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Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

Utility of 18F-fluorodeoxyglucose positron emission tomography in presurgical evaluation of patients with epilepsy: A multicenter study

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Abstract

Objective: 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) is widely used in presurgical assessment in patients with drug-resistant focal epilepsy (DRE) if magnetic resonance imaging (MRI) and scalp electroencephalography (EEG) do not localize the seizure onset zone or are discordant.

Methods: In this multicenter, retrospective observational cohort study, we included consecutive patients with DRE who had undergone FDG-PET as part of their presurgical workup. We assessed the utility of FDG-PET, which was defined as contributing to the decision-making process to refer for resection or intracranial EEG (iEEG) or to conclude surgery was not feasible.

Results: We included 951 patients in this study; 479 had temporal lobe epilepsy (TLE), 219 extratemporal epilepsy (ETLE), and 253 epilepsy of uncertain lobar origin. FDG-PET showed a distinct hypometabolism in 62% and was concordant with ictal EEG in 74% in TLE and in 56% in ETLE ($p < .001$). FDG-PET was useful in presurgical decision-making in 396 patients (47%) and most beneficial in TLE compared to ETLE (58% vs. 44%, $p = .001$). Overall, FDG-PET contributed to recommending resection in 78 cases (20%) and iEEG in 187 cases (47%); in 131 patients (33%), FDG-PET resulted in a conclusion that resection was not feasible. In TLE, seizure-freedom 1 year after surgery did not differ significantly ($p = .48$) between patients with negative MRI and EEG-PET concordance ($n = 30$, 65%) and those with positive MRI and concordant EEG ($n = 46$, 68%). In ETLE, half of patients with negative MRI and EEG-PET concordance and three quarters with positive MRI and concordant EEG were seizure-free postsurgery ($n = 5$ vs. $n = 6$, $p = .28$).

Significance: This is the largest reported cohort of patients with DRE who received presurgical FDG-PET, showing that FDG-PET is a useful diagnostic tool. MRI-negative and MRI-positive cases with concordant FDG-PET results (with

either EEG or MRI) had a comparable outcome after surgery. These findings confirm the significance of FDG-PET in presurgical epilepsy diagnostics.

KEYWORDS

drug-resistant epilepsy, epilepsy surgery, 18F-fluorodeoxyglucose PET, presurgical assessment

1 | INTRODUCTION

Approximately one third of patients with focal epilepsy have drug-resistant epilepsy (DRE) and continue to have seizures despite adequate treatment with at least two antiseizure medications (ASMs).[1,2] In patients with temporal lobe epilepsy (TLE), resective surgery shows a significantly better seizure outcome than ongoing medical therapy with ASMs alone.[3–5] Following resective surgery for unilateral mesial temporal sclerosis on magnetic resonance imaging (MRI), the seizure remission rate is between 60% and 80% if neuroimaging findings are concordant with seizure semiology, ictal electroencephalography (EEG), and neuropsychological data.[3,5–7] For extratemporal lobe epilepsy (ETLE), outcome following epilepsy surgery is generally less favorable, with 40%–60% of patients entering remission.[8–10]

About one quarter of patients with DRE undergoing presurgical evaluation have an MRI scan that is negative, that is, nonlesional, equivocal, or discordant with clinical and EEG data, necessitating the use of additional tests to localize the seizure onset zone.[11] 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) has been used for >30 years to assist in the localization of seizure foci. The characteristic finding in focal epilepsy is a reduction in interictal glucose uptake (hypometabolism) in and around the seizure onset zone. FDG-PET can provide lateralizing or localizing information in 60%–90% of patients with TLE and in 30%–60% of patients with ETLE.[12–17]

