CHAPTER 4

CHAPTER 4

The added value of [18F]fluor-D-deoxyglucose positron emission tomography in screening for temporal lobe epilepsy surgery.

SG Uijl

FSS Leijten

JBAM Arends

J Parra

AC van Huffelen

KGM Moons

Epilepsia 2007;48:2121-2129.

Abstract

Purpose. FDG-PET is an expensive, invasive, and not widely available technique used in the presurgical evaluation of temporal lobe epilepsy. We assessed its added value to the decision-making process in relation to other commonly used tests.

Methods. In a retrospective study of a large series of consecutive patients referred to the national Dutch epilepsy surgery program between 1996 and 2002, the contribution of FDG-PET, MRI, and video-EEG monitoring findings, alone or in combination, to the decision whether to perform surgery was investigated. The impact of FDG-PET was quantified by comparing documented decisions concerning surgery before and after FDG-PET results.

Results. Of 469 included patients, 110 (23%) underwent FDG-PET. In 78 of these patients (71%), FDG-PET findings led clinicians to change the decision they had made based on MRI and video-EEG monitoring findings. In 17% of all referred patients, the decision regarding surgical candidacy was based on FDG-PET findings. FDG-PET was most useful when previous MRI results were normal ($p<0.0001$) or did not show unilateral temporal abnormalities ($p<0.0001$), or when ictal EEG results were not consistent with MRI findings ($p<0.0001$) or videotaped seizure semiology ($p=0.027$). The positive and negative predictive values for MRI and video-EEG monitoring, which ranged from 0.48 to 0.67, were improved to 0.62 to 0.86 in combination with FDG-PET.

Conclusions. In patients referred for TLE surgery, FDG-PET findings can form the basis for deciding whether a patient is eligible for surgery, and especially when MRI or video-EEG monitoring are nonlocalizing.

Introduction

[18F]-Fluoro-D-deoxyglucose Positron Emission Tomography (FDG-PET) is used in the complex presurgical evaluation of patients with medically intractable temporal lobe epilepsy (TLE).[17;75-77] However, because the technique is invasive and expensive, requiring the injection of radioactivity, and not widely available because cyclotron facilities are needed,[54] it is important to know its diagnostic value compared with that of more routinely performed investigations such as MRI and video-EEG seizure recordings.

Recent studies suggest that FDG-PET is indicated in patients with TLE if MRI does not localize the source in one temporal lobe (either because it is negative or shows bilateral abnormalities), or if ictal EEG findings show a unilateral temporal onset that is not consistent with MRI findings.[78-80] Although several studies have investigated the contribution of FDG-PET to identifying the lobe of seizure onset in patients with TLE, in most studies FDG-PET was evaluated in isolation, without reference to existing MRI and video-EEG monitoring results.[56] Medical decisions are usually based on the results of several investigations and are hardly ever based on a single test result.[3] This is also true for the diagnostic work-up of patients regarding their eligibility for TLE surgery, in which FDG-PET is never performed first. The aim of this study was to determine the clinical or added value of FDG-PET on the decision-making process regarding TLE surgery in the setting of a tertiary referral center. We were particularly interested in determining the contribution of FDG-PET relative to that of MRI and video-EEG monitoring.

Methods

Patients and setting

In the Netherlands, all patients referred for epilepsy surgery enter the Dutch Collaborative Epilepsy Surgery Program (DCESP), a tertiary referral program. Patients undergo a standardized presurgical work-up, including patient history, routine EEGs, MRI, and prolonged video-EEG monitoring of seizures.[17] After these tests, a national multidisciplinary taskforce determines the eligibility of the patient

for surgery and whether additional tests, such as FDG-PET, ictal SPECT, fMRI, MEG, or intracranial EEG monitoring, are needed. The results of ancillary tests are discussed in the ensuing monthly taskforce meeting and a new consensus decision is reached regarding eligibility for TLE surgery, or whether further testing, especially intracranial monitoring, is needed. Only surgical candidates undergo a neuropsychological test and a Wada procedure as well.

