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Position Paper

Measurement of Clinical and Subclinical Tumour Response Using [18F]-fluorodeoxyglucose and Positron Emission Tomography: Review and 1999 EORTC Recommendations

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[18F]-fluorodeoxyglucose ([18F]-FDG) uptake is enhanced in most malignant tumours which in turn can be measured using positron emission tomography (PET). A number of small clinical trials have indicated that quantification of the change in tumour [18F]-FDG uptake may provide an early, sensitive, pharmacodynamic marker of the tumoricidal effect of anticancer drugs. This may allow for the introduction of subclinical response for anticancer drug evaluation in early clinical trials and improvements in patient management. For comparison of results from smaller clinical trials and larger-scale multicentre trials a consensus is desirable for: (i) common measurement criteria; and (ii) reporting of alterations in [18F]-FDG uptake with treatment. This paper summarises the current status of the technique and recommendations on the measurement of [18F]-FDG uptake for tumour response monitoring from a consensus meeting of the European Organization for Research and Treatment of Cancer (EORTC) PET study group held in Brussels in February 1998 and confirmed at a subsequent meeting in March 1999.

Key words: medical oncology, positron emission tomography, drug evaluation, fluorodeoxyglucose
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INTRODUCTION

[18F]-Fluorodeoxyglucose ([18F]-FDG), a glucose analogue, demonstrates enhanced uptake in the majority of malignant tumours due to increased transport and fixation as [18F]-FDG-6-phosphate by hexokinase [1–4]. [18F]-FDG-6-phosphate is effectively 'trapped' as it is not a substrate for the subsequent enzymatically driven pathways for glucose and the rate of dephosphorylation is slow (Figure 1). The enhanced uptake is used for diagnosis, staging and detection of residual/recurrent cancer within diagnostic nuclear medicine. Increased tumour [18F]-FDG uptake as measured by positron emission tomography (PET), although a function of proliferative activity [5, 6], is also broadly related to viable tumour cell number [7, 8]. If [18F]-FDG uptake is representative of tumour cell viability, then reduction in [18F]-FDG uptake with effective tumour therapy should reflect the tumour cell killing rate. A number of small clinical trials have indicated that quantification of changes in [18F]-FDG uptake may provide an early and sensitive pharmacodynamic marker of the tumoricidal effect of antiproliferative chemotherapy drugs. [18F]-FDG PET may have a role in improved monitoring of tumour response to anticancer drugs at a clinical

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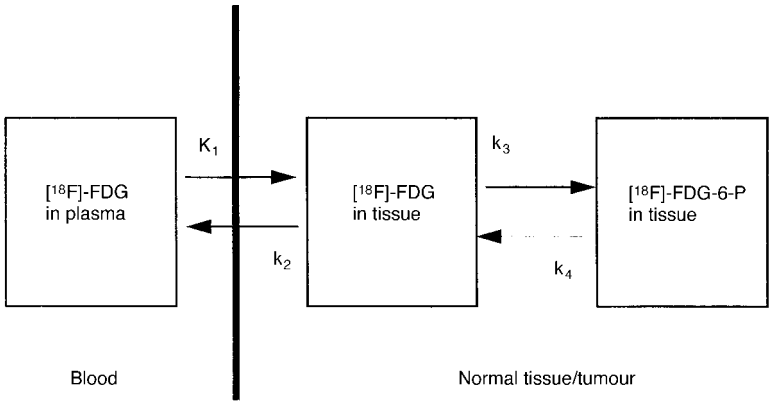

Figure 1. Diagram showing the uptake and metabolism of [^{18}F]-Fluorodeoxyglucose in normal tissue and tumour. The rate constants K_1, k_2, k_3 and k_4 are determined using kinetic modelling and define delivery, washout, fixation by hexokinase and dephosphorylation respectively.

and subclinical level as previously described by the European Organization for Research and Treatment of Cancer (EORTC) PET study group [9]. This may provide better and earlier assessment of chemotherapy drug efficacy in clinical trials and patient management. The methods of measurement of [^{18}F]-FDG uptake are, however, currently diverse and timing with respect to chemotherapy variable.

The EORTC PET study group held a consensus meeting in February 1998 to review the current status of the technique. This was updated at a meeting during the EORTC strategy meeting in March 1999. The group were able to make initial recommendations for a common measurement standard and criteria for reporting alterations in [^{18}F]-FDG uptake to assess clinical and subclinical response. These recommendations, based on presently available data, are not intended to have implications for regulatory authorities but rather to provide a common framework for data comparison. These recommendations will be subject to review on a three yearly cycle as these data mature. The group emphasised the multidisplinary nature of measuring and interpreting [^{18}F]-FDG tumour uptake and actively encourages the full participation of the oncologist.

MATERIALS AND METHODS

A number of methods have been used to assess tumour [^{18}F]-FDG uptake (Table 1) and can be divided into two categories: (i) assessment of [^{18}F]-FDG accumulated at the time of measurement using visual interpretation and semiquantitative indices; and (ii) assessment of the rate of [^{18}F]-FDG uptake over the measurement time using a kinetic approach.

