PERGAMON

European Journal of Cancer 39 (2003) 1525–1534

European Journal of Cancer

www.ejconline.com

Review

PET scan imaging in oncology☆

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Received 25 February 2003; received in revised form 2 April 2003; accepted 4 April 2003

Abstract

With the emergence of positron emission tomography (PET) from research laboratories into routine clinical use, it is important to redefine the most appropriate use of each imaging technique. The aim of this review article is to show the potential of PET in oncology. We discuss the most promising indications and the perspectives for the future. We will also point out the shortcomings and the important questions to be answered before fully considering PET as a necessary tool in the day-to-day practice of oncology. Although many studies have documented the high accuracy of ^{18}F-FDG PET for the detection and staging of malignant tumours and for the monitoring of therapy results in these patients, it is very important to assess the impact of the technique on patient outcome and to show cost-effectiveness from the societal viewpoint.

Keywords: Fluorodeoxyglucose; Positron emission tomography; Staging

1. Introduction

Medical imaging technology is rapidly expanding and has a major impact on rising healthcare costs. With the emergence of positron emission tomography (PET) from research laboratories into routine clinical use, it is important to redefine the most appropriate use of each imaging technique [1]. The spectrum of medical imaging in oncology has recently been reviewed in a Special Issue of the *European Journal of Cancer*. Major advances have been made in the development and application of imaging techniques in oncology. The future prospects of virtual colonoscopy [2], functional computed tomography (CT) [3], magnetic resonance spectroscopy [4], functional ultrasound [5], functional magnetic resonance imaging (MRI) [6] and gamma camera imaging [7] have been examined and discussed in the Special Issue. The aim of this review is to show the most promising indications of PET in the routine clinical practice of oncology. The role of PET for *in vivo* pharmacokinetic and pharmacodynamic measurements [8] and for imaging of gene expression [9] has been reviewed elsewhere.

Conventional imaging modalities such as CT and MRI depend on structural or anatomical abnormalities to detect disease. In contrast, PET has the ability to detect cancer based on molecular and biochemical processes within the tumour tissues. PET uses radioisotopes of natural elements, oxygen-15, carbon-11, nitrogen-13 and fluorine-18. These radioisotopes retain their normal biological function and allow the synthesis of numerous positron-emitting radiopharmaceuticals. PET imaging can provide quantitative information regarding blood flow, receptor status and metabolic processes. The most widely used radiotracer in oncology at this time is the glucose analogue ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Increased glycolysis is one of the most distinctive biochemical features of malignant cells because of the inefficient metabolism of glucose in malignant tumours. It results from the amplification of the glucose transporter proteins at the tumour cell surface, as well as from increased activity of various key enzymes,

☆ Part of the manuscript was presented at the 27th ESMO Congress, 19–22 October 2002, Nice, France.

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doi:10.1016/S0959-8049(03)00374-5

including hexokinase. Like glucose, ^{18}F-FDG is transported into cells by a glucose transporter protein and rapidly converted into ^{18}F-FDG-6-phosphate. As the latter is not a substrate for glucose-6-phosphate isomerase, it is biochemically trapped in metabolising tissues [10]. ^{18}F-FDG has distinct advantages when compared with other positron-emitting radiopharmaceuticals. It can be efficiently radiolabelled by an automated method and its longer half-life (110 min compared with 20 min for carbon-11, for example) provides an opportunity for off-site preparation avoiding the need for an on-site cyclotron.

2. Potential clinical applications of ^{18}F-FDG PET

We will review the most promising clinical indications for the use of PET. In every situation, we will discuss the most convincing data, but also the shortcomings as well as questions for the future. Although PET may be useful in other tumours not listed in this review, the available data are too scarce to allow recommendations.

2.1. Qualitative PET studies

2.1.1. Screening

^{18}F-FDG PET has been used for cancer screening in asymptomatic patients [11]. Within 1 year after screening, malignant tumours were discovered in 67 of the 3165 participants (2.1%). PET findings were falsely-negative in 31 of the 67 patients (46%), including 14 of the 31 tumours (45%) of urological origin. Unfortunately, the frequency of false-positive results has not yet been analysed. The authors concluded that, because of the substantial cost of PET examination, it should not be used as a screening test in an unselected general population.

2.1.2. Differential diagnosis: benign versus malignant lesion

PET is an accurate non-invasive imaging test for the differential diagnosis of pulmonary nodules and larger mass lesions [12]. A meta-analysis of 40 studies totaling 1474 focal pulmonary lesions of any size reported a sensitivity and specificity for the detection of tumoral lesions by PET of 96.8 and 77.8%, respectively. Shortcomings discussed by the authors included the poor methodological quality of most studies, their small sample size and the often incomplete blinding. Whereas few data exist for nodules smaller than 1 cm in diameter, the performance of PET appears to be similar for nodules measuring at least 1 cm in diameter and larger mass lesions. In current practice, PET operates at a point on the Receiver Operating Characteristic (ROC) curve that favours sensitivity over specificity. This approach is appropriate because the consequences of a false-negative test result (delayed detection of malignancy and possible missed opportunity for surgical cure) are more undesirable than the consequences of a false-positive test result (unnecessary biopsy or surgery). Cost-effectiveness has to be considered. Using a decision tree sensitivity analysis, Gambhir and colleagues [13] suggested that the most cost-effective approach consists of combining CT and PET and proceeding to biopsy or surgery only for lesions that are positive on PET. PET is only indicated if further evaluation and/or treatment is planned according to the result of the PET scan. A CT-guided needle biopsy is much less expensive than PET [12]. If a CT-guided biopsy can easily be performed, PET may only be indicated when a definitive diagnosis has not been obtained by this procedure. Further evaluation of the accuracy and cost-effectiveness of PET is warranted in this selected patient population. For cost-effectiveness, one should also take into account that PET contributes to a better staging (see below) in patients with non-small cell lung cancer (NSCLC).

^{18}F-FDG PET has been suggested to provide excellent accuracy for non-invasive evaluation of suspicious pancreatic masses [14]. However, recent publications reported that PET imaging provides only poor diagnostic accuracy (69%) for characterising pancreatic masses [15]. In a study of 103 patients, Kasperk and colleagues [16] could not identify a single case where PET would have changed the surgical strategy. They observed a considerable rate of false-negative results. In particular, PET missed some pT1 tumours, the stage most amenable to surgical cure. However, falsely-positive PET results, as in the case of stenosing papillitis or chronic pancreatitis, might lead to inappropriate surgical interventions. Therefore, PET cannot clarify situations where conventional diagnostic methods leave some doubt about the nature of the pancreatic disease.

