a routine test; computed tomography revealed multiple, bilobar abnormal foci in the liver, and, after an extensive work-up to rule out other possible causes, he was referred to us with the suspected diagnosis of Hodgkin's lymphoma. A bone marrow biopsy of the iliac crest, however, yielded no evidence of lymphomatous infiltration. The hepatic foci that were thought to be a manifestation of lymphoma *(Figure)* were found, on biopsy and histological examination, to have the typical appearance of IgG4-associated cholangiitis, with up to 200 IgG4-positive plasma cells per high-power field. Serologic testing revealed a markedly elevated IgG4 concentration (2528.5 mg/dL). Short-term high-dose steroid treatment was given, followed by immune suppression with azathioprine. The liver values returned to normal, the serum IgG4 level fell to 678.4 mg/dL, and the hepatic nodules were no longer visible on a follow-up magnetic resonance scan 5 months later. As this case illustrates, IgG4-associated disease can mimic Hodgkin's lymphoma both histologically and in imaging studies.

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