The present study is a retrospective cohort study including all consecutive patients referred to the national DCESP for evaluation for eligibility for TLE surgery between January 1996 and July 2002. We specifically chose this starting date because this is when a standardized 1.5 Tesla MRI protocol, including coronal FLAIR images, was introduced.[62] The role of FDG-PET in the diagnostic work-up of epilepsy patients has not changed since then.[78-80] Furthermore, we included data from patients referred between 1986 and 1996, when FDG-PET was performed more or less regardless of previously obtained MRI and video-EEG results, in a sensitivity analysis to evaluate selection or work-up bias in our cohort. We focused on patients referred for TLE surgery. Thus patients were excluded if a definite extratemporal seizure origin was established at the start of the presurgical work-up, that is if the semiology of the seizure onset included a longstanding or evolving somatosensory aura, generalized hypertonia or atonia, in combination with an MRI without temporal lobe abnormalities.

Diagnostic tests

Data were collected during the regular diagnostic work-up, in which all individual test results from the presurgical work-up and all taskforce decisions before and after each test were systematically documented in a clinical database. For the present analysis, the results of FDG-PET, MRI, and video-EEG monitoring were recoded into a research database. To ensure uniform coding of all test results, kappa analyses were regularly performed among the scoring researchers (SU, AC) and two independent experts (FL, JA). After preparatory training, kappa values of 0.70 or higher were obtained for coding of all the items.[18;19]

MR imaging was performed on a 1.5 Tesla machine, including coronal T2-weighted spin-echo and coronal fast fluid-attenuated inversion recovery (FLAIR) techniques. Quantitative MRI image studies, e.g. volumetry or measurement of T2 relaxation time, were not performed. MRI results were coded into four categories: no abnormalities, unilateral temporal abnormalities, bilateral temporal abnormalities, or other abnormalities. We evaluated three aspects of video-EEG monitoring, namely, long-term interictal EEG, seizure semiology, and ictal EEG. Interictal EEG was coded dichotomously as showing or not showing unilateral temporal lobe abnormalities, i.e. focal slow waves, epileptiform spikes, or sharp waves at electrodes over the temporal lobe with 90% predominance on one side. Videotaped seizure semiology was coded dichotomously as the presence or absence of typically temporal semiology,[60] defined as a seizure duration longer than 1 minute including at least four of the following five characteristics: abdominal or experiential aura, impaired consciousness, occurrence of automatisms, unilateral arm dystonia, or pronounced postictal confusion.[59-61] Semiology was considered lateralized if there was ictal or postictal dysphasia or early ictal contralateral arm dystonia.[60] Ictal EEG findings were coded dichotomously as the presence or absence of a unilateral regional or (delayed) focal temporal seizure onset.[63]

Interictal FDG-PET was performed using a Siemens ECAT 951/31R camera (Liège, Belgium) or a Siemens ECAT exact HR+ PET scanner (Amsterdam, both Siemens CTI PET Systems, Knoxville, TN, USA). A static PET study was obtained 30 to 60 minutes after intravenous injection of ^{18}FDG. The protocol has been described in earlier publications.[75;76] FDG-PET results were classified into three categories: normal, showing unilateral temporal hypometabolism, or otherwise (mainly, bitemporal or extratemporal hypometabolism). Combinations of unilateral temporal hypometabolism with confined ipsilateral frontobasal, ipsilateral thalamic, or contralateral cerebellar hypometabolism were considered compatible with unilateral temporal abnormalities.[81;82]

Outcome

There is no single or established reference standard for decision-making regarding TLE surgery. In the absence of such a reference standard, a consensus decision based on all available diagnostic information is often used as outcome measure or reference.[2;8;9] In the Dutch national presurgical work-up program, the consensus decision is made by a multidisciplinary taskforce consisting of neurosurgeons, neurologists, neurophysiologists, neuropsychologists, and radiologists, on the basis of available evidence. The taskforce also establishes whether additional tests are required. All these decisions are fully documented, which gave us the opportunity to compare each decision before and after FDG-PET was performed and to study whether the FDG-PET results indeed changed a decision made on the basis of MRI and video-EEG monitoring findings.