2.1.3. Cancer of unknown origin: detection of the primary site

Two to four percent of all cancer patients present with an initial diagnosis of cancer of unknown primary (CUP). The prognosis and treatment strategy is mostly influenced by the presence of a disseminated disease. For localised disease, curative treatment is more likely and individual therapeutic concepts are of major importance. Several studies investigated the diagnostic contribution of PET for localisation of an unknown primary tumour [17–22]. PET is able to identify the primary in some patients (Fig. 1). Unfortunately, in most studies, the impact of the PET result on therapeutic management has not been sufficiently investigated. Rades and colleagues [22] reported that PET allowed detection of the primary site in 43% (18/42 patients) of the study population that included only localised CUP based on conventional staging procedures. Dissemination was detected by PET in 16 of 42 patients (38%). In 29 of 42 patients (69%), the PET result influenced the selection of the definitive treatment.

2.1.4. Staging at initial diagnosis

The impact of PET on the quality of staging at diagnosis has been shown for various tumours. The highest number of patients has been studied in the field of NSCLC. The assessment of solitary pulmonary nodules of unknown origin and the initial staging of lung cancer were the first two indications covered by Medicare in the United States of America (USA) since January 1998. A meta-analysis has firmly established the higher accuracy of metabolic staging compared with anatomical staging in the detection of mediastinal lymph node metastases [23]. The staging performance for detecting lymph node infiltration in the mediastinum obtained by PET in 14 studies including 514 patients was compared with the results obtained by CT in 29 studies including 2226 patients. The overall sensitivity and specificity were 79 and 91%, respectively, for PET and 60 and 77%, respectively, for CT. The whole-body PET study also allows the detection of unknown distant metastases [24] and we can reasonably conclude that the use of PET leads to more accurate staging than other conventional non-invasive staging techniques [25]. ^{18}F-FDG PET has been found to be cost-effective by avoiding surgery that would not benefit the patient [26]. The PLUS (PET in LUng cancer Staging) study further supports the value of ^{18}F-FDG PET in NSCLC [27]. Before surgery (mediastinoscopy or thoracotomy), 188 patients from nine hospitals were randomly assigned to either conventional work-up or conventional work-up and PET. In the conventional work-up group, 39 (41%) patients had a futile thoracotomy, compared with 19 (21%) in the conventional work-up + PET group. The addition of PET to conventional work-up prevented unnecessary surgery in 1 out of 5 patients. A second randomised trial including 179 patients did not confirm these data, but it was only presented as a scientific communication at the 2001 American Society of Clinical Oncologists (ASCO) meeting and the article is not available yet [28]. Recent data also show that ^{18}F-FDG PET cannot replace preoperative surgical staging in NSCLC [29]. The overall accuracy of ^{18}F-FDG PET was lower than previously reported. ^{18}F-FDG PET imaging correctly identified nodal stage (N0–N1 versus N2) in 50 out of 61 patients (82%), while overstaging occurred in 8 patients (13%) and understaging in 3 patients (5%). The superiority of invasive staging procedures is not surprising. Microscopic disease will always remain beyond the detection capacity of PET. For the same reason, PET will not replace sentinel lymph node biopsy in melanoma [30,31] or in breast cancer [32].

2.1.5. Restaging (staging at relapse)

Surgical reintervention can potentially cure a fraction of patients with recurrent cancer. One of the best examples in this indication is recurrent colorectal cancer (Fig. 2). In patients with elevated serum carcinoembryonic antigen (CEA) levels, but negative conventional imaging, occult disease can be identified accurately with ^{18}F-FDG PET [33,34]. The timing of staging procedures (conventional staging followed by PET) may explain part of the superiority of PET over conventional staging procedures, in particular for rapidly growing, poorly differentiated tumours. Accurate staging of recurrence is of particular importance in patients considered for curative surgery of hepatic metastatic disease. The meta-analysis performed by Huebner and colleagues [35] showed a sensitivity of 97% and a specificity of 76% for PET in detecting recurrent disease. Patient management was modified in 29% of the cases, both by upstaging and downstaging disease. Unfortunately, as pointed out by Huebner and colleagues, the methodological quality of many of the studies included in the meta-analysis was sub-optimal. In our opinion, because of the lower specificity of PET, a positive study has to be confirmed by a conventional radiological study or a biopsy before starting systemic salvage therapy or excluding a patient for potential curative surgery. However, PET is the best non-invasive staging procedure to select appropriate candidates with apparently localised metastatic disease who may benefit from surgical resection [34,36,37]. At equivalent specificity, PET is more sensitive than ultrasonography, CT and MRI for detecting liver metastases from gastrointestinal tumours [38].

2.1.6. End-of-treatment evaluation

One of the most challenging aspects in cancer imaging is the assessment of response to treatment. Unfortunately, there are no reliable radiographic characteristics for CT or other conventional imaging techniques that permit differentiation between malignant and fibrotic or necrotic tissue.

^{18}F-FDG PET is the best non-invasive imaging technique for end-of-treatment evaluation of patients with lymphoma. We studied 54 patients with Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL) and found a significantly better positive predictive value for residual disease than CT (100% versus 42%) and a comparable negative predictive value (83% versus 87%) [39]. PET was a very strong predictor of progression-free and overall survival. The accuracy of PET in the field of NHL has been confirmed by other investigators [40,41], but recent publications indicate that this value may be lower in patients suffering from HD [42,43]. A histological confirmation of residual disease is always necessary before starting salvage chemotherapy because active inflammatory lesions can be falsely interpreted as residual tumour [44].

Although the optimal management of residual masses in patients with bulky seminoma is still controversial, a surgical resection is now performed in many centres if the residual mass is larger than 3 cm because there is a 30–40% risk of residual tumour. Unfortunately, resections are technically difficult because of desmoplastic

reaction and fibrosis and are associated with considerable morbidity. An early report from the Indiana University showed no interest for PET in this indication, but important informations such as the technical specifications of the PET scanner and, more importantly, the minimum interval between chemotherapy and PET, were not reported [45]. Recently, De Santis and colleagues found much more promising results [46]. All 14 residual lesions greater than 3 cm and 22 (96%) of the 23 lesions $\leqslant 3$ cm were correctly classified by PET. The positive predictive value (8/8: 100%) and negative predictive value (28/29: 97%) of ^{18}F-FDG PET were superior to data obtained by assessing residual tumour size ($\leqslant 3$ cm or >3 cm).