Visual interpretation and semiquantitative indices

The underlying assumptions for visual and semiquantitative indices are that [^{18}F]-FDG uptake is virtually complete and that dephosphorylation of [^{18}F]-FDG-6-phosphate is negligible at the time of measurement. Static or whole-body images may be used for this type of assessment. Static images are a snapshot of the dynamic process of [^{18}F]-FDG metabolism. Static images over a single scanning position are usually corrected for the effects of attenuation using a separate transmission scan. Whole-body images are acquired at multiple axial positions to provide greater axial coverage. These images are usually of lower statistical quality (shorter scan duration) and are not generally corrected for attenuation.

Table 1. *Comparison of advantages and disadvantages of different approaches to methods of interpreting* [^{18}F]*-FDG uptake in tumours*

Method	Advantages	Disadvantages
Visual	Static/whole body image No blood sampling	Non-quantitative Dependence on: Uptake time Glucose levels Partial volume effects
Standardised uptake value (SUV)	Static/whole body image Semiquantitative No blood sampling Computation easy	Dependence on: Uptake time Glucose levels Body weight Partial volume effects
Kinetic analysis	Dynamic data acquisition Quantitative Less dependence on uptake time	Dependence on: Partial volume effects Arterial blood sampling/surrogate input function Computation more complex

Visual and SUV analysis give an assessment of the amount of [^{18}F]-FDG accumulated within the tumour at the time of measurement. Kinetic methods give an assessment of the rate of [^{18}F]-FDG uptake over the time of measurement.

Apparent [18F]-FDG uptake will vary with depth of the tumour in the body and type of surrounding tissue in the absence of attenuation correction. Visual assessment is based on changes in contrast between the tumour and the immediately surrounding tissue.

For attenuation-corrected, quantitative PET images the tissue radiotracer concentration can be measured. The standardised uptake value (SUV), also referred to as the differential uptake ratio (DUR) and differential absorption ratio (DAR), has been widely used for tumour [18F]-FDG uptake assessment. The tumour radiotracer concentration (Q [MBq/l]) is then normalised by division by injected activity (Q_{inj} [MBq]) and multiplication by body weight (W [kg]) providing a simple semi-quantitative index of [18F]-FDG uptake [10].

$$SUV_{BW} = \frac{Q \times W}{Q_{inj}}$$

The SUV_{BW} is a unitless measurement with the assumption that both tumour and other body tissues have the density of water, i.e. 1kg is equivalent to 1litre. SUV_{BW}s are positively correlated with body weight due to reduced uptake of [18F]-FDG in fat. A significant loss of body weight during therapy could affect the use of serial measurements of SUV_{BW}. Correction of SUV by body surface area (SUV_{BSM}) or lean body mass (SUV_{LBM}) reduces this dependency on body weight [11, 12]. The assumption that [18F]-FDG uptake is complete and irreversible at 60 min has not been found to be valid in all tumours, and measurements are therefore often being made during the uptake phase [2, 13]. Comparative measurements are valid if the plasma clearance of [18F]-FDG is comparable between sequential studies but this is dependent on circulating glucose levels and dietary status and requires the sampling of blood. SUV analyses in diagnostic oncology have been used to differentiate benign from malignant disease and stage tumours. The most literature is in lung cancer and this is a reimbursable application in the U.S.A. [14].

Kinetic modelling

Kinetic modelling approaches have been used to derive the metabolic rate for glucose (MR_{glu} [μmoles/min/ml]) using measurements of the time course of radioactivity in tissue (using PET) and in arterial blood (delivery of the tracer). The latter usually requires arterial catheterisation and rapid arterial blood sampling. Traditionally, MR_{glu} in the brain was determined from a static scan in conjunction with the measured arterial concentration and average population rate constants for [18F]-FDG neurological studies, the so-called 'autoradiographic' method [15, 16]. With improvements in scanner technology, it became possible to estimate rate constants in individual subjects using dynamic image acquisition from radiotracer injections [16, 17]. This may be a preferable approach for tumour imaging where both transport and phosphorylation by hexokinase are increased to differing degrees. In high grade glioma, MR_{glu} values derived using the autoradiographic approach are closely related to kinetic measurements of MR_{glu} [1]. Broader application of the method to other tumours would require the acquisition and validation of typical rate constants for other malignant tumours. Both models assume homogeneous tissue compartments which, of course, may not apply to heterogeneous tumours. Inclusion of additional parameters for blood volume and dephosphorylation within the model, although not directly used in the calculation of MR_{glu}, affect the estimated values of the other rate constants and, therefore, the magnitude of MR_{glu}. The rate constants (K_1 [ml/min/ml], k_2 & k_3, [/min]) are related to glucose metabolism by the lumped constant (LC) using the circulating glucose level (C_{glu}, [μmoles/ml]). The lumped constant relates the different affinities of FDG and glucose for transport and phosphorylation. The metabolic rate for glucose (MR_{glu} [μmoles/min/ml]) is given by:

$$MR_{glu} = \frac{C_{glu}}{LC} \times \frac{K_1 k_3}{(k_2 + k_3)} = \frac{C_{glu}}{LC} \times K_i$$

Patlak analysis may be used to linearise the mathematical solution for radiotracers which are irreversibly 'trapped' simplifying computation of the influx rate constant (K_i [ml/min/ml]) [18]. Computation of the influx rate constant assumes that effective equilibrium between tissue precursor pools and plasma has been achieved and the rate of dephosphorylation is assumed to be zero. This method is less sensitive to noise in the PET data and can be used for pixel by pixel analysis of PET images.