Data analysis

We estimated the association between MRI, long-term interictal EEG, videotaped seizure semiology, ictal EEG, and FDG-PET findings and the final decision regarding TLE surgery as outcome measure. We quantified the contribution of each test by calculating the positive and negative decision predictive value, i.e. the predictive values of each test with the decision for surgery (yes or no) as outcome. To quantify the added value of FDG-PET, two by two tables for the results from FDG-PET in combination with MRI and with video-EEG monitoring were calculated. Results were considered concordant when both tests showed unilateral temporal abnormalities on the same side, and discordant when both tests showed unilateral temporal abnormalities on opposite sides. Other combinations were defined as indecisive. All statistical analyses were performed using SPSS 12.0 (Chicago, IL, USA).

Sensitivity analysis

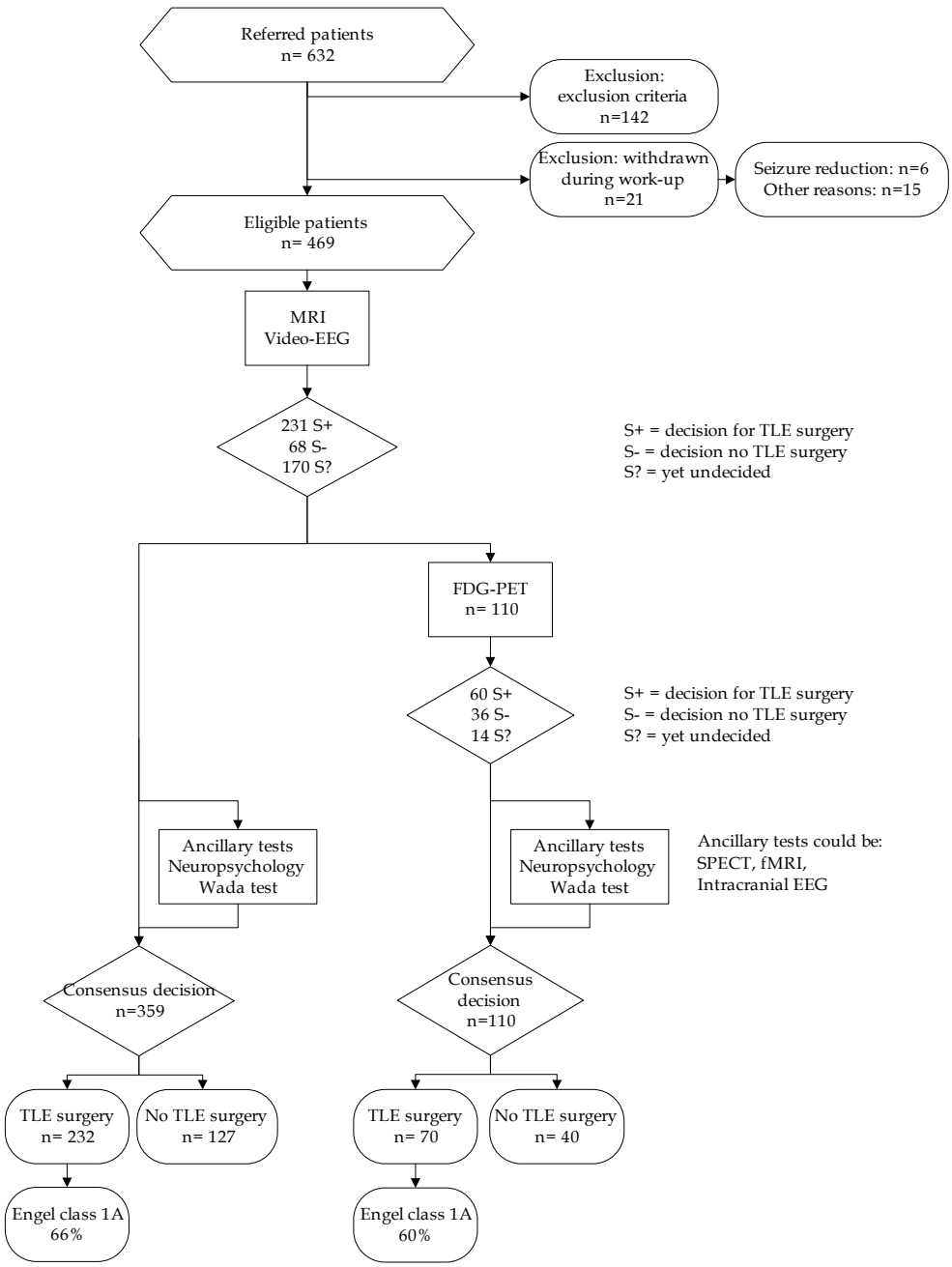
FDG-PET was not performed in all patients, which may have introduced work-up bias due to selective referral for FDG-PET on the basis of previous test results.[2;8;9]