Kollmannsberger and colleagues [47] compared prospectively ^{18}F-FDG PET with established criteria for the assessment of response in patients with non-seminomatous germ cell carcinoma. The sensitivity and specificity were 59 and 92%, respectively, for PET, 55 and 86% for radiological monitoring and 42 and 100% for tumour marker changes. The positive and negative predictive values for PET were 91 and 62%, respectively. PET may add important information in patients with multiple, incompletely resectable, residual masses, in particular in patients with serum tumour marker-negative disease. Unfortunately, a negative PET after the end of treatment does not allow one to avoid surgery, because 37% of all negative PET masses either

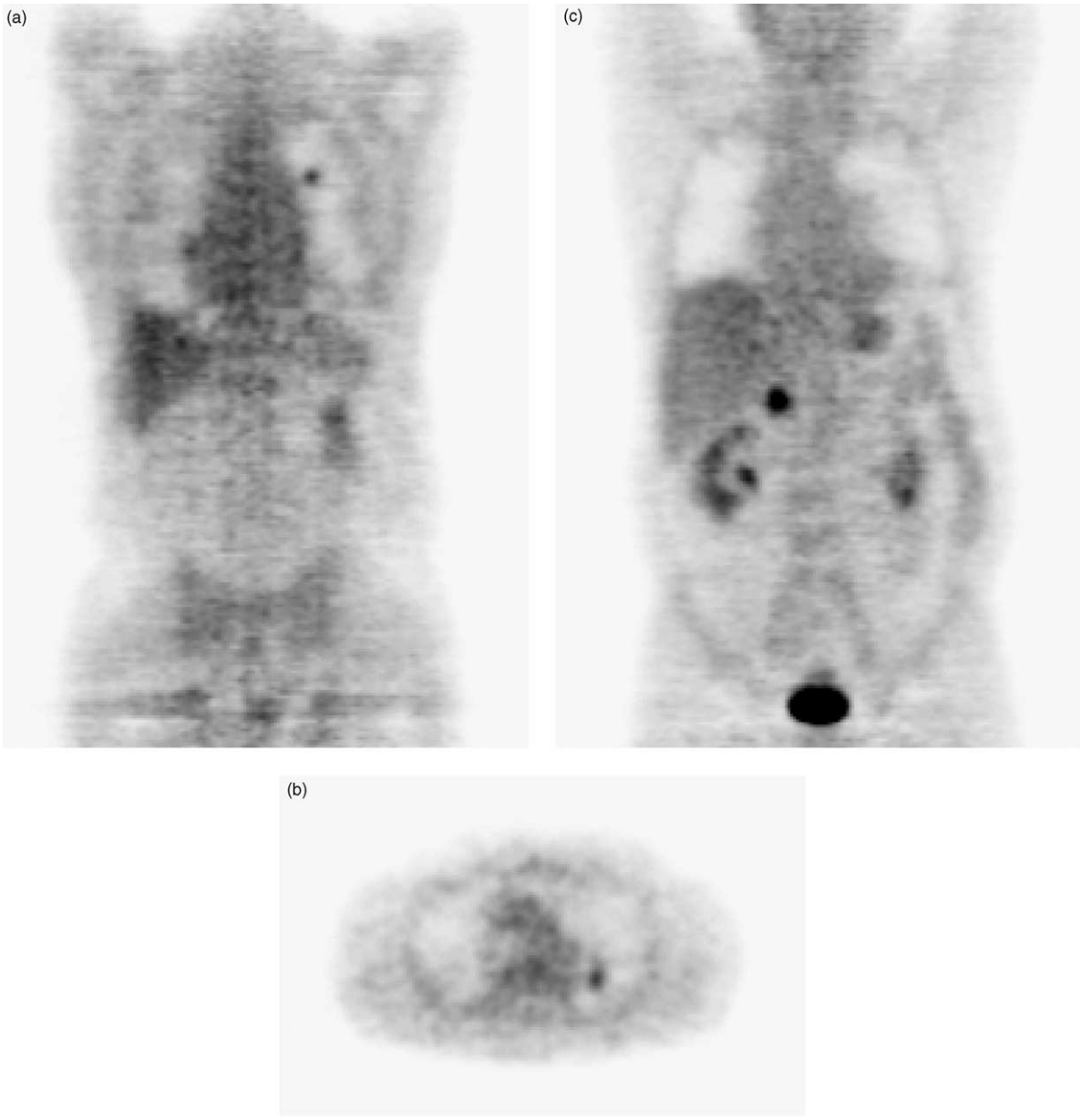

Fig. 1. PET scan in a 69-year-old patient with a brain metastasis of unknown origin. FDG-PET shows a lung lesion (a and b) as well as a right adrenal metastasis (c).

progressed during 6 months of follow-up or histological examination revealed mature teratoma. The surgical resection of all residual masses, if technically possible, remains the recommended standard of care.

Neither physical nor conventional radiological examinations are adequate for the early detection of recurrent or residual disease in head-and-neck cancer patients treated with radiotherapy. Early and late posttreatment changes, particularly oedema and fibrosis, may lead to interpretation errors. Surgeons are often reluctant to obtain multiple or deep biopsy specimens in previously irradiated tissues for fear of initiating or aggravating radionecrosis. A critical review by Schechter and colleagues [48] concluded that ^{18}F-FDG PET may contribute to the detection of residual or early recurrent tumours, allowing a timely institution of salvage therapy. Unfortunately, a high false-positive rate is observed when patients are investigated earlier than 12 weeks after irradiation [49] and the ideal time to perform ^{18}F-FDG PET has yet to be determined [48]. Further studies with cost-benefit analyses are needed.