Patients with negative MRI have a less favorable postsurgical seizure outcome than those with a discrete lesion that is concordant with seizure semiology and EEG.[18] However, if FDG-PET hypometabolism in patients with negative MRI and TLE is congruent with the electroclinical seizure onset zone, seizure outcome is similar to patients with a positive, that is, lesional MRI.[19,20] Fewer data on this subject are available for ETLE. Some evidence suggests less favorable postsurgical outcome for MRI-negative cases compared to MRI-positive patients with ETLE and FDG-PET hypometabolism.[21,22] Others showed equally favorable results not only for MRI-negative and MRI-positive ETLE cases, but also in comparison to TLE.[23] Surgical outcome was most favorable in patients with ETLE and focal cortical dysplasia (FCD).[21,24]

Key Points

- FDG-PET is valuable to localize the seizure onset zone when MRI and scalp EEG are not localizing or are discordant
- We pooled almost 1000 epilepsy patients from four centers with FDG-PET scans assessing the utility of FDG-PET and postoperative outcome
- We showed that FDG-PET was useful in the presurgical decision-making in about half of the epilepsy patients
- In TLE, 1-year seizure outcome is as good in cases with negative MRI and positive FDG-PET as in those with positive MRI-EEG concordance
- In ETLE, half of the patients with negative or equivocal MRI and positive FDG-PET also have a good postoperative outcome

In the current multicenter study, data from four epilepsy centers in Germany, India, UK, and USA in almost 1000 epilepsy patients were pooled. By including consecutive patients with DRE who received FDG-PET as part of their assessment for epilepsy surgery, we present data out of clinical practice drawn from representative tertiary epilepsy centers, thereby creating a "realistic" picture of the utility of FDG-PET by avoiding selection bias. To this end, we evaluated the significance of interictal FDG-PET for the decision-making process in presurgical assessment in patients with negative, positive, and equivocal MRI in both temporal and extratemporal lobe epilepsies. Furthermore, in patients with negative compared to those with positive MRI, we assess the impact of FDG-PET findings on 1-year postsurgical seizure outcome.

2 | MATERIALS AND METHODS

2.1 | Study setting

In this retrospective study, we included consecutive patients with DRE who received FDG-PET as part of their assessment for epilepsy surgery between January 2003 and

December 2016. Four centers contributed: Department of Radiology and Radiological Sciences at Johns Hopkins School of Medicine in Baltimore, Maryland, USA; Epilepsy Center Berlin-Brandenburg in Berlin, Germany; Department of Clinical and Experimental Epilepsy at the National Hospital for Neurology and Neurosurgery in London, UK; and Department of Neurology at Sree Chitra Tirunal Institute for Medical Sciences and Technology in Trivandrum, India. Some of the data from Baltimore, London, and Trivandrum included in this study have been published previously.[25–27]

To avoid selection bias, no preselection of included patients was done; all consecutively treated patients who met the inclusion criteria (presurgical assessment, FDG-PET) in the respective observational period at each participating center were included. Only patients with missing data on FDG-PET findings and postsurgical outcome were excluded. No validation of MRI, FDG-PET, and EEG readings was performed; all information is based on available medical records. After pooling the data, all centers were asked to provide additional data to streamline availability of variables and to close data gaps where possible.

Approval of institutional review boards has been given at all four centers. Clinical information was obtained from medical records. Informed consent by each patient was not required by the institutional review boards. Information was shared between centers pseudonymized; identifying characteristics such as name or date of birth were not shared.

2.2 | Demographic and clinical data collection

Clinical variables comprised sex, age at epilepsy onset, age at time of FDG-PET, duration of epilepsy, use of intracranial EEG (iEEG), histopathology, and seizure outcome 1 year after surgery (International League Against Epilepsy [ILAE] classification[28]). Epilepsy syndromes were defined by seizure semiology and verified with ictal EEG recordings on video-EEG telemetry, and allocated to TLE, ETLE, and epilepsy of uncertain lobar origin.