The best way to control for this bias is to impute the "missing" values.[66;83] In the Netherlands in the early years of PET before 1996, when MRI did not yet include coronal FLAIR images, FDG-PET was performed more or less regardless of previously obtained MRI and video-EEG results. This gave us the opportunity to perform a sensitivity analysis to evaluate the potential work-up bias in our data. To this end, we used the data of all patients referred for evaluation of TLE surgery between 1986 and 2002 (803 patients in total) to build a prediction model, using binary logistic regression, in which the intermediate consensus decision after FDG-PET (surgery versus no surgery) was the dependent variable and all other available test results and patient information were the independent variables or predictors. This prediction model was then applied to the data of the patients evaluated from 1996 to 2002, to impute a (virtual) intermediate consensus decision after FDG-PET for the patients who did not undergo FDG-PET. The impact of FDG-PET on the decision to operate was estimated in the imputated cohort and compared with the observed percentage based on the patients who actually underwent FDG-PET in that same cohort.

Results

Between January 1996 and July 2002, 632 patients were referred to the national DCESP for evaluation for epilepsy surgery (figure 4.1). Of these, 142 were excluded because the epileptogenic focus was considered to be extratemporal. Twenty-one patients withdrew from the diagnostic work-up. Therefore, 469 patients were included in the present analysis, of whom 302 (232+70; 60%) underwent surgery. FDG-PET was performed in 110 patients (23%), 70 of whom (64%) were considered eligible for surgery as compared with 232 of 359 patients (65%) who did not undergo FDG-PET. One year after surgery, 64% of all operated patients were completely seizure-free without auras (Engel class 1A); this was the case for 60% of the patients who had undergone FDG-PET. This difference was not statistically significant. The mean follow-up after surgery was 4.2 years, which ranged from 1 to 10 years. Of all operated patients, 51% reached complete seizure freedom at last

Figure 4.1. Patient flow chart, including the diagnostic tests and decisions



follow-up; this was the case in 48% of patients who had undergone FDG-PET. Again, this difference was not statistically significant.

On the basis of MRI and video-EEG findings, 231 patients were considered eligible for TLE surgery (figure 4.2); the taskforce nevertheless decided to perform FDG-PET in 16 of these patients (7%), in most cases because the MRI was not localizing or simply to confirm MRI findings. On the basis of FDG-PET findings, the decision to operate was changed, or intracranial monitoring was requested, in 4 of these patients (25%). Of the 68 patients considered ineligible for surgery on the basis of MRI and video-EEG findings, the taskforce reconsidered and decided to perform FDG-PET in 10 patients (15%). One patient was subsequently considered eligible for surgery; however, this patient did not become seizure-free after surgery. Most patients who underwent FDG-PET had inconclusive results after MRI and video-EEG monitoring. Of the 84 of 170 patients with inconclusive results who underwent FDG-PET, FDG-PET led to a final decision in 72 patients (figure 4.2: 47+25; 86%). Compared with the rest of the cohort, these 72 patients more often had normal MRI findings ($p<0.0001$), less often unilateral temporal abnormalities on MRI ($p<0.0001$), MRI and ictal EEG were less often concordant ($p<0.0001$), and videotaped semiology and ictal EEG were less often concordant ($p=0.027$) (table 4.1). The outcome after surgery of the operated patients with inconclusive results after MRI and video-EEG monitoring who underwent FDG-PET (63% seizure free) was comparable to that of all operated patients (64% seizure free). In total, FDG-PET findings were conclusive regarding surgical candidacy in 78 (figure 2: 4+2+72) of 469 patients (17%) referred for TLE surgery or in 78 of 110 patients (71%) investigated with FDG-PET. With the exception of interictal video-EEG, all included tests (MRI, video-EEG monitoring and FDG-PET findings) were associated with the final consensus decision regarding surgical candidacy (table 4.2). However, in isolation, none of the tests showed good prediction or discrimination for this decision.