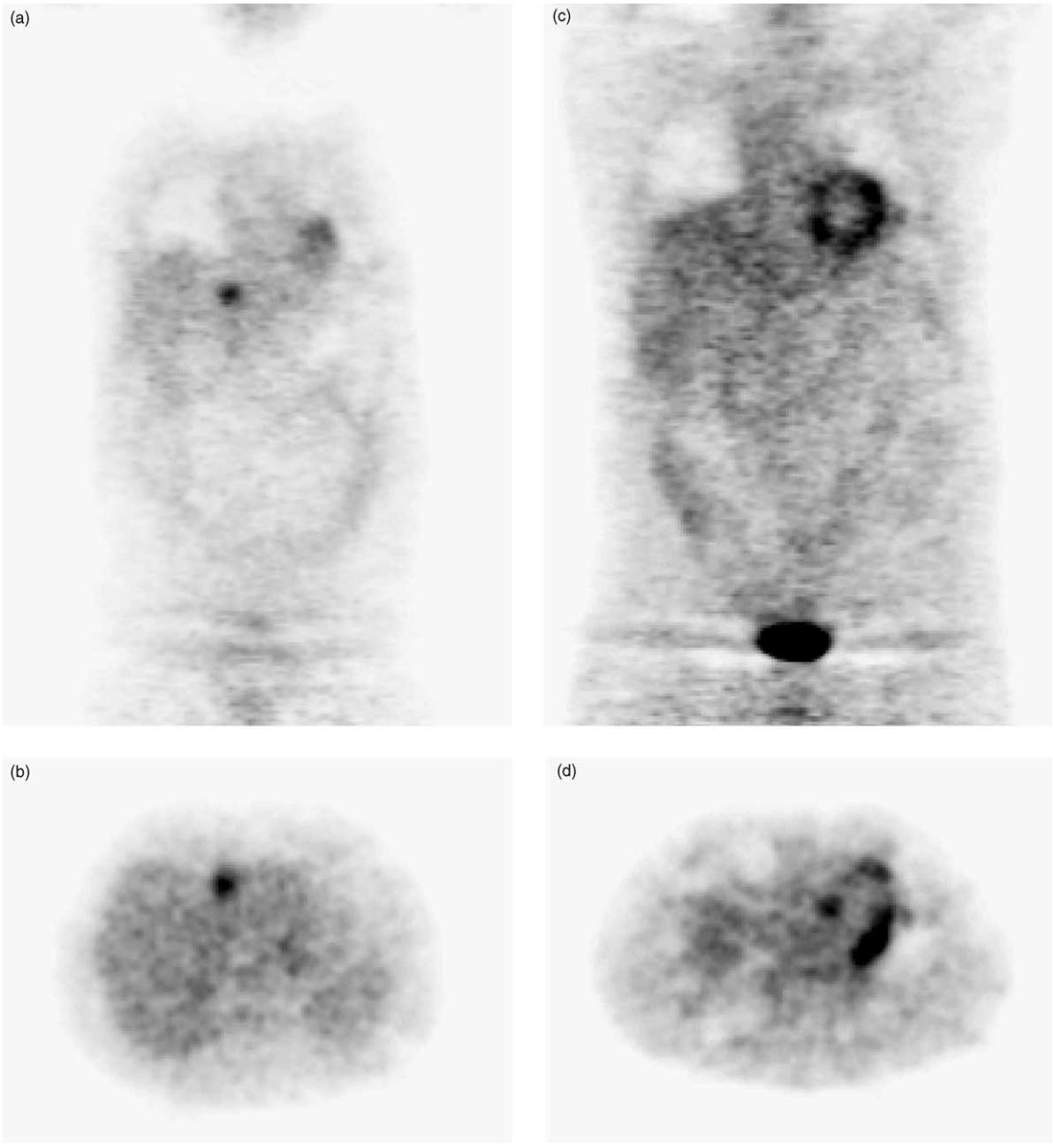

Fig. 2. PET scan in a 69-year-old patient with a previous history of colon cancer. A routine follow-up liver ultrasound had indicated a suspicious lesion, but the spiral CT was negative. PET confirmed the presence of a liver metastasis (a and b) and also showed a small lesion in the left lung, next to the heart (c and d).

The evaluation of brain tumours is the longest established oncological application of PET. Therapeutic response of cerebral gliomas is usually monitored with CT or magnetic resonance imaging (MRI), but the limitations of these techniques are very well known when they are used to differentiate recurrence of brain tumour from benign posttherapeutic lesions. PET has been shown to be more accurate in this regard, but ^{18}F-FDG is clearly not the best radiotracer. In fact, the high glucose utilisation of grey matter, resulting in low contrast between tumour tissue and normal grey matter, complicates the identification and delineation of tumour tissue by ^{18}F-FDG PET. A better radiotracer is ^{11}C-methionine that evaluates the amino acid metabolism of brain tumours [50]. Furthermore, amino acid imaging is less influenced by inflammation. Unfortunately, the short half-life of carbon-11 of only 20 min restricts the use of this tracer to PET centres with on-site cyclotrons.

2.1.7. Routine follow-up of asymptomatic patients

Intensive follow-up evaluation for diseases such as breast cancer or NSCLC is of questionable value because these tumours are generally incurable once metastases develop and early detection of relapse is unlikely to result in increased survival. In contrast, salvage therapies for recurrent HD are effective in many patients, justifying closer follow-up observation. We examined the value of PET for the detection of preclinical relapse in HD [51]. Among the 36 patients included in our study, 1 had residual tumour and 4 patients apparently in complete remission relapsed during a follow-up of 5–24 months. All five events were correctly identified early by PET. 2 patients presented B symptoms and the 3 others were asymptomatic at the time of diagnosis of residual disease or relapse. PET was positive up to 9 months before histological confirmation. Although our data clearly indicate the potential of ^{18}F-FDG PET to detect preclinical relapse, the high rate of false-positivity ($6/11 = 55\%$) has to be pointed out. Further studies are warranted to determine the impact of earlier diagnosis of residual or recurrent disease on outcome.

^{18}F-FDG PET is very sensitive in detecting metastatic disease in patients with melanoma and can thus identify unsuspected disease [52,53]. Unfortunately, at this time, the early diagnosis of metastatic disease probably has no impact on outcome as systemic treatment results for melanoma remains extremely disappointing (Fig. 3).

