

## INVITED COMMENTARY

## Fluor-18-deoxyglucose positron emission tomography in differentiated thyroid cancer

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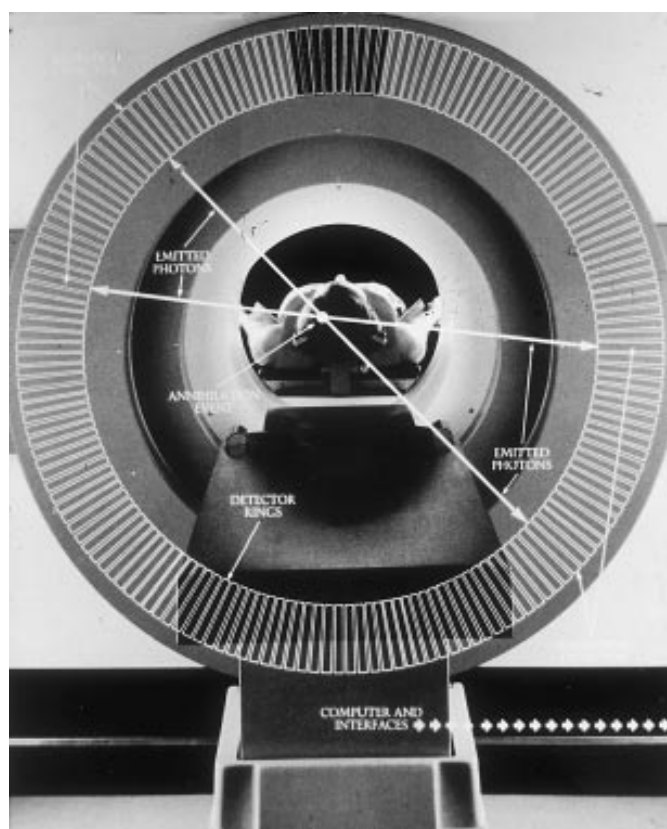
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Owing to the development of high resolution scanners and the new possibility of whole body scanning in recent years positron emission tomography has become more and more important in diagnostic imaging, especially for the diagnosis of malignant tumors and their metastases.

Positron emission tomography (PET) is a special nuclear medical imaging technique, which is **quantitative** (correcting for radiation absorption by transmission measurements), and **tomographic** (imaging primarily a transversal body section as a tomographic field of view,

i.e. a volume in time (4D) for a kinetic analysis or a sequence of fields of view to obtain whole body data sets). The radionuclides used emit a positron which is converted into a pair of photons after a short path of a few millimeters in the tissue ('annihilation event'). The coincidence detection of the two photons, which are travelling on a line in opposite directions permits a sensitive electronic collimation as a first step in the localisation of the site of the radionuclide decay (see Fig. 1).

With positron emitters of biochemically interesting elements such as carbon-11 ( $^{11}\text{C}$ ), oxygen-15 ( $^{15}\text{O}$ ),



**Figure 1** Schematic picture of a PET scanner with multiple single crystals in the ring detector. The coincidence allows only the registration of the photon pair and enables the correct identification of the emitting place. Scattered photons are eliminated. No lead collimation is needed.

nitrogen-13 ( $^{13}\text{N}$ ) and fluor-18 ( $^{18}\text{F}$ ) the radioactive labeling of most organic compounds will become possible. Especially interesting today is fluor-18 deoxyglucose ( $^{18}\text{F}$ FDG) which is used to trace the glucose metabolism of the brain, the myocardium, and malignant tumors.

The elevated glucose metabolism in malignant tumor tissue has been known since the *in vitro* experiments of Warburg (1). Due to the introduction of  $^{18}\text{F}$ FDG and the new PET scanners with a large field-of-view, the *in vivo* visualization of regional glucose metabolism becomes possible. This technique recently proved to be extremely useful for tumor imaging using whole body PET (WB-PET) and  $^{18}\text{F}$ FDG (2, 3). Metabolically very active tissue such as that found in malignant tumors traps  $^{18}\text{F}$ FDG which is taken up by the cells like glucose although it cannot be metabolized as glucose. This technique has a high sensitivity and a spatial resolution of less than 5 mm, but the clinical relevance and indications of this expensive imaging technique are not yet fully established.