Factors affecting measurements of tumour MR_{glu} include heterogeneity resulting in tumour elements with different [18F]-FDG kinetics contributing to the PET signal. Lack of equilibrium between the tissue precursor pools and the arterial plasma can result in underestimation of k_2 and k_3 and non-linearity of Patlak plots. An acquisition time of 60–120 min for normal brain reduces errors due to heterogeneity to acceptable levels [19, 20]. Inclusion of k_4 results in improved model fits for the normal brain [21] however, this has also been attributed to heterogeneity [21]. Values for the lumped constant have been historically determined for normal brain and vary significantly for tumours. Recent measurements of the lumped constant for glioma have resulted in values greater than one [22]. The lumped constant is often set to one for tumour evaluation in the absence of a measured value. Measurements using kinetic methods are dependent on the model formulation [21] and to a much lesser degree on the time of measurement. For all the kinetic methods, monitoring of the arterial [18F]-FDG plasma concentration can be a burden to both the operator and patient. Various approaches have been used to provide a surrogate for this, including: arterialised-venous sampling, measuring the arterial radiotracer concentration using the left ventricle (if it is in the imaging field of view) and a population estimate of the input function shape scaled using a single or small number of blood samples.

Comparison of methods

SUVs and metabolic rates for [18F]-FDG, derived for diagnostic tumour imaging, are correlated with coefficients of 0.91 [23] and 0.84 [24]. This correlation is improved when the SUV is normalised using patient body surface area rather than weight. Both measurements have been used successfully to assess alterations in tumour [18F]-FDG uptake with chemotherapy. One report has assessed both the SUV_{BW} and influx rate constant to measure alterations in [18F]-FDG uptake with chemohormonotherapy in primary breast cancer. A reduction in SUV_{BW} in responding subjects was accompanied by comparable or greater decreases in the influx rate constant derived using Patlak analysis [2]. Measurement of

the influx rate constant may prove to be more sensitive than the SUV_{BW} for assessing alterations in [^{18}F]-FDG uptake, although this was not a conclusion drawn by the authors in their paper. This warrants further evaluation, particularly in the context of measurement of subclinical response, where alterations in tumour [^{18}F]-FDG uptake in responding patients may be small.

Other factors which can affect [^{18}F]-FDG uptake measurement

The precision and accuracy of [^{18}F]-FDG uptake measurements depend on the performance characteristics of the PET scanner, scan duration, measurement of injected activity and, for kinetic analysis, the measurement of arterial radiotracer concentration. All methods of quantification may be affected by partial volume which is a function of the scanner resolution, range 6 mm–1.2 cm for a typical PET scanner. A tumour with dimensions less than two times the resolution of the scanner, will have a reduced apparent [^{18}F]-FDG concentration. Partial volume correction has been shown to improve the diagnostic accuracy of SUV measurements [25]. The methods employed usually use phantom measurements and assume that tumours have a spherical or ellipsoid geometry. In the absence of partial volume correction for smaller tumours quantification of SUV or MR_{glu} will be underestimated.

The definition of tumour region to be sampled on the PET image, 'region of interest' (ROI), will affect the value of SUV and MR_{glu}. Tumours are heterogeneous and contain non-tumour elements, including fibrotic, necrotic and cystic regions. Total tumour volume and the distribution of viable tumour may change over the time course of serial scanning for response assessment. This becomes more likely as the period between the pretreatment and post-treatment scan is extended. ROI definition on subsequent scans may be further compromised by alteration of the patient position, the location of the tumour in relation to internal organs and the paucity of anatomical detail on [^{18}F]-FDG PET scans.

Circulating glucose levels have an impact on tumour [^{18}F]-FDG uptake [26] and uptake is enhanced in the fasting state. There is little difference between circulating glucose levels for overnight fasting and shorter fasting periods [26–28]. Furthermore, circulating glucose levels are elevated in patients with diabetes mellitus in the fasting state and this reduces [^{18}F]-FDG tumour uptake. In pancreatic cancer where the diabetic condition is common it has been identified as the main limitation for accurate tumour visualisation with PET [29]. Insulin may be used to manipulate circulating glucose levels, however, this requires careful patient monitoring and may decrease tumour to normal tissue contrast due to increased [^{18}F]-FDG uptake in striated and smooth muscle. Normalisation of SUV_{BW} for circulating glucose levels corrects for differences between fasted and glucose loaded study groups, although considerable changes in individual patterns remained with SUV_{BW}s [27]. Under euglycaemic conditions (<6.5 mmol/l), SUV_{BW} was not related to circulating glucose levels [23]. However, correction of SUV_{BSA} for circulating glucose levels improves the correlation with MR_{glu} [24]. Various drugs, including steroids, have been shown to affect cerebral uptake of [^{18}F]-FDG. Chronic administration of dexamethasone reduces cerebral uptake of [^{18}F]-FDG [30]. A recent study has reported that brain tumour glucose metabolism is not affected by dexamethasone (4–32 mg/day) [31].