2.2. Quantitative PET studies

2.2.1. Standardised uptake value (SUV): a new prognostic factor

The tissue radiotracer concentration can be measured for attenuation-corrected PET images. The standardised uptake value (SUV) is a simple semi-quantitative index widely used for tumour ^{18}F-FDG uptake assessment. It is obtained by dividing the tumour radiotracer concentration (MBq/l) by the injected activity (MBq) and multiplying it by the body weight (kg). Other normalisations and corrections can be applied (i.e. body surface area or lean body mass, blood glucose level), improving the accuracy of the measurement [54]. The SUV is an unitless measurement based on the assumption that both tumour and other body tissues have the density of water, i.e. 1 kg is equivalent to 1 l. Retrospective studies have shown a relationship between the amount of ^{18}F-FDG uptake in various tumour lesions and prognosis. For example, in the field of NSCLC, Ahuja and colleagues [55] found a statistically shorter median survival in patients with higher SUV values. In the 118 patients with SUV values <10, a median survival of 24.6 months was reported, whereas the 37 patients with SUV values >10 had a median survival of only 11.4 months. Vansteenkiste and colleagues [56] found that a cut-off SUV of 7 had the best discriminative value for prognosis. Among 91 patients with resectable NSCLC, patients with SUV of 7 or less had a much better survival rate than patients with a SUV above 7. Patients with a resected tumour less than 3 cm in diameter had an expected 2-year survival of 86% if the SUV was below 7, and 60% if it was above 7; all but 4 patients with resected tumours larger than 3 cm had a SUV of more than 7 and an expected 2-year survival of 43%. In both studies, multivariate analysis demonstrated that the results of the PET scan provided prognostic information, independent of other clinical and image findings. It is reasonable to hypothesise that there is no true cut-off point, but rather a transition zone, where the prognosis gradually worsens [56]. The best cut-off point has to be determined by prospective studies. More importantly, it remains to be shown that this independent prognostic factor is complementary to other well-known factors for the selection of adjuvant treatment protocols and that more appropriate treatment results in a better outcome.

2.2.2. Measurement of clinical and subclinical tumour response

An emerging area of clinical utility for PET is the monitoring of tumour response to therapy. ^{18}F-FDG PET may be useful for early treatment evaluation after a few cycles of chemotherapy [57,58]. Accurate assessment of response to both chemotherapy and radiation therapy, often preceding CT scan changes, has been reported in various tumours [59]. This may justify the use of subclinical response as a criteria for the evaluation of anticancer drugs in early clinical trials and may provide some improvement in patient management. However, methodological developments in this area are still required before PET can be considered a standard technique in this indication. A consensus is

necessary for common measurement criteria and standardised reporting of alterations in ^{18}F-FDG uptake with treatment. In 1999, the EORTC PET study group produced guidelines for the use of ^{18}F-FDG PET to assess response [59]. They published recommendations for patient preparation, timing of ^{18}F-FDG PET and methods to measure ^{18}F-FDG uptake. From the literature, it appears that a 15–30% reduction in SUV after one cycle of chemotherapy or a reduction greater than 25% after 2–3 cycles is observed in responding tumours. This metabolic response precedes tumour shrinkage and clinical response. However, monitoring early tumour response with PET is still in its infancy. Overestimation and underestimation of tumoral ^{18}F-FDG uptake is possible. The presence of inflammatory cells after therapy may result in persistently high ^{18}F-FDG uptake despite tumour response to treatment. It has even been demonstrated that these cells may show higher