So far,  $^{18}\text{F}$ FDG has been the most widely used marker but other markers are presently under investigation ( $^{18}\text{F}$ -thymidine,  $^{11}\text{C}$ - or  $^{18}\text{F}$ -amino acids and others).

At the second Consensus Conference at the University of Ulm held in September 1997 under the chairmanship of Reske (4), the German Society of Nuclear Medicine tried to summarize the present status of the PET-tumor diagnostic experience and elaborated an indication list for these examinations.

Up until now there have only been few  $^{18}\text{F}$ FDG-PET studies on differentiated thyroid carcinomas which describe a large number of cases (5–9). These studies compared  $^{18}\text{F}$ FDG-WB-PET with the conventional radioiodine ( $^{131}\text{I}$ ) and two other compounds, technetium-99m-Sesta-MIBI (isonitril) and thallium-201-chloride. In addition, there are some other publications describing only a few cases of thyroid cancers (10–13). Therefore, a multicenter study has been started including cooperation with seven nuclear medicine departments in Germany: Aachen (Cremerius), Bonn (Grünwald), Essen (Brandt-Mainz), Hannover (Burchert & Hiltermann), Köln (Scheidhauer), Münster (Lerch), Tübingen (Feine & Lietzenmayer); 268 cases were collected of which 222 were fully evaluable. All these cases were examined with  $^{131}\text{I}$  and  $^{18}\text{F}$ FDG, and some partially also with MIBI. The first results of this study have been presented at the above-mentioned Consensus Conference (in 1997) by Grünwald (included in (4)). The preliminary data for tumor/metastases detection of differentiated thyroid cancer are:  $^{18}\text{F}$ FDG-PET: sensitivity 75%, specificity 90%;  $^{131}\text{I}$ : sensitivity 50%, specificity 99%;  $^{99\text{m}}\text{Tc}$  MIBI: sensitivity 53%, specificity 92%.

The sensitivity for the combination of  $^{18}\text{F}$ FDG- and  $^{131}\text{I}$ -WB scanning was found to be 93% for the detection of tumor/metastases. In more than 60% of the cases the studies confirmed the assumption (5, 6)

that differentiated papillary and follicular thyroid carcinomas tended to accumulate either  $^{131}\text{I}$  or  $^{18}\text{F}$ FDG and that the same tumor would not usually take up both.

The thyroid carcinomas and their metastases show either some iodine uptake combined with low  $^{18}\text{F}$ FDG trapping, or no  $^{131}\text{I}$  uptake combined with high  $^{18}\text{F}$ FDG trapping. Therefore the hypothesis is that persistent iodine metabolism is consistent with better cell differentiation while the loss of this ability together with an increased glucose metabolism is consistent with dedifferentiation.

Based on several observations, one indication for  $^{18}\text{F}$ FDG-WB-PET is the follow-up of thyroid cancers patients with increased or increasing thyroglobulin levels but negative  $^{131}\text{I}$  scan, and negative CT, MRI and ultrasound. Small cervical metastases, often found in the neck region, offer the possibility of curative surgery.

The fundamental difference between  $^{131}\text{I}$  imaging and  $^{18}\text{F}$ FDG-PET is illustrated in two figures: Fig. 2 shows a patient with metastases of a follicular thyroid cancer and high  $^{131}\text{I}$  uptake (Fig. 2a) but no  $^{18}\text{F}$ FDG trapping (Fig. 2b). This clear difference in uptake is, however, not always found since in five cases (5, 6) we were able to detect in the same patient metastases trapping only  $^{131}\text{I}$  and other metastases trapping only  $^{18}\text{F}$ FDG (Fig. 3a,b). In rare cases one can even observe uptake of both tracers in the same region. These differences probably reflect varying cell differentiation in different parts of the cancer and support the use of  $^{18}\text{F}$ FDG-WB-PET scan in selected cases of suspected metastatic thyroid cancers. These observations strongly suggest that  $^{18}\text{F}$ FDG-PET may have prognostic value.