Figure 4.2. Decision-making process per step of the presurgical work-up

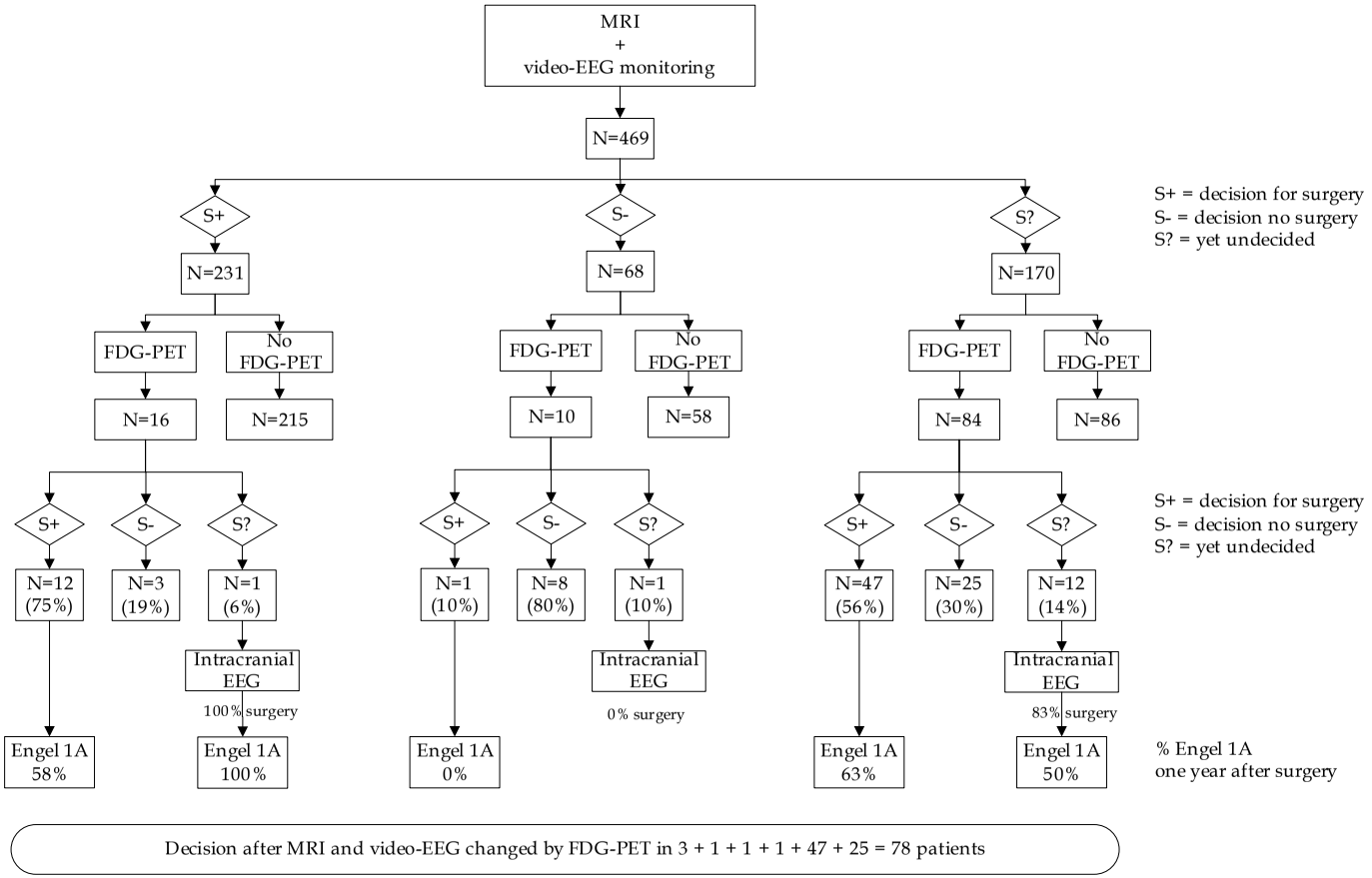


Table 4.1. Characteristics of the patient group with indecisive results after MRI and video EEG in whom FDG-PET results forced a decision compared to the rest of the cohort

	Decision forced by FDG-PET	
	Yes (N=72)	*No (N=397)*
Age (mean ± standard deviation)	33 ± 12	31 ± 13
Male sex	35 (0.49)	195 (0.49)
MRI normal	28 (0.39)	17 (0.04) **
MRI unilateral temporal	34 (0.47)	276 (0.70) **
MRI bilateral temporal	3 (0.04)	21 (0.05)
Interictal video-EEG unilateral temporal	21 (0.29)	129 (0.33)
Videotaped semiology temporal	30 (0.42)	206 (0.52)
Ictal video-EEG unilateral temporal	40 (0.56)	255 (0.64)
Concordance MRI – interictal video-EEG	23 (0.32)	142 (0.36)
Concordance MRI – videotaped semiology	13 (0.18)	106 (0.27)
Concordance interictal video-EEG – videotaped semiology	17 (0.24)	109 (0.28)
Concordance MRI – ictal video-EEG	14 (0.19)	179 (0.45) **
Concordance interictal video-EEG – ictal video-EEG	9 (0.13)	69 (0.17)
Concordance videotaped semiology – ictal video-EEG	11 (0.15)	105 (0.26) *

*Values represent number of patients (fraction), except for age; * Significant at 0.05-level; ** Significant at 0.01-level; Group differences were tested with Mann-Whitney U test (age) or chi-square*