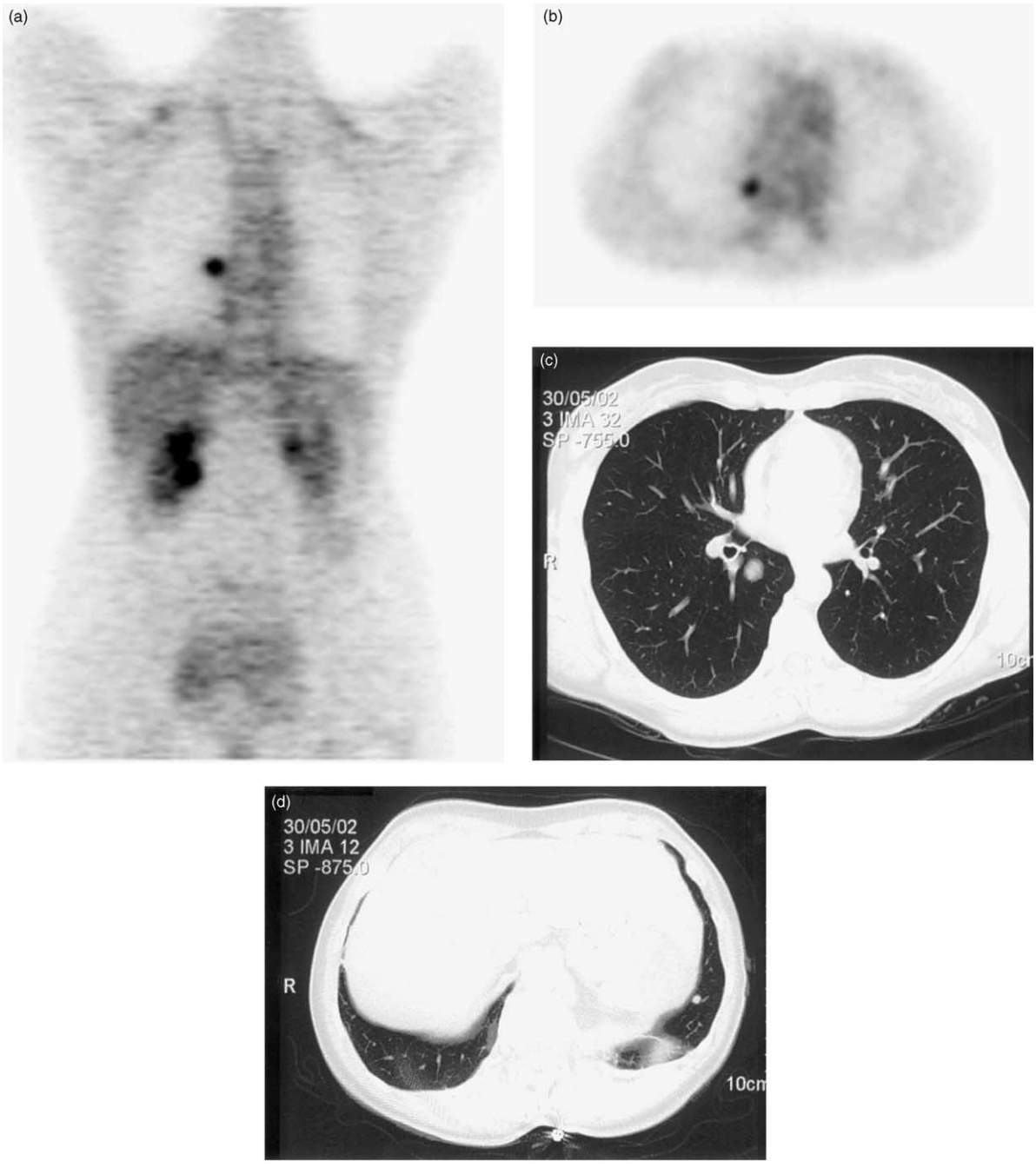

Fig. 3. Routine follow-up of a 52-year-old woman suffering from a high-risk melanoma was performed by whole-body PET every 6 months. Two years after diagnosis, PET suspected an asymptomatic isolated lung metastasis (a and b). CT confirmed not only this metastasis (c), but identified a second pulmonary metastasis (d). Although cisplatin-based polychemotherapy was immediately administrated, the patient developed symptomatic disease progression (lung, bone and brain) 2 months later.

^{18}F-FDG uptake than do viable tumour cells. The optimal timing of posttherapy ^{18}F-FDG scans has yet to be determined in order to reduce the rate of false-positive scans related to uptake by host inflammatory cells. Another potential problem for PET interpretation and calculation of tumoral ^{18}F-FDG uptake is that tumours are non-homogeneous: clusters of normal cells alternate with clusters of malignant cells. This phenomenon occurs on a microscopic scale far beyond the resolution of PET. Necrosis, fibrosis and oedema may also be present in parts of the tumour. Consequently, ^{18}F-FDG uptake does not fully reflect the metabolic status of the tumoral tissue. False-negative PET studies can also be due to partial volume effect related to the limited spatial resolution of the technique, leading to an underestimation of uptake in small residual tumours. Finally, it may not be possible to make accurate assessments on hypometabolic tumours. Uptake of ^{18}F-FDG is related to both the proliferative activity and the number of viable tumor cells. Lower ^{18}F-FDG uptake and sometimes false-negative PET studies are more frequently observed in well differentiated, slowly proliferating tumours, such as prostate cancer, even when metastatic [60] or low grade NHL [61].

3. Perspectives

Many studies have documented the high accuracy of ^{18}F-FDG PET for the detection and staging of malignant tumours and for the monitoring of therapy results in these patients. However, as recently discussed in this journal by Laking and colleagues [62], it is very important to prove the impact of PET on patient outcome and to show cost-effectiveness from the societal viewpoint. Providing this kind of evidence is difficult, time-consuming and costly. PET is clearly more expensive than most other imaging techniques. In order to modify the daily practice of clinical oncology, it has to demonstrate its capability to either favourably alter patient management or constitute an economically viable alternative to other tumour assessment strategies. Through better selection of the most appropriate management, the ultimate goal should be to increase survival in subgroups of patients (for instance, operability of NSCLC or liver metastases) or to improve their quality of life. Establishing new reference standards with functional criteria will require some changes in our approach to technology assessment. Oncologists need to take an increased interest in functional imaging research, as they have primary expertise in the development and use of treatments modifying cell and tissue function. At this time, most published data present only a retrospective evaluation of management and cost impact. Decision models cannot be any better than the data that go into them. Only randomised controlled trials are able to detect sources of bias. The place of PET has to be defined in carefully designed algorithms adapted to each clinical situation and supported by prospective cost-effectiveness studies whenever these are clinically and ethically feasible.

The limitations of ^{18}F-FDG PET have to be pointed out. ^{18}F-FDG is not a tumour-specific agent. Causes of normal variants and benign diseases that may mimic more serious disorders have been reviewed [63]. High ^{18}F-FDG uptake is observed in macrophages and other inflammatory cells. Appropriate selection, referral and timing of scans in defined clinical situations, along with knowledge of the potential pitfalls, will lead to a reduction in interpretation errors. PET scans also need to be interpreted in conjunction with a pertinent clinical history to help minimise the number of false-positive studies. Other tracers designed to evaluate amino acid uptake, protein synthesis (FET: fluor-18-fluoroethyltyrosine, FMT: fluor-18-alphamethyltyrosine) or DNA synthesis and proliferation (FLT: fluor-18-fluorothymidine) have been proposed as tumour imaging agents. Research is ongoing to develop new tracers that target specific biological properties of cancer cells. Oncological research aims at more specific tumour targeting and improvements in the delivery and scheduling of anticancer therapies. As PET is able to quantitatively assess biochemical and physiological processes *in vivo*, it may contribute to select the best treatment for an individual patient and to objectively assess response early after the start of this treatment.

Another exciting development is the emergence of combined PET/CT devices. They allow simultaneous assessment of anatomical informations obtained from CT and functional data from PET. Anatomical landmarks provided by CT will greatly facilitate the assignment of biological abnormalities to anatomical structures, thereby improving the specificity of the test. For example, the accurate localisation of involved lymph nodes will further facilitate staging.

4. Conclusions

There is a bright future for PET in oncology. PET is very promising in many clinical situations, such as the diagnosis of pulmonary nodules, staging of lung cancer, end of treatment evaluation in lymphoma and restaging of a suspected relapse of colon cancer. However, further prospective studies of cost-effectiveness are clearly needed that would permit the optimal use of limited resources available for technology assessment. PET does not replace other imaging modalities such as CT, but seems to be very helpful in specific situations in which CT has known limitations, such as differentiation of benign from malignant lymph nodes or other lesions, differentiation of residual tumour from scar tissue,

detection of unsuspected distant metastases and monitoring of therapy results. In the future, PET may have a major impact on the practice of oncology by selecting and monitoring the most appropriate treatment for an individual patient.