2.3 | FDG-PET scans

Patients were fasted for 4–6 h before FDG-PET scanning and rested in a quiet, dark room with eyes patched and ears plugged for 30 min before and at least 30 min after FDG administration. The FDG-PET scan was performed 30–60 min after intravenous injection of 18F-labeled FDG. All patients were scanned on General Electric PET/computed tomography (CT) scanners with similar performance and acquisition parameters. At all sites, image interpretation was performed visually by neurological PET experts, with the addition of semiquantitative analysis using 3D-SSP Neurostat[29] at the London site. Assessment was further supplemented by Hermes Brass (Hermes Medical Solutions) and MRI-PET coregistration in Berlin (using Slicer 4.10.2[30]), and CT-PET coregistration and fusion directly from the PET/CT scanner in Trivandrum (see Table S1). No quantitative analysis using, for example, Statistical Parametric Mapping (SPM), was applied.

The following variables were included in this study: presence of FDG-PET hypometabolism, lateralization of hypometabolism (right, left, bilateral), localization of hypometabolism (mesial temporal, neocortical temporal, mesial and neocortical temporal, temporal+, extratemporal, diffuse), extension of hypometabolism (*focal*, 1 lobe; *regional*, >1 lobe including hypometabolism in adjacent lobes, e.g., temporoparietal, temporofrontal, frontoparietal; *diffuse*, >2 lobes or including whole hemisphere), and concordance of FDG-PET and ictal EEG (nonconcordant/nonlocalizing, lobar concordance, hemispheric concordance).

2.4 | MRI scans

All centers used standard clinical MRI sequences,[31] including a 1-mm slice thickness T1 multiplanar reconstruction, 2-mm slice coronal and sagittal fluid-attenuated inversion recovery (FLAIR), hemosensitive sequence (T2*/susceptibility-weighted imaging/inversion recovery), and axial T2-weighted imaging through temporal lobes. MRI was read at each site by either a neuroradiologist with experience in reading MRI in epilepsy or a "general" neuroradiologist and additionally an experienced epileptologist.

MRIs were performed on both 1.5-T and 3-T scanners across centers (for further details, see Table S1):

We acquired the following data regarding patients' MRI: presence of epileptogenic lesion on MRI (negative, positive, equivocal), lateralization of MRI lesion (right, left, bilateral), localization of MRI lesion (mesial temporal, neocortical temporal, mesial and neocortical temporal, temporal+, extratemporal), epileptogenic MRI pathology (mesial temporal sclerosis, focal cortical dysplasia, gliosis/focal atrophy, neoplasm, others, dual), number of 1.5-T versus 3-T MRI, and concordance of MRI and EEG findings.

Equivocal MRI includes results such as a slight hyperintense signal, swelling, or subtle gray–white matter blurring that was indicative of an epileptogenic lesion but did not meet full diagnostic criteria.

2.5 | Electroencephalography

All patients were investigated using scalp video-EEG telemetry. At all four centers, the international 10–20 or 10–10 system was used with a minimum of 21 electrodes. Information about ictal findings including lateralization (right, left, bilateral) and localization (temporal, temporal+, extratemporal, uncertain) was included in this study. Additionally, information about whether patients received iEEG was included, although no details about the results of the recordings were considered.

2.6 | Definition of utility of FDG-PET for decision-making

To assess the utility of FDG-PET for decision-making and how its results influenced the decision process for epilepsy surgery, we reviewed and recorded the conclusion of multidisciplinary meetings as well as the above mentioned clinical data. In a second step, a consensus was reached among several investigators (M.S., J.D., M.H., and M.I.-F.) about a definition of utility of FDG-PET, which was then applied to the data. FDG-PET was considered useful if it led directly to recommendation for resection, helped in tailoring electrode placement for iEEG, led to the post hoc discovery of an MRI lesion, led to lateralization of the epileptogenic zone, helped in delineating the extent of the epileptogenic zone, or led to the decision that surgery was not feasible. The decision for infeasibility of surgery was made if FDG-PET indicated multifocal epilepsy or a widespread abnormality. FDG-PET was deemed not useful in patients with congruence of an epileptogenic lesion and electroclinical findings (Figure 1).