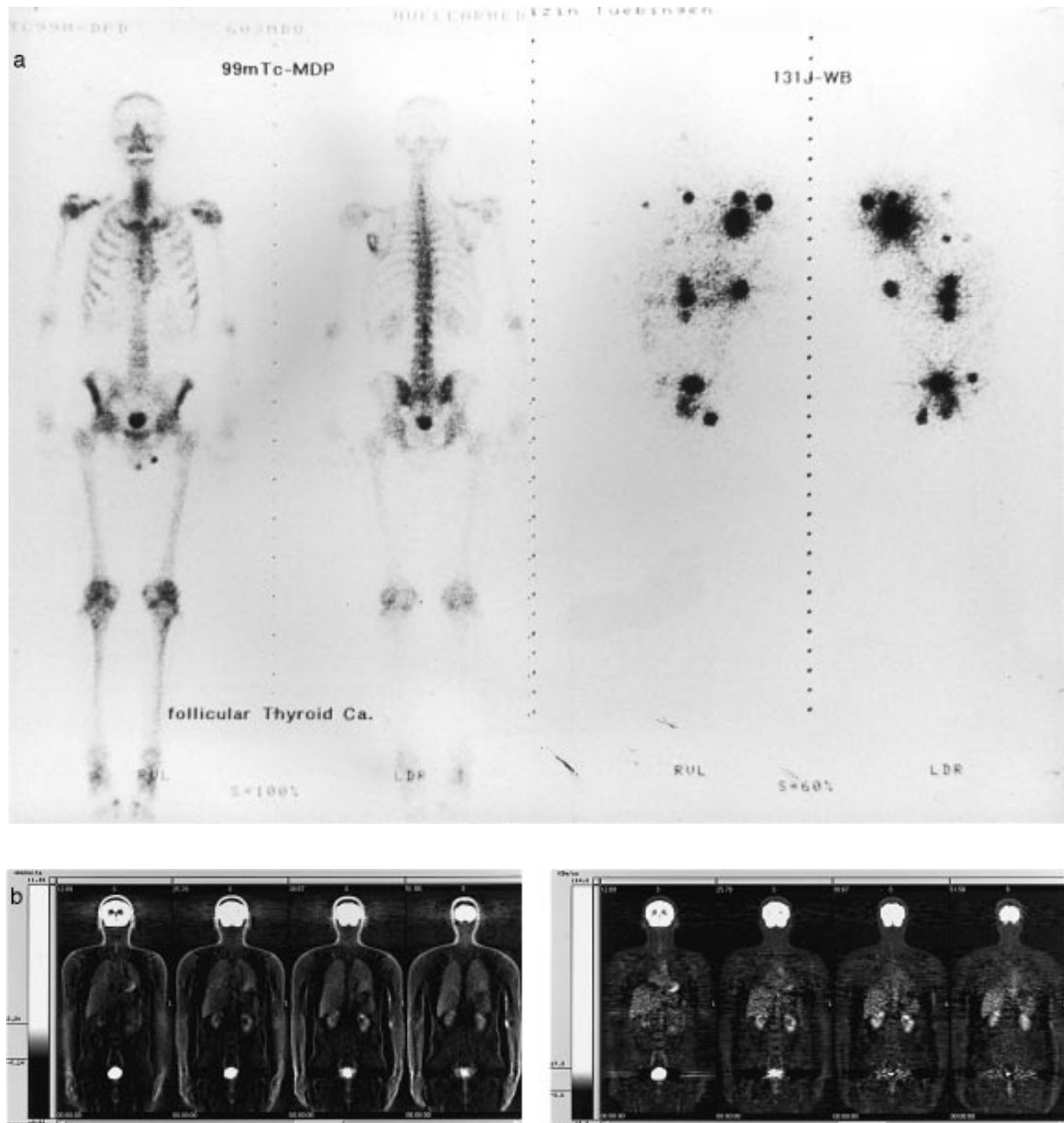
This switch from normal to high glucose metabolism visible by the trapping of  $^{18}\text{F}$ FDG may be generally interesting in tumor metabolism and imaging. Until now there have been no publications on experimental work to verify this assumption. However there are some clinical observations in other tumors.