Table 4.3 shows the contribution of FDG-PET combined with MRI and ictal EEG to the decision whether to perform surgery. The first row of each combination can be seen as 'the combined positive test result' and therefore reflects the positive decision predictive value (PDPV) of that test combination. The last row

Table 4.2. Two by two tables and decision predictive values (95% confidence intervals) of FDG-PET, MRI and video-EEG monitoring with the decision for or against surgery after the FDG-PET scan

	Decision after FDG-PET:				*Positive decision predictive value*[d]	*Negative decision predictive value*[e]
	Surgery N=60	*No surgery*[b] N=50	*Total* N=110	*P-value*[c]		
FDG-PET				0.009		
Unilateral temporal	41	22	63		0.65	0.60
Inconclusive[a] / normal	19	28	47		(0.53-0.77)	(0.45-0.72)
MRI				0.009		
Unilateral temporal	35	17	52		0.67	0.57
Inconclusive[a] / normal	25	33	58		(0.54-0.78)	(0.44-0.69)
Video-EEG interictal				NS		
Unilateral temporal	22	15	37		0.59	0.48
Inconclusive[a]	38	35	73		(0.43-0.74)	(0.37-0.59)
Video-EEG semiology				0.033		
Definitely temporal	32	17	49		0.65	0.54
Not localizing	28	33	61		(0.51-0.77)	(0.42-0.66)
Video-EEG ictal				0.035		
Unilateral temporal	39	23	62		0.63	0.56
Inconclusive[a]	21	27	48		(0.50-0.74)	(0.42-0.69)

