Eur J Nucl Med Mol Imaging (2005) 32:342–343
DOI 10.1007/s00259-005-1775-2
Published online: 22 February 2005

Against

The idea of using imaging for whole-body cancer screening is alluring. Every nuclear medicine physician working with ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) has observed patients with malignancies unrelated to the referral diagnosis. In a series of such clinically unexpected results, Agress and Cooper showed that 'incidental' does not mean 'negligible'; considerable pathology, especially in the colon, may be detected [1]. These observations suggest the use of FDG-PET for health screening. The justification for such an approach, however, is far from clear, and many prerequisites will have to be met before FDG-PET can be recommended for this purpose.

Bayes theorem

The following considerations with respect to screening programmes have been published on the WHO homepage (http://www.who.int/cancer/detection/en/): "A screening test aims to be sure that as few as possible with the disease get through undetected (high sensitivity) and as few as possible without the disease are subject to further diagnostic tests (high specificity). Given high sensitivity and specificity, the likelihood that a positive screening test will give a correct result (positive predictive value) strongly depends on the prevalence of the disease within the population. If the prevalence of the disease is very low, even the best screening test will not be an effective public health programme" [2]. For example, if a diagnostic test has a sensitivity and specificity of 90% but the prevalence of a disease is as low as 1%, only one out of ten positive test results will be cancer related. The mathematical basis for these considerations was introduced by Bayes more than 200 years ago [3]. It is far from proven that FDG-PET has a 90% accuracy in patients with asymptomatic neoplastic disease. Even in malignancies in which FDG-PET has a well-defined role, the results in the early detection of disease are less favourable. For example in colon cancer, FDG-PET regularly fails to detect small precancerous or malignant lesions and specificity is limited by the presence of inflammatory or unspecific bowel disease [4, 5]. It is, however, the resection of small lesions which may decrease cancer-related mortality.

The opinions expressed within the Controversies section represent the views of the authors only. The article arguing for this proposition is published at http://dx.doi.org/10.1007/s00259-005-1774-3

Eligibility for FDG-PET screening

The definition of populations at risk is a major issue in developing screening programmes. Furthermore, it has to be proved that cancer is not only diagnosed at earlier stages but that specific cancer mortality of the screened population decreases. Prospective randomised trials on FDG-PET as a screening tool are not yet available. Potential sources of bias in such studies have been discussed elsewhere [6]. The data that are available suggest positive FDG-PET findings in about 1–2% of the screened population [7–9]. Thus, on average, 50–100 FDG-PET scans have to be performed to identify one patient with malignancy. Furthermore, in some of these studies the authors do not state whether the patients had participated in other screening programmes (e.g. patient history, faecal occult blood testing, colonoscopy and mammography). So it is unclear whether or not the FDG-PET-positive lesions would have been missed by routine diagnostic techniques. Clinical follow-up for 6–10 months is a gold standard for negative findings in these studies. This period is too short to exclude the presence of small malignant lesions, e.g. in the colon. Inclusion criteria have not been reported in detail in the aforementioned studies, and results may be more favourable in well-defined populations. The definition of subjects at risk by use of a simple questionnaire has been studied in much detail in cardiovascular disease (e.g. [10]). It is, however, more difficult to identify high-risk patients when assessing cancer in general.

Cost-effectiveness is another issue in this context, which will not be addressed in detail since there are no substantial data for FDG-PET in the setting of screening. Data on secondary expenses caused by false positive findings are also not available.

FDG-PET-negative tumours

As FDG-PET holds promise for whole-body tumour screening, subjects who have been screened may have a confidence which is not substantiated. It is well known that some common tumours may be negative on FDG-PET. Patients might regard further screening tests as unnecessary and early-stage malignancy might be missed. Prostate cancer in male subjects and breast cancer in women are examples of such tumours. An FDG-PET scan is not a substitute for the respective screening programmes for these cancers, although FDG-PET may provide valuable information in restaging breast cancer [11]. Recent data on the Japanese screening programme were reported in the "News and Views" section of this journal. A total of 253 malignancies were detected within 10 years. Half of these tumours did not show increased glucose metabolism but were detected by ultrasound, CT, MRI or laboratory tests. A total of 21,804 FDG-PET studies were performed in 8,615 persons to achieve this rate of detection [12].

The WHO has published further prerequisites for establishing a screening programme. These include the definition of guidelines addressing eligibility for participation in the programme, well-defined criteria for image interpretation and defined mechanisms for the treatment of abnormalities. Quality control mechanisms and expenses are other topics dealt with by the WHO. These questions have not yet been addressed sufficiently for FDG-PET in screening.