In 1987 Di Chiro (14) found no  $^{18}\text{F}$ FDG uptake in brain tumors, astrocytoma grades I and II, but a high uptake in grades III and IV. We observed nine children with  $^{131}\text{I}$ -MIBG-positive (Meta-Iodo-Benzyle-Guanidine, a presynaptic adrenergic marker) neuroblastomas and high  $^{18}\text{F}$ FDG trapping, and two children with ganglioneuromas, higher differentiated neuromas, without uptake (15, 16). One of these two children had a small  $^{18}\text{F}$ FDG uptake area in the  $^{131}\text{I}$ -MIBG-positive tumor, histologically confirmed as blastomatous degeneration.

Studies by Shulkin *et al.* in 1996 (17) found 16 of 17 cases of neuroblastomas were  $^{18}\text{F}$ FDG positive, and Maurea *et al.* (18) found that all five malignant adrenergic tumors studied were  $^{18}\text{F}$ FDG positive, while all five benign adrenal lesions studied were  $^{18}\text{F}$ FDG negative. Boland *et al.* (19) described twenty-four cases of adrenal tumors in which the malignant tumors had significantly higher  $^{18}\text{F}$ FDG uptake. Shulkin *et al.*

in 1992 (20) found that in the detection of the primary tumors nine out of ten were positive, and in another study the same authors (1993, (21)) found two MIBG-negative tumors were  $^{18}\text{F}$ FDG positive.

In parathyroid tumors Neumann *et al.* (22) described nineteen benign adenomas which were  $^{18}\text{F}$ FDG negative, and one malignant tumor which was positive. Simon *et al.* (23) found one medullary C-cell carcinoma  $^{18}\text{F}$ FDG



**Figure 2** A 51-year-old male with follicular carcinoma, post thyroidectomy. To determine if there were additional non-iodine-trapping metastases  $^{18}\text{F}$ FDG-WB-PET was performed showing no  $^{18}\text{F}$ FDG accumulation. (a) Left: bone scan with  $^{99\text{m}}\text{Tc}$ -MDP (conventional scan technique), showing only some pathologic uptake in the left scapula caused by a pathologic fracture. Right:  $^{131}\text{I}$  scan with multiple trapping metastases, mostly in the skeleton, not seen in the bone scan, typical of a highly differentiated, iodine-trapping follicular thyroid carcinoma. (b)  $^{18}\text{F}$ FDG-WB-PET-negative scan (non-corrected scan (left) and corrected for attenuation (right)).