[a] Inconclusive = not localizing to one temporal lobe; [b] For this analysis, the patient was ineligible for surgery when no consensus decision was reached after the FDG-PET; [c] Based on Chi square test; NS = not significant at 0.05-level; [d] Positive decision predictive value is the proportion of patients accurately predicted to be eligible for surgery; [e] Negative decision predictive value is the proportion of patients accurately predicted not to be eligible for surgery

can be seen as 'the combined negative test result', and therefore as the negative decision predictive value (NDPV) of that test combination. These values can be compared to the PDPV and NDPV of each test in isolation (table 2). Addition of FDG-PET improved the PDPV and NDPV of MRI from 0.67 and 0.57 to 0.77 and 0.68, respectively, and the PDPV and NDPV of ictal EEG from 0.63 and 0.56 to 0.80 and 0.67, respectively. The PDPV and NDPV of long-term interictal EEG increased from 0.59 and 0.48 to 0.71 and 0.62, and the PDPV and NDPV of seizure semiology increased from 0.65 and 0.54 to 0.86 and 0.70, respectively (data not shown).

Table 4.3. FDG-PET in combination with MRI and ictal EEG in relation to the decision for or against TLE surgery.

MRI	***FDG-PET***	***Decision after PET***		
		Surgery	***No surgery*** [b]	***Total***
Unilateral temporal	Unilateral temporal	26 (0.77[c])	8 (0.23)	*34*
Unilateral temporal	Inconclusive[a] / normal	9 (0.56)	7 (0.44)	*16*
Unilateral temporal	Discordant	0	2	*2*
Inconclusive[a] / normal	Unilateral temporal	15 (0.56)	12 (0.44)	*27*
Inconclusive[a] / normal	Inconclusive[a] / normal	10 (0.32)	21 (0.68[d])	*31*
Ictal EEG	***FDG-PET***			
Unilateral temporal	Unilateral temporal	28 (0.80[c])	7 (0.20)	*35*
Unilateral temporal	Inconclusive[a] / normal	11 (0.48)	12 (0.52)	*23*
Unilateral temporal	Discordant	0	4	*4*
Inconclusive[a]	Unilateral temporal	13 (0.54)	11 (0.46)	*24*
Inconclusive[a]	Inconclusive[a] / normal	8 (0.33)	16 (0.67[d])	*24*

Values represent number of patients (fraction of row total); [a] Inconclusive = not localizing to one temporal lobe; [b] For this analysis, a patient was considered ineligible for surgery when no consensus decision was reached after the FDG-PET; [c] Equivalent to the positive decision predictive value of combination of test results; [d] Equivalent to the negative decision predictive value of combination of test results

FDG-PET findings were discordant with MRI or video-EEG findings in nine patients, one of whom was still considered eligible for surgery. This patient did not become seizure-free.

Table 4.4. Sensitivity analysis: observed decisions for or against surgery and estimated decisions after imputation of FDG-PET results

Decision before FDG-PET	*Decision after FDG-PET*	*Observed (see figure 4.2)*				*After imputation*			
		N	*Cases*	*Fraction*	*95%CI*	*N*	*Cases*	*Fraction*	*95%CI*
Surgery	Surgery	16	12	0.75	0.51-0.90	232	197	0.85	0.80-0.89
	No surgery		3	0.19	0.07-0.43		32	0.14	0.11-0.23
No surgery	Surgery	10	1	0.10	0.02-0.40	NP			
	No surgery		8	0.80	0.49-0.94				
Indecisive	Surgery	84	47	0.56	0.45-0.66	169	110	0.65	0.58-0.72
	No surgery		25	0.30	0.21-0.40		44	0.26	0.20-0.33

95%CI = 95% confidence interval; NP= analysis not performed

Sensitivity analysis

Table 4.4 shows the results after imputation of the decisions expected to have been made if the patients who had not undergone FDG-PET had undergone FDG-PET. The proportion of decisions regarding surgical candidacy hardly changed after imputation in the patients who were considered eligible for surgery on the basis of MRI or video-EEG findings and in the patients with inconclusive results before FDG-PET. This indicates that the observed results (figure 4.2) for these patient groups were unlikely to have been biased. Unfortunately, imputation was methodologically impossible for the patients considered ineligible for surgery on the basis of MRI and video-EEG findings (the second arm in figure 4.2) as there were only ten cases in this group, of whom only one was considered eligible for surgery after FDG-PET.