REVIEW OF CLINICAL STUDIES

Reduction in [^{18}F]-FDG uptake with effective chemotherapy may provide an early marker of response at a clinical and subclinical level. Figure 2 is a hypothetical illustration of how alterations in [^{18}F]-FDG uptake may be related to clinical outcome. An assessment of changes in tumour [^{18}F]-FDG uptake with chemotherapy was undertaken through review of published papers, including those of members of the EORTC PET study group, and discussion at the February 1998 meeting. The current imaging strategy is to acquire a pretreatment PET scan and a subsequent scan at some point during the treatment schedule or soon after the completion of treatment. Given the different chemosensitivities of tumours, tumour heterogeneity, modes of drug action and scheduling it would be difficult to define an optimum scan time in absolute terms. Surveying the current clinical data does, however, give an indication of an appropriate scanning window of opportunity and alterations in tumour [^{18}F]-FDG uptake which can be expected with chemotherapy (Table 2). A review of the relationship between [^{18}F]-FDG uptake and response is presented for various tumour categories below.

Alterations in MR_{glu} in malignant glioma have been assessed using the autoradiographic model with arterialised-venous sampling. There was no definitive relationship between changes in MR_{glu} (−16.7% to +65%) and clinical outcome 1–7 days after intra-arterial chemotherapy with a nitrosourea derivative ($n=10$) [32]. Subjects had been previously treated with a variable number of cycles of nitrosourea. MR_{glu} increased by 20–100% above baseline levels at 24 h and decreased to between 22% above and 24% below baseline levels at 30 days after combination chemotherapy ($n=6$) for tumour to contralateral brain MR_{glu} ratios [33]. All subjects were clinically stable or improved slightly during the time they were studied. [^{18}F]-FDG–PET performed within 24 h of administration of carmustine showed variable changes in tumour MR_{glu}, with increased uptake possibly predicting a longer survival ($n=10$) [34]. A reduction in MR_{glu} of 31% to 67% has been demonstrated within one month of completion of combination chemotherapy and radiotherapy. Computed tomography (CT) scan assessment in comparison only showed slight to moderate morphological changes, although all subjects ($n=7$) showed clinical improvement [35]. In high

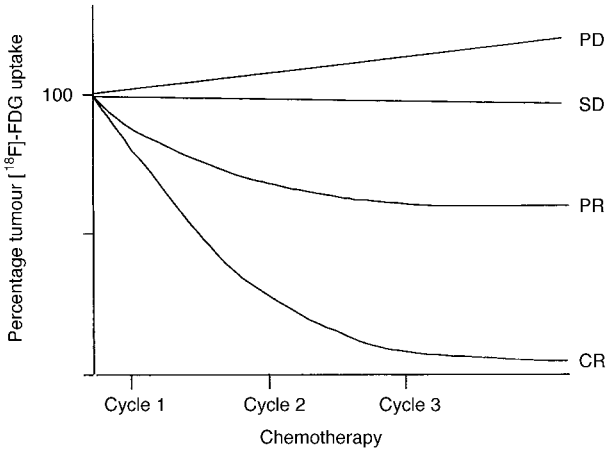

Figure 2. Hypothetical illustration of how tumour [^{18}F]-FDG uptake may be related to clinical outcome. PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response [9].

grade astrocytoma ($n = 8$) a decrease in tumour MR_{glu} of greater than 25%, 7–14 days after a single cycle of chemotherapy (temozolomide) corresponded with partial response assessed after two cycles of treatment as clinical improvement and a reduction in size [36]. One patient pretreated with temozolomide showed no change in MR_{glu} but had a measurable response after five cycles of treatment. This study used dynamic image acquisition with continuous measurement of the arterial radiotracer concentration to measure MR_{glu}. In medulloblastoma ($n = 5$) and neuroectodermal tumour ($n = 2$) receiving high-dose polychemotherapy [18F]-FDG-PET scans were performed before treatment and at

Table 2. Alterations in [18F]*-FDG tumour uptake with chemotherapy for studies reviewed in this paper with method of quantification, scan time and conventional response assessment*