References

1. Jerusalem G, Hustinx R, Beguin Y, Fillet G. The value of positron emission tomography (PET) imaging in disease staging and therapy assessment. *Ann Oncol* 2002, **13**(Suppl. 4), 227–234.
2. Gluecker TM, Fletcher JG. CT colonography (virtual colonoscopy) for the detection of colorectal polyps and neoplasms. current status and future developments. *Eur J Cancer* 2002, **38**, 2070–2078.
3. Miles KA. Functional computed tomography in oncology. *Eur J Cancer* 2002, **38**, 2079–2084.
4. Griffiths JR, Tate AR, Howe FA, Stubbs M. Magnetic resonance spectroscopy of cancer—practicalities of multi-centre trials and early results in non-Hodgkin's lymphoma. *Eur J Cancer* 2002, **38**, 2085–2093.
5. Blomley MJ, Eckersley RJ. Functional ultrasound methods in oncological imaging. *Eur J Cancer* 2002, **38**, 2108–2115.
6. Padhani AR. Functional MRI for anticancer therapy assessment. *Eur J Cancer* 2002, **38**, 2116–2127.
7. Evans JW, Peters AM. Gamma camera imaging in malignancy. *Eur J Cancer* 2002, **38**, 2157–2172.
8. Gupta N, Price PM, Aboagye EO. PET for in vivo pharmacokinetic and pharmacodynamic measurements. *Eur J Cancer* 2002, **38**, 2094–2107.
9. Blasberg R. PET imaging of gene expression. *Eur J Cancer* 2002, **38**, 2137–2146.
10. Gallagher BM, Fowler JS, Gutterson NI, *et al*. Metabolic trapping as a principle of radiopharmaceutical design: some factors resposible for the biodistribution of [18F] 2-deoxy-2-fluoro-D-glucose. *J Nucl Med* 1978, **19**, 1154–1161.
11. Yasuda S, Ide M, Fujii H, *et al*. Application of positron emission tomography imaging to cancer screening. *Br J Cancer* 2000, **83**, 1607–1611.
12. Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA* 2001, **285**, 914–924.
13. Gambhir SS, Shepherd JE, Shah BD, *et al*. Analytical decision model for the cost-effective management of solitary pulmonary nodules. *J Clin Oncol* 1998, **16**, 2113–2125.
14. Sperti C, Pasquali C, Chierichetti F, *et al*. Value of 18-fluorodeoxyglucose positron emission tomography in the management of patients with cystic tumors of the pancreas. *Ann Surg* 2001, **234**, 675–680.
15. Sendler A, Avril N, Helmberger H, *et al*. Preoperative evaluation of pancreatic masses with positron emission tomography using 18F-fluorodeoxyglucose: diagnostic limitations. *World J Surg* 2000, **24**, 1121–1129.
16. Kasperk RK, Riesener KP, Wilms K, Schumpelick V. Limited value of positron emission tomography in treatment of pancreatic cancer: surgeon's view. *World J Surg* 2001, **25**, 1134–1139.
17. Kole AC, Nieweg OE, Pruim J, *et al*. Detection of unknown occult primary tumors using positron emission tomography. *Cancer* 1998, **82**, 1160–1166.
18. Aassar OS, Fischbein NJ, Caputo GR, *et al*. Metastatic head and neck cancer: role and usefulness of FDG PET in locating occult primary tumors. *Radiology* 1999, **210**, 177–181.
19. Greven KM, Keyes JW Jr, Williams DW III, McGuirt WF, Joyce WT III. Occult primary tumors of the head and neck: lack of benefit from positron emission tomography imaging with 2-[F-18]fluoro-2-deoxy-D-glucose. *Cancer* 1999, **86**, 114–118.
20. Lassen U, Daugaard G, Eigtved A, Damgaard K, Friberg L. 18F-FDG whole body positron emission tomography (PET) in patients with unknown primary tumours (UPT). *Eur J Cancer* 1999, **35**, 1076–1082.
21. Bohuslavizki KH, Klutmann S, Kroger S, *et al*. FDG PET detection of unknown primary tumors. *J Nucl Med* 2000, **41**, 816–822.
22. Rades D, Kuhnel G, Wildfang I, *et al*. Localised disease in cancer of unknown primary (CUP): the value of positron emission tomography (PET) for individual therapeutic management. *Ann Oncol* 2001, **12**, 1605–1609.
23. Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s—meta-analytic comparison of PET and CT. *Radiology* 1999, **213**, 530–536.
24. Pieterman RM, van Putten JW, Meuzelaar JJ, *et al*. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *N Engl J Med* 2000, **343**, 254–261.
25. Laking G, Price P. 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) and the staging of early lung cancer. *Thorax* 2001, **56**(Suppl. 2), ii38–ii44.
26. Gambhir SS, Hoh CK, Phelps ME, Madar I, Maddahi J. Decision tree sensitivity analysis for cost-effectiveness of FDG-PET in the staging and management of non-small-cell lung carcinoma. *J Nucl Med* 1996, **37**, 1428–1436.
27. van Tinteren H, Hoekstra OS, Smit EF, *et al*. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 2002, **359**, 1388–1393.
28. Boyer MJ, Viney R, Fulham M. A randomized trial of conventional staging (CS) in patients (pts) with stage 1 or 2 non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2002, **20**, 309a (abstr #1233).
29. Poncelet AJ, Lonneux M, Coche E, Weynand B, Noirhomme P. PET-FDG scan enhances but does not replace preoperative surgical staging in non-small cell lung carcinoma. *Eur J Cardiothorac Surg* 2001, **20**, 468–474.
30. Wagner JD, Schauwecker D, Davidson D, *et al*. Prospective study of fluorodeoxyglucose-positron emission tomography imaging of lymph node basins in melanoma patients undergoing sentinel node biopsy. *J Clin Oncol* 1999, **17**, 1508–1515.
31. Acland KM, Healy C, Calonje E, *et al*. Comparison of positron emission tomography scanning and sentinel node biopsy in the detection of micrometastases of primary cutaneous malignant melanoma. *J Clin Oncol* 2001, **19**, 2674–2678.
32. Avril N, Dose J, Janicke F, *et al*. Assessment of axillary lymph node involvement in breast cancer patients with positron emission tomography using radiolabeled 2-(fluorine-18)-fluoro-2-deoxy-D-glucose. *J Natl Cancer Inst* 1996, **88**, 1204–1209.
33. Flanagan FL, Dehdashti F, Ogunbiyi OA, Kodner IJ, Siegel BA. Utility of FDG-PET for investigating unexplained plasma CEA elevation in patients with colorectal cancer. *Ann Surg* 1998, **227**, 319–323.
34. Simo M, Lomena F, Setoain J, *et al*. FDG-PET improves the management of patients with suspected recurrence of colorectal cancer. *Nucl Med Commun* 2002, **23**, 975–982.
35. Huebner RH, Park KC, Shepherd JE, *et al*. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. *J Nucl Med* 2000, **41**, 1177–1189.
36. Strasberg SM, Dehdashti F, Siegel BA, Drebin JA, Linehan D. Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma: a prospective database study. *Ann Surg* 2001, **233**, 293–299.
37. Ruers TJ, Langenhoff BS, Neeleman N, *et al*. Value of positron emission tomography with [F-18]fluorodeoxyglucose in patients