Radiation protection

While radiation exposure due to FDG-PET is regarded as negligible in patients with proven cancers or a high probability of malignancy, the use of FDG-PET in the general population is a different matter. The effective dose of FDG-PET can be estimated at about 10 mSv, when 370 MBq is injected [13]. According to the International Commission on Radiation Protection (ICRP), the risk of radiation-induced cancer is as high as 5/10,000 for an effective dose of 10 mSv [14]. Although these figures are estimates only, they are widely used in radiation protection. Applying these data to FDG-PET screening, one radiation-induced cancer is to be expected with 2,000 FDG-PET studies. If only 1–2% of these studies are positive, this means one additional cancer for the detection of cancer in 20–40 patients. This risk can only be accepted if a benefit for the majority of patients has clearly been demonstrated.

Regulatory restrictions in many countries, e.g. in Germany, prohibit the use of ionising radiation without a "legitimate indication". The use of FDG-PET in normal examinees may only be legally approved after a formal application for a scientific project. Thus performing FDG-PET as a screening test in healthy persons is legally not possible in many countries.

Conclusion

In summary, the authors believe that it is too early to recommend FDG-PET as a screening tool. General reflections on sensitivity and specificity, on cost-effectiveness and on radiation protection support scepticism about the future introduction of FDG-PET in this setting. The authors advocate extending research on the use of FDG-PET in well-defined clinical situations when malignancy is known or is strongly suspected to be present. This may include clinical studies on the use of FDG-PET as a second-line diagnostic tool in a screened population, as reported by Pastorino et al. [15].

Matthias Weckesser (✉), **Otmar Schober**
Department of Nuclear Medicine, Münster University, Albert-Schweitzer-Strasse 33, 48149, Münster, Germany
e-mail: m.weckesser@uni-muenster.de
Tel.: +49-251-8347362, Fax: +49-251-8347383

References

1. Agress H Jr, Cooper BZ. Detection of clinically unexpected malignant and premalignant tumors with whole-body FDG PET: histopathologic comparison. Radiology 2004;230:417–22.
2. http://www.who.int/cancer/detection/en/
3. Bayes T. An essay toward solving a problem in the doctrine of chances. Philos Trans R Soc Lond 1763;53:370–418.
4. Drenth JP, Nagengast FM, Oyen WJ. Evaluation of (pre-) malignant colonic abnormalities: endoscopic validation of FDG-PET findings. Eur J Nucl Med 2001;28:1766–9.
5. Yasuda S, Fujii H, Nakahara T, Nishiumi N, Takahashi W, Ide M, et al. ^{18}F-FDG PET detection of colonic adenomas. J Nucl Med 2001;42:989–92.
6. Patz EF Jr, Goodman PC, Bepler G. Screening for lung cancer. N Engl J Med 2000;30(343):1627–33.
7. Chen YK, Kao CH, Liao AC, Shen YY, Su CT. Colorectal cancer screening in asymptomatic adults: the role of FDG PET scan. Anticancer Res 2003;23:4357–61.
8. Shen YY, Su CT, Chen GJ, Chen YK, Liao AC, Tsai FS. The value of ^{18}F-fluorodeoxyglucose positron emission tomography with the additional help of tumor markers in cancer screening. Neoplasma 2003;50:217–21.
9. Yasuda S, Ide M, Fujii H, Nakahara T, Mochizuki Y, Takahashi W, et al. Application of positron emission tomography imaging to cancer screening. Br J Cancer 2000; 83:1607–11.
10. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation 2002;105:310–5.
11. Smith JA, Andreopoulou E. An overview of the status of imaging screening technology for breast cancer. Ann Oncol 2004;15:I18–26.
12. Ell PJ. News and views. Eur J Nucl Med Mol Imaging 2005;31:127–38.
13. Deloar HM, Fujiwara T, Shidahara M, Nakamura T, Watabe H, Narita Y, et al. Estimation of absorbed dose for 2-[F-18] fluoro-2-deoxy-D-glucose using whole-body positron emission tomography and magnetic resonance imaging. Eur J Nucl Med 1998;25:565–74.
14. International Commission on Radiological Protection, Report No. 60 (1991) Recommendations of the International Commission on Radiological Protection.
15. Pastorino U, Bellomi M, Landoni C, De Fiori E, Arnaldi P, Picchio M, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet 2003;362:593–97.