		[18F]-FDG PET			Clinical response assessment		
Tumour [Ref.]	Chemotherapy	Method	Time	% Change	Method	Time	Response
Glioma ($n = 7$) [35]	Radiotherapy + combination chemotherapy	MR_{glu}	24 ± 13 days after completion	− 31 to − 67	Clinical	After therapy	Improved
Glioma ($n = 10$) [32]	Nitrosourea	MR_{glu}	1–7 days variable no of cycles	− 16.7 to + 65	Clinical	4–68 weeks	Variable
Glioma ($n = 5$) [33]	Multidrug chemotherapy	MR_{glu}	1 day after one cycle	+ 20 to + 100	Clinically	Stable during study	
			7–10 days after 1 cycle	+ 6 to + 14			
			30 days after 1 cycle	− 24 to + 22			Greatest decrease in [18F]-FDG corresponded with radiological response
Glioma ($n = 10$) [34]	Carmustine	MR_{glu}	24 h after one cycle	− 25 to + 49			Increased uptake correlated with patient survival
Glioma ($n = 8$) [36]	Temozolomide	MR_{glu}	7–14 days after one cycle	< 25	Clinical CT	8 weeks	PD/SD size increase
				> 25	Clinical CT	8 weeks	PR size decrease
Medulloblastoma ($n = 7$) [37]	Combination chemotherapy	MR_{glu}	After one/two cycles	− 40 to − 66			Remission/new metastases
				25 to − 36			died
Head and neck ($n = 11$) [38]	Cisplatin and 5-fluorouracil (5-FU)	SUV	1 week after first cycle	∼ − 22	CT volume		Decrease
				∼ + 1	CT volume		Increase
Breast cancer ($n = 11$) [2]	Hormone chemotherapy	SUV	Day 8	∼ − 22	Mammography	Cycle 9	Response PR/CR
			End cycle 1	∼ − 32	Biopsy	Cycle 9	PR/CR
			End cycle 2	∼ − 40			
			End cycle 3	∼48			
		MR_{glu}	Day 8	∼ − 24			
			End cycle 1	∼ − 42			
			End cycle 2	∼ − 47			
			End cycle 3	∼ − 53			PD
			No significant alteration in [18F]-FDG uptake				
Breast cancer ($n = 8$) [39]	Multidrug chemotherapy	SUV	One cycle	No uptake to + 25%	CT	Cycle 3/4	PR
			2/3 cycles	No uptake to − 20%	CT	Cycle 3/4	PR
Colorectal liver metastases] ($n = 18$) [40]	Protracted 5-FU ± interferon	SUV	1–2 weeks	∼ − 10	CT	8 weeks	PD
			4–5 weeks	∼ − 17			
			1–2 weeks	∼ − 9	CT	8 weeks	PR
			4–5 weeks	∼ − 30			

PD, progressive disease; PR, partial response; CR, complete response; SD, stable disease; MR_{glu}, metabolic rate for glucose; SUV, standardised uptake value; CT, computed tomography.

various points in the cycle. There was a tendency to longer remission in children with a larger reduction in MR_{glu} [37].

In head and neck cancer ($n = 11$) [^{18}F]-FDG uptake was assessed using SUV_{BW}s, pretreatment and 1 week after the first chemotherapeutic cycle of cisplatin and 5-fluorouracil (5-Fu) [38]. Alterations in [^{18}F]-FDG uptake were highly correlated with estimates of tumour growth rate from volumetric CT measurements. Pretreatment SUV was 3.6 ± 1.3 and post-treatment was 2.8 ± 0.8 for the group showing a reduction in tumour growth rate, representing an overall decrease of approximately 22%. Increased (Table 2) and in one case a reduced (11%) tumour [^{18}F]-FDG uptake (data not shown) was associated with tumour growth.

For primary breast cancer ($n = 11$) treated with hormonochemotherapy, [^{18}F]-FDG-PET scans were performed pretreatment, at day 8 after initial hormone and chemotherapy, after one cycle (day 21), two cycles (day 42) and three cycles (day 63) [2]. 4 subjects achieved complete response, 4 achieved partial response and 3 did not respond according to mammography criteria, although 2 showed some tumour shrinkage. Tumour [^{18}F]-FDG uptake measured using SUV_{BW}s was $68 \pm 8\%$ ($P < 0.025$) of pretreatment values after the first full cycle (21 days) of treatment and $52 \pm 4\%$ after the third cycle (63 days) of treatment in responding subjects. The net influx rate constant (K_i) was 58% after one cycle and 53% after three cycles of chemotherapy for the same subject group. Reduction in SUV paralleled reductions in both K_i and k_3, but k_3 was more variable. No significant alteration in [^{18}F]-FDG uptake was demonstrated for the non-responding patient group. There was no significant alteration in tumour size during the period of the PET measurements.

In locally advanced cancer or metastatic breast cancer ($n = 8$), [^{18}F]-FDG uptake was evaluated in four primary tumours and seven metastatic lesions [39]. Seven lesions were classified as partial response, 2 as complete response and 1 as progressive disease by computed tomography (CT) measurement after the third or fourth chemotherapy course. [^{18}F]-FDG PET scans were performed pretreatment, 6–13 days after the first cycle and 4–14 days after the third cycle of polychemotherapy. Summarising the data presented in this report, [^{18}F]-FDG uptake was approximately 92% after the first cycle and 44% after the third/fourth cycle of baseline SUV_{BW} values. In this case where the tumour was no longer detected on PET the decrease in uptake was assumed to be 100%. One patient who later responded to therapy had increased [^{18}F]-FDG uptake after the first cycle of treatment.

In liver metastases from colorectal cancer (18 subjects, 27 tumours) [^{18}F]-FDG-PET scans were performed pretreatment, 1–2 and 4–5 weeks into protracted infusion of 5 FU ± interferon [40]. [^{18}F]-FDG uptake quantified using SUV_{BW} was 91% at 1–2 weeks and 69% at 4–5 weeks of pretreatment values in responding tumours. Reduction in [^{18}F]-FDG uptake was not significantly different between the responding and non-responding groups at 1–2 weeks.

In lymphoma ($n = 11$), imaged using [^{18}F]-FDG with gamma camera scintigraphy, [^{18}F]-FDG uptake was reduced to normal tissue levels after two courses in subjects achieving complete remission. High uptake reflected treatment failure and intermediate uptake was associated with variable outcome [41]. Similar results have been obtained at other centres [42].