2.7 | Seizure outcome after surgery

The follow-up period was 12 months after epilepsy surgery. For the purpose of this study, we defined *good outcome* as ILAE 1 and 2 and *improved outcome* as ILAE 3 and 4 for the follow-up period of 1 year after surgery.[5,18,28]

2.8 | Subgroup analysis

In clinical practice, the additional diagnostic value of an FDG-PET scan is determined by its concordance with ictal EEG in the case of negative MRI or discordance between MRI and EEG in cases with an epileptogenic lesion on MRI. In individuals with a clear lesion on MRI and concordant ictal EEG, FDG-PET is generally regarded not to be necessary,[6,32] although there might be cases were some of those patients profit from an FDG-PET scan, for example, when seizure onset on EEG is widespread.[33] However, for our analysis, we treated the cohort of patients with positive MRI and concordant EEG ($n = 115$) as a comparison group to cases with negative and equivocal MRI and excluded this group from the utility analysis for decision-making (see Results section).

Therefore, we divided patients into the following four subgroups for further analyses (overall and within TLE and ETLE patients):

- *Negative MRI* and spatial concordance of ictal scalp EEG and FDG-PET hypometabolism (*EEG-PET concordance*; including both focal and regional hypometabolism on FDG-PET);
- *Equivocal MRI* and *EEG-PET concordance*;
- *Positive MRI* with discordant ictal scalp EEG but concordant FDG-PET hypometabolism (*MRI-PET concordance*); and
- *Positive MRI* with concordant ictal scalp EEG (*EEG-MRI concordance*), which was used as reference, because FDG-PET would not have been necessary in those cases.

2.9 | Statistical analysis

All statistical analysis was done using IBM SPSS Statistics 24. Categorical variables were tested with a 2×2 contingency table using the chi-squared test; for sample sizes $n > 50$ the chi-squared test, between 20 and 50 chi-squared test with Yates correction, and <20 and/or expected cell frequencies <5 Fisher exact test was used.

For quantitative variables such as age and duration of epilepsy, median and interquartile range were computed.

Missing data were labeled as 999999 in SPSS and were excluded from the particular analyses. Cases where relevant data like details about FDG-PET results and epilepsy subtype were missing were excluded completely (see Figure S1).

We computed odds ratios (ORs) and the 95% confidence intervals (CIs) by calculating standard error and using the logarithm of the OR (ln[OR]; 1.96 is the critical value for 95% CI)[34]:

$$95\%\ \mathrm{CI} = e^{\ln(\mathrm{OR})-1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}};\ e^{\ln(\mathrm{OR})+1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$$

All tests were two-sided, and p-values $< .05$ were considered statistically significant.