Discussion

In 71% of the TLE patients who underwent FDG-PET, the FDG-PET results influenced the decision whether or not temporal lobe surgery could be performed, and in 17% of all referrals for TLE surgery, FDG-PET findings were conclusive regarding surgical candidacy. One year after surgery, 64% of operated patients were seizure free (Engel class 1A). These findings indicate that FDG-PET has important added value for the decision-making process regarding TLE surgery in a tertiary referral setting. This is supported by the increased positive and negative decision predictive values of MRI and video-EEG monitoring in combination with FDG-PET. FDG-PET seemed especially valuable when MRI findings were normal, or when ictal EEG and MRI findings were not concordant - which is in line with indications for FDG-PET in the literature. [78-80] Nevertheless, only 84 of 170 patients (49%) with indecisive results after MRI and video-EEG underwent FDG-PET. One can only guess why FDG-PET was not performed in the other patients. In the Netherlands, PET has always been available for epilepsy surgery purposes (although at first carried out in Liège, Belgium) and because most people have full medical insurance, financial considerations were unlikely to have had a role.

Although the role of FDG-PET in TLE surgery has been studied before, most studies have assessed FDG-PET as a single diagnostic test only or in relation to seizure outcome in operated patients only (the prognostic value of FDG-PET).[56] DellaBadia et al. did address the contribution of a combination of sleep-deprived EEG, MRI, and FDG-PET to the decision-making process.[36] They found that FDG-PET was the most sensitive test when used in isolation. The positive predictive value of the combination of any two tests (with or without FDG-PET) was higher than that of FDG-PET in isolation. However, DellaBadia et al. investigated fewer patients (69 versus 110 in our study). Ollenberger et al. also showed that FDG-PET had an impact on the clinical management of children referred for epilepsy surgery,[84] based on clinicians' personal point of view. They recommended that all children with epilepsy should undergo FDG-PET. However, most of the children in Ollenberger et al's study had extratemporal epileptic foci.

Some methodological limitations of our study need to be addressed. First, our study outcome was the final consensus decision on operability reached by our national taskforce. Although this is the best alternative in the absence of a formal reference standard[2;3;8;9] and the outcome one year after surgery (64% seizure free) was comparable to that reported in the literature,[13;14] there is no way to know whether patients were inappropriately rejected for surgery. Formally, only a randomized design (to operate or not) in patients referred for TLE surgery could settle this issue – which would in our view be unethical.

Second, the consensus decision of the multidisciplinary taskforce was based on all available information, including the results of FDG-PET under investigation. This might have introduced incorporation bias, which could have led to overestimation of the accuracy measures in tables 4.2 and 4.3.[8;9;20] However, as we had systematically documented all intermediate consensus decisions before and after FDG-PET, we could study the change in decision-making due to the FDG-PET results, bypassing this incorporation bias.

Third, in 75% of FDG-PET investigations a flumazenil PET (FMZ-PET)

was performed along with FDG-PET as part of scientific research.[75] In these patients, the consensus decision after FDG-PET might have been influenced by the results of the FMZ-PET investigation. However, FMZ-PET results were similar or less informative than the FDG-PET results in most patients (90%), which is in agreement with earlier studies showing that FMZ-PET is not superior to FDG-PET in detecting the ictal onset zone.[75;85]

Lastly, since the results of MRI, video-EEG, and PET studies were reduced to a few variables, some diagnostic information may have been missed or simplified. The choice of test result categories, however, was based on the literature, clinical practice, and considerations of objectivity and reproducibility.

We conclude that FDG-PET has added value to clinical decision-making in patients referred for TLE surgery. FDG-PET seems especially valuable when MRI and video-EEG monitoring are unable to localize the epileptic focus. FDG-PET findings influenced clinical decision-making in 71% of the patients investigated with FDG-PET and were conclusive regarding surgical eligibility in 17% of patients referred for TLE surgery.