In germ cell tumours, seminoma ($n = 2$) and malignant teratoma ($n = 3$) treated with single-agent therapy, carboplatin or combination therapy, a reduction in [^{18}F]-FDG uptake, measured using tumour to normal tissue ratios at 2–4 weeks, corresponded with the response measured on CT at the end of therapy [43].

In locally advanced soft tissue sarcoma ($n = 20$), patients who were treated with hyperthermic isolated limb perfusion and a cocktail of rTNF-alpha, rTNF-gamma and melphalan, it was shown that the pretreatment [^{18}FDG] uptake was predictive of the probability of achieving remission [44]. However, the lack of changes in [^{18}FDG] uptake on the post-treatment scan precluded the ability to distinguish between partial and complete response. Uptake was seen in a rim of tissue which on histological examination consisted of pseudocapsule and inflammatory tissue and may have been a confounding factor in signal interpretation.

Owing to the existence of factors which can confound the measurement of [^{18}F]-FDG, care is necessary in data interpretation. For instance, radiotherapy may cause an inflammatory response, particularly in the mucosa, and [^{18}F]-FDG uptake associated with activated macrophages and neutrophils may confound signal interpretation. In colorectal cancer treated with external beam and neutron therapy, a reduction in [^{18}F]-FDG uptake measured using SUV_{BW} values was seen in only 50% of subjects despite good palliative results in the whole cohort [45]. This was attributed to [^{18}F]-FDG uptake in activated white cells involved in an inflammatory response. In glioma and head and neck tumours, a reduction in [^{18}F]-FDG uptake has been correlated with response to radiotherapy [46, 47] and inflammatory changes would not appear to be a confounding factor in these studies.

The time between treatment and imaging is also important with regard to data interpretation. For example, tumour [^{18}F]-FDG uptake was increased in high grade glioma when PET studies were performed within 24 h of chemotherapy administration [33, 34]. This would appear to be a transient phenomenon since studies performed 7–14 days after initiation of chemotherapy showed a reduction in tumour [^{18}F]-FDG uptake in responding tumours [2, 30, 36]. This early 'flare' phenomenon may have prognostic significance, however, it would be a confounding factor in studies specifically designed to detect reduction in tumour [^{18}F]-FDG uptake as a measure of clinical and subclinical response to chemotherapy. In testicular tumours there is also evidence of a transitory reduction in [^{18}F]-FDG uptake up to 2 weeks postchemotherapy resulting in false-negative results for imaging residual tumour [48].

Summarising, a mean reduction in [^{18}F]-FDG SUV with effective chemotherapy, across tumour types and chemotherapeutic schedules was seen for responding patients [2, 38–40] (Figure 3). A reduction of 10–30% was seen in the SUV_{BW} value after one cycle of chemotherapy in patients responding to treatment. This increased to 40–50% after three cycles or at the end of treatment. A reduction of 25% in MR_{glu} in high grade glioma [35] and 42% in the influx rate constant for breast cancer [2] were seen after one cycle of chemotherapy. Early reduction in [^{18}F]-FDG uptake probably occurs prior to tumour shrinkage and appears indicative of the level of change one would expect for subclinical response and this may be useful in a phase I setting [9]. A reduction of [^{18}F]-FDG uptake of 15–20% may be significant in this context

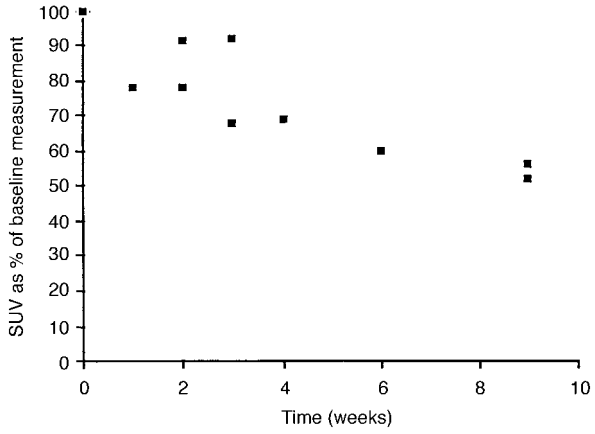

Figure 3. SUV as a percentage of the baseline measurement plotted against time (weeks) for responding tumours, different chemotherapy regimes and tumour types [2, 38–40].

depending on the precision of measurement. In terms of clinical response a reduction of greater than 25% was seen at some time point in the treatment of responding tumours in terms of the SUV, with measurement becoming more reliable after two or three cycles of chemotherapy. None of the studies reported a significant reduction in [18F]-FDG uptake in non-responding tumours.