with colorectal liver metastases: a prospective study. *J Clin Oncol* 2002, **20**, 388–395.
38. Kinkel K, Lu Y, Both M, Warren RS, Thoeni RF. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. *Radiology* 2002, **224**, 748–756.
39. Jerusalem G, Beguin Y, Fassotte MF, *et al*. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for post-treatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood* 1999, **94**, 429–433.
40. Zinzani PL, Magagnoli M, Chierichetti F, *et al*. The role of positron emission tomography (PET) in the management of lymphoma patients. *Ann Oncol* 1999, **10**, 1181–1184.
41. Spaepen K, Stroobants S, Dupont P, *et al*. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is [18F]FDG-PET a valid alternative to conventional diagnostic methods? *J Clin Oncol* 2001, **19**, 414–419.
42. de Wit M, Bohuslavizki KH, Buchert R, *et al*. 18FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's lymphoma. *Ann Oncol* 2001, **12**, 29–37.
43. Weihrauch MR, Re D, Scheidhauer K, *et al*. Thoracic positron emission tomography using (18)F-fluorodeoxyglucose for the evaluation of residual mediastinal Hodgkin disease. *Blood* 2001, **98**, 2930–2934.
44. Jerusalem G, Beguin Y. Commentary on "Positron emission tomography in lymphoma: comparison with computed tomography and gallium-67 single photon emission computed tomography". *Clin Lymphoma* 2000, **1**, 75–76.
45. Ganjoo KN, Chan RJ, Sharma M, Einhorn LH. Positron emission tomography scans in the evaluation of postchemotherapy residual masses in patients with seminoma. *J Clin Oncol* 1999, **17**, 3457–3460.
46. De Santis M, Bokemeyer C, Becherer A, *et al*. Predictive impact of 2-18fluoro-2-deoxy-D-glucose positron emission tomography for residual postchemotherapy masses in patients with bulky seminoma. *J Clin Oncol* 2001, **19**, 3740–3744.
47. Kollmannsberger C, Oechsle K, Dohmen BM, *et al*. Prospective comparison of [18F]fluorodeoxyglucose positron emission tomography with conventional assessment by computed tomography scans and serum tumor markers for the evaluation of residual masses in patients with nonseminomatous germ cell carcinoma. *Cancer* 2002, **94**, 2353–2362.
48. Schechter NR, Gillenwater AM, Byers RM, *et al*. Can positron emission tomography improve the quality of care for head-and-neck cancer patients? *Int J Radiat Oncol Biol Phys* 2001, **51**, 4–9.
49. Lonneux M, Lawson G, Ide C, *et al*. Positron emission tomography with fluorodeoxyglucose for suspected head and neck tumor recurrence in the symptomatic patient. *Laryngoscope* 2000, **110**, 1493–1497.
50. Ogawa T, Kanno I, Shishido F, *et al*. Clinical value of PET with 18F-fluorodeoxyglucose and L-methyl-11C-methionine for diagnosis of recurrent brain tumor and radiation injury. *Acta Radiol* 1991, **22**, 197–202.
51. Jerusalem G, Beguin Y, Fassotte MF, *et al*. Early detection of relapse by whole-body positron emission tomography (PET) in the follow-up of patients with Hodgkin's disease (HD). *Ann Oncol* 2003, **14**, 123–130.
52. Tyler DS, Onaitis M, Kherani A, *et al*. Positron emission tomography scanning in malignant melanoma. *Cancer* 2000, **89**, 1019–1025.
53. Mijnhout GS, Hoekstra OS, van Tulder MW, Teule GJ, Deville WL. Systematic review of the diagnostic accuracy of (18)F-fluorodeoxyglucose positron emission tomography in melanoma patients. *Cancer* 2001, **91**, 1530–1542.
54. Hoekstra CJ, Hoekstra OS, Stroobants SG, *et al*. Methods to monitor response to chemotherapy in non-small cell lung cancer with 18F-FDG PET. *J Nucl Med* 2002, **43**, 1304–1309.
55. Ahuja V, Coleman RE, Herndon J, Patz Jr EF. The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with non small cell lung carcinoma. *Cancer* 1998, **83**, 918–924.
56. Vansteenkiste JF, Stroobants SG, Dupont PJ, *et al*. Prognostic importance of the standardized uptake value on (18)F-fluoro-2-deoxy-glucose-positron emission tomography scan in non-small-cell lung cancer: an analysis of 125 cases. Leuven Lung Cancer Group. *J Clin Oncol* 1999, **17**, 3201–3206.
57. Jerusalem G, Beguin Y, Fassotte MF, *et al*. Persistent tumor 18F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma. *Haematologica* 2000, **85**, 613–618.
58. Jerusalem G, Beguin Y, Fassotte MF, *et al*. [Early treatment evaluation by positron emission tomography]. *Med Hyg* 2000, **58**, 1629–1632, [in French].
59. Young H, Baum R, Cremerius U, *et al*. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer* 1999, **35**, 1773–1782.
60. Shreve PD, Grossman HB, Gross MD, Wahl RL. Metastatic prostate cancer: initial findings of PET with 2-deoxy-2-[F-18]fluoro-D-glucose. *Radiology* 1996, **199**, 751–756.
61. Jerusalem G, Beguin Y, Najjar F, *et al*. Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) for the staging of low grade non-Hodgkin's lymphoma (NHL). *Ann Oncol* 2001, **12**, 825–830.
62. Laking GR, Price PM, Sculpher MJ. Assessment of the technology for functional imaging in cancer. *Eur J Cancer* 2002, **38**, 2194–2199.
63. Cook GJ, Fogelman I, Maisey MN. Normal physiological and benign pathological variants of 18-fluoro-2-deoxyglucose positron-emission tomography scanning: potential for error in interpretation. *Semin Nucl Med* 1996, **26**, 308–314.