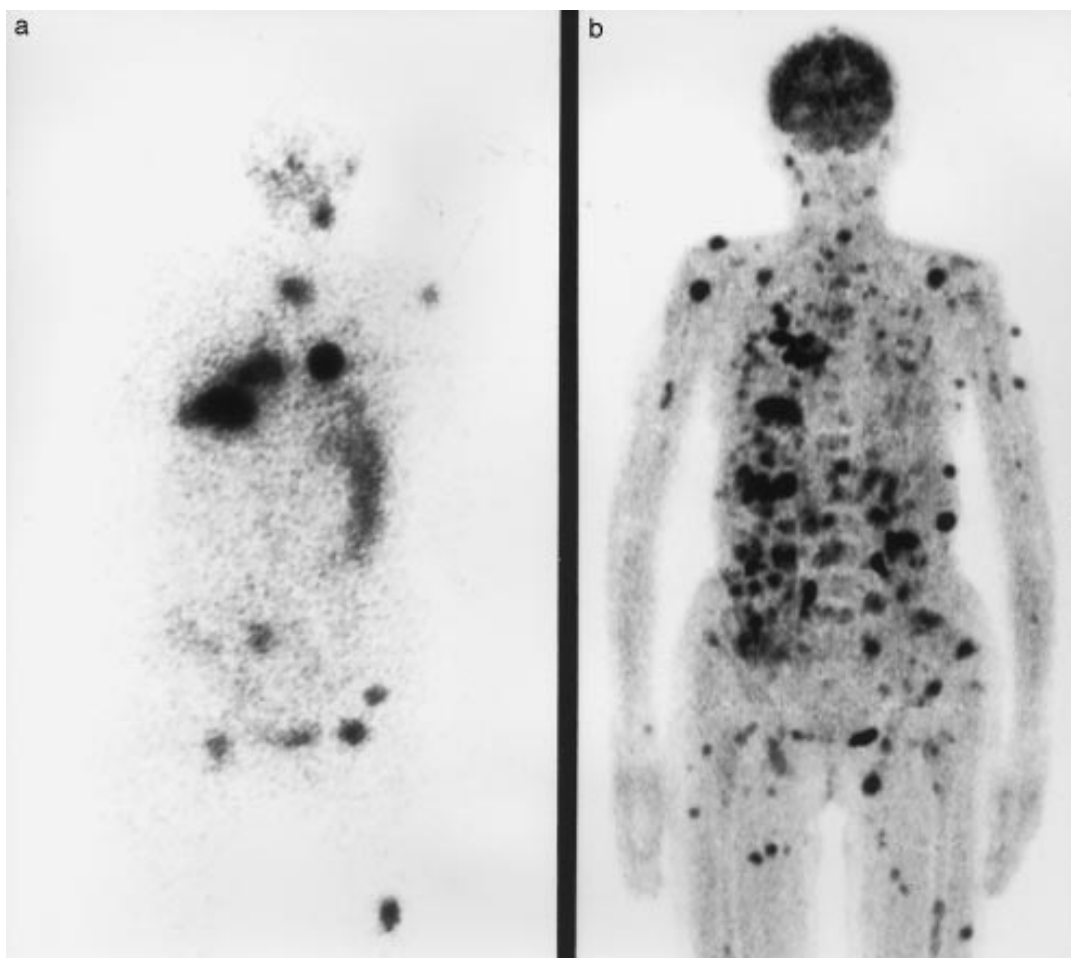
positive. We found two cases positive, four cases negative (15, 16).

In summary, benign or better differentiated tumors/adenomas seem to be  $^{18}\text{F}$ FDG negative, and the malignant ones seem to be mostly positive. Systematic studies and experimental work are necessary to confirm this hypothesis.

It is important to realize that  $^{18}\text{F}$ FDG trapping is not tumor specific. It is not only malignant tumors which have a high uptake, but also lymph nodes with inflammation or other inflamed tissues. Active normal muscle shows well visible  $^{18}\text{F}$ FDG uptake in the PET scans. Also Graves' disease may show an elevated glucose metabolism with significantly higher  $^{18}\text{F}$ FDG trapping than normal thyroid tissue (24). The same group found considerable variation in  $^{18}\text{F}$ FDG uptake in both cold and hot nodules ranging from non-visualization of the

nodule to greatly increased uptake in twenty-three nodules. Adler and colleagues (25, 26) in 1993/1994 described special standardized dose-uptake ratios (DUR) which should have allowed separation of benign thyroid adenomas and malignant thyroid cancers but the number of observations is too small to come to definite conclusions. The use of these so-called standardized uptake values (SUV) for differential diagnosis will need a thorough evaluation anyway.

In summary, recent years have seen the development of an interesting new field in the diagnostic imaging of the metabolism and the detection of malignant tumors with  $^{18}\text{F}$ FDG-PET. For endocrine active tumors, especially thyroid tumors, new aspects are opening up. Other positron-labeled metabolic compounds will follow giving impetus for further research in this field.



**Figure 3** A 63-year-old female, with variable differentiated papillary thyroid carcinoma, admitted to the Nuclear Medicine Department for treatment of hyperthyroidism due to hormone-producing metastases. (a) In the iodine scan before radioiodine therapy good uptake in the metastases is seen but no uptake in multiple other metastases known partially from X-ray examinations. (b)  $^{18}\text{F}$ FDG-WB-PET shows three times more metastases, all unmarked by  $^{131}\text{I}$ . The patient has a mixture of various differentiated metastases of the papillary carcinoma.

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