DISCUSSION AND RECOMMENDATIONS

Patient preparation

Attention to patient preparation improves the quality of [18F]-FDG imaging of tumours. The recommendations of the EORTC PET study group were:

1. Patients should be fasted for oncology studies in order to enhance and standardise tumour [18F]-FDG uptake. For scans performed in the morning, overnight fasting is recommended. For studies performed in the afternoon, a light breakfast followed by a 6-h fast is recommended. Circulating glucose levels should be measured prior to administration of [18F]-FDG using a venous blood sample. Levels of 4–7 mmol/l can be expected in the fasting patient. There was no agreement as to the optimal procedure for adjusting glucose levels in hyperglycaemic patients.
2. In type I diabetes resulting from insulin deficiency, scanning in the morning after an overnight fast would be appropriate. In type II diabetes, insulin may be administered at the discretion of the clinician and its use should be documented.
3. Good hydration is required as the primary route of excretion for [18F]-FDG is renal. For examinations in the pelvis or kidney region, 20–40 mg frusemide may be administered within 10 min of the [18F]-FDG injection. All subjects should be well hydrated and should, where feasible, drink 500 ml of water after injection.
4. A record of the patient's medication should be kept as medication may affect [18F]-FDG uptake. These data may be reviewed in the future by the EORTC PET study group to assess drug interaction with tumour and normal tissue [18F]-FDG uptake.
5. Diazepam may be used at the discretion of the clinician to encourage muscle relaxation and reduce muscular uptake. This is of particular importance for examination in the head and neck region, where enhanced [18F]-FDG uptake is common in the muscles of the neck. Diazepam administration should be documented.

Timing of [18F]-FDG PET scans

The available data are not yet sufficient to define the optimal time after injection when SUV measurements could be performed or the optimal interval between scans. Therefore, the EORTC PET study group recommendations are:

1. Pretreatment and post-treatment scans should be acquired for comparison.
2. The pretreatment scan should be acquired as close as possible to the commencement of treatment (not more than 2 weeks).
3. The timing of the post-treatment scans should be tailored to the end-point under assessment, subclinical or clinical response, and the chemoresponsiveness of the tumour type.
4. A period of 1–2 weeks between completion of the chemotherapy cycle and the [18F]-FDG PET scan may avoid transient increases and decreases in tumour [18F]-FDG uptake confounding response assessment. This condition may be less appropriate to protracted infusional or oral administration protocols [39].
5. The relationship between radiotherapy and changes in tumour [18F]-FDG uptake is as yet unclear and more data are required for guidelines where this modality is under evaluation. In addition, acute inflammatory reactions, for instance in the mucosa, may result in enhanced [18F]-FDG uptake making interpretation of PET data more problematic.

Attenuation correction and dose of [18F]-FDG

It was not possible to recommend a standard dose of [18F]-FDG to be used or a standard procedure for attenuation correction. These variables were centre-dependent. It was, however, recommended that the dose of [18F]-FDG and the procedure for attenuation correction be recorded.

Methods to measure [18F]-FDG uptake

The EORTC PET study group has taken into consideration the available information on SUV and kinetic methods to assess [18F]-FDG tumour uptake. Both methods are subject to error as assumptions concerning [18F]-FDG kinetics are not fully adhered to for tumour imaging, with more assumptions being made when measurement methods are simplified, particularly concerning plasma clearance of [18F]-FDG. SUVs and MR_{glu} measurements are correlated in comparative studies for measurement of individual tumour [18F]-FDG uptake. Both methods have been successfully used to assess alterations in tumour [18F]-FDG uptake with chemotherapy. Multiple follow-up scans to monitor therapeutic response encourage a minimalist approach to scan time and invasive blood sampling to improve patient compliance, an important feature of successful clinical trials, cost-effectiveness and patient throughput on busy PET scanners. Taking all these factors into account the EORTC PET study group considered that the SUV_{BSA} should be the minimum standard of measurement but expressed caution as to its value in accurately measuring small changes in tumour [18F]-FDG uptake. It needs to be remembered however, that the numerical range of these values would be radically different

from those of conventional SUV-LBM (reduced by a factor of 50 or so). This measurement would be complemented where feasible with a kinetic approach to provide data to assess this more complicated and possibly accurate measurement approach for sensitivity and specificity for tumour response monitoring over and above that provided by the SUV. The specific recommendations of the EORTC PET study group are:

1. Measurement of [^{18}F]-FDG tumour uptake using the SUV normalised for body surface area (SUV_{BSA}, [m^2]) may be sufficient for measuring alterations in tumour [^{18}F]-FDG uptake. However, recent publications have suggested that: (i) FDG PET with kinetic analysis is better at discriminating malignant disease in germ cell tumours [49] than SUV_{LBm}; (ii) MR_{glu} is a better discriminator of subclinical response than SUV in brain tumours [50]. The static scan used to quantify tumour radiotracer concentration should be started 50–70 min after administration of [^{18}F]-FDG and be standardised for serial scans in the same subject. The SUV is calculated using the tumour radiotracer concentration (Q [MBq/l]), body surface area (BSA [m^2]) and injected activity (Q_{inj} [MBq]):

$$SUV_{BSA} = \frac{Q \times \text{BSA}}{Q_{inj}}$$

   No correction for circulating glucose levels has been incorporated into the SUV calculation as the benefit under fasting conditions remains unclear and the result will be a function of the accuracy and precision of the glucose measurement. This will be reviewed as further data become available. The body surface area is calculated from the subject's weight (W [kg]) and height (H [cm]) and an appropriate algorithm is given by [12]:

$$\text{BSA} = W^{0.425} \times H^{0.725} \times 0.00718$$

2. The Patlak approach is the kinetic approach of choice within the EORTC PET study group with dynamic image acquisition of at least 60 min duration with direct sampling of the arterial [^{18}F]-FDG concentration or an appropriate alternative for this input function. Compartmental modelling may also be useful to determine the presence of k_4 where direct sampling of the arterial [^{18}F]-FDG concentration is available.

Tumour sampling

Tumours are heterogeneous and contain non-tumour elements such as fibrosis, necrosis and oedema. ROIs sampled for response monitoring should ideally contain only viable tumour. Alterations in the pattern of tumour [^{18}F]-FDG uptake need to be taken into consideration when sampling and reporting alterations in uptake using ROI analysis. Co-registration algorithms outside the brain had not been as helpful as hoped and this was seen as a difficulty in accurately comparing scans. Thus, the specific recommendations of the EORTC PET study group are:

1. Tumour regions defined on the pretreatment scan should be drawn on the region of high [^{18}F]-FDG uptake representing viable tumour. Whole tumour uptake should also be recorded.
2. The same ROI volumes should be sampled on subsequent scans and positioned as close to the original tumour volume as possible. The way co-registration has been performed should be recorded.
3. Uptake measurements should be made for the mean and maximum tumour ROI counts per pixel per second calibrated as MBq/l.
4. Alterations in the extent of [^{18}F]-FDG uptake should be documented, i.e. increase in orthogonal tumour dimensions including the longest tumour dimension.
5. Partial volume may affect the measurement of [^{18}F]-FDG uptake. Tumour size from anatomical imaging in relation to the PET scanner resolution should be documented where possible.

Further research is required to optimise tumour sampling for response assessment to account effectively for the effects of partial volume, assess whether alterations in maximal or average tumour uptake provide better response markers and to assess the impact of alterations in tumour volume in conjunction with alterations in the magnitude of tumour [^{18}F]-FDG uptake.

Reproducibility

From the limited published [51] and unpublished data available within the EORTC PET study group, the reproducibility of tumour measurements performed on conventional PET scanners made with no intervening chemotherapy is of the order of 10–20% for ROI-based kinetic and SUV analysis. The EORTC PET study group recommends that, where possible, reproducibility data for tumour [^{18}F]-FDG measurement should be collected to assess precisely the level of change which can be measured. This is particularly relevant for the measurement of subclinical responses where small changes in [^{18}F]-FDG uptake may be significant.

Definition of [^{18}F]*-FDG tumour response*

On review of the literature, it appears that reduction in SUV or MR_{glu} after one cycle of chemotherapy (15–30%) can predict response and that this precedes tumour shrinkage and clinical response. A reduction of greater than 25% was seen at some time point in the treatment of responding tumours in terms of the SUV with the measurement becoming more reliable after two or three cycles of chemotherapy. The following EORTC 1999 criteria were proposed for reporting the results of tumour [^{18}F]-FDG measurements for clinical and subclinical response assessments:

1. Progressive metabolic disease (PMD) to be classified as an increase in [^{18}F]-FDG tumour SUV of greater than 25% within the tumour region defined on the baseline scan, visible increase in the extent of [^{18}F]-FDG tumour uptake (>20% in the longest dimension) or the appearance of new [^{18}F]-FDG uptake in metastatic lesions.
2. Stable metabolic disease (SMD) would be classified as an increase in tumour [^{18}F]-FDG SUV of less than 25% or a decrease of less than 15% and no visible increase in extent of [^{18}F]-FDG tumour uptake (>20% in the longest dimension).
3. Partial metabolic response (PMR) would be classified as a reduction of a minimum of 15–25% in tumour [^{18}F]-FDG SUV after one cycle of chemotherapy, and

greater than 25% after more than one treatment cycle. Reporting would need to be accompanied by adequate and disclosed reproducibility measurements from each centre. An empirical 25% was found to be a useful cut-off point, but there is a need for a reproducibility analysis to determine the appropriate cut-offs for statistical significance. A reduction in the extent of the tumour [18F]-FDG uptake is not a requirement for partial metabolic response.

4. Complete metabolic response (CMR) would be complete resolution of [18F]-FDG uptake within the tumour volume so that it was indistinguishable from surrounding normal tissue.

It may not be possible to make accurate assessments on hypometabolic tumours. These criteria have been derived from a number of small-scale clinical research studies and further validation as part of larger scale clinical trials in each tumour system is required. In particular, further response and reproducibility data are required to verify a minimum of 15% reduction in tumour [18F]-FDG SUV as a measure of subclinical response after one cycle of chemotherapy.

CONCLUSIONS

Monitoring tumour response with [18F]-FDG PET is in its infancy. There is a requirement for larger-scale trials together with collection of reproducibility data, to assess the technique in relation to other methods of response assessment and clinical end-points. The EORTC PET study group has proposed a common method of assessing tumour [18F]-FDG uptake and reporting of response data. This is not intended to be exclusive of other measurements, but to provide a framework for comparison between studies and centres to facilitate assessment of this technique. These recommendations will be reviewed in the year 2002. Thought still needs to be given to the broader perspective of assessing the prognostic value of [18F]-FDG PET within clinical trials.

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