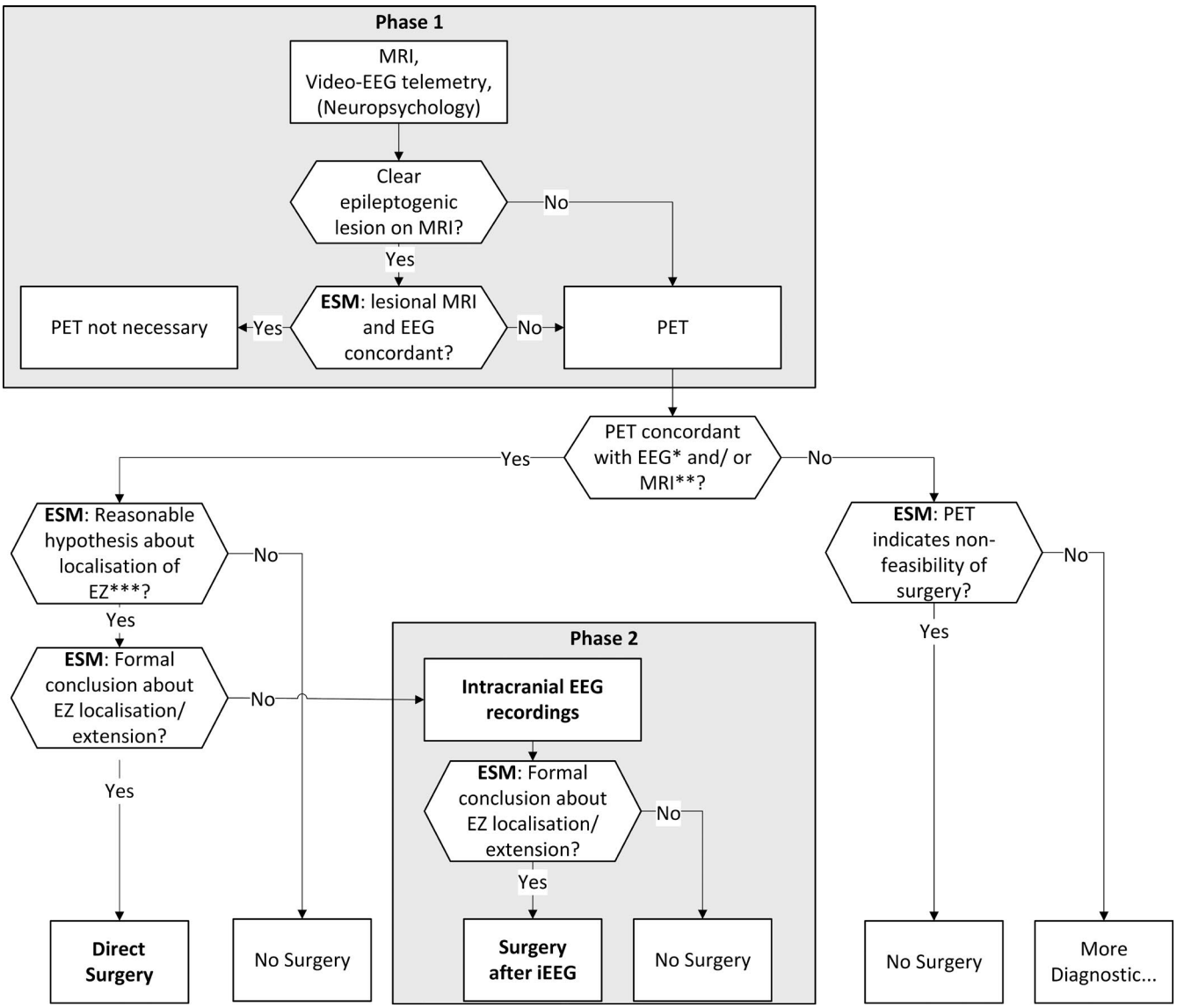


FIGURE 1 Decision-making process in epilepsy surgery. In patients with concordance of lesional magnetic resonance imaging (MRI) and ictal electroencephalography (EEG), 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is generally considered not to be necessary. Some patients with these characteristics were included in this study. Phases 1 and 2 are as defined by Ryvlin et al.[56] ESM, interdisciplinary epilepsy surgery meeting; EZ, epileptogenic zone; iEEG, intracranial EEG (subdural electrodes or stereo-EEG); PET, as in FDG-PET. *Cases with negative MRI. **Cases with positive or equivocal MRI. ***Decision not to proceed to surgery can also apply to cases with significant overlap between EZ and eloquent areas of the brain. "More Diagnostic...": depending on local resources, this includes ictal single photon emission computed tomography, EEG–functional MRI, electrical source imaging based on EEG, or magnetoencephalographic data, and depending on the results could later lead to iEEG planning

3 | RESULTS

3.1 | General study population

At the four centers, 979 patients underwent FDG-PET as part of their presurgical workup between 2003 and 2016. We excluded 28 patients because information about FDG-PET and/or about final decision of the epilepsy surgery meeting was not available. Thus, 951 patients were included in the study (Figure S1). Of those, 436 (46%) were female. The majority were adults, as only 33 (3.5%) patients were younger than 18 years. Further clinical characteristics of the study population are summarized in Table 1 (for more details, see Table S2).

Half of the patients were classified as having TLE (n = 479, 50%), 219 (23%) as ETLE, and 253 (27%) as epilepsy of uncertain lobar origin.

Of the total group, 275 patients (29%) had a positive MRI, 578 (61%) had a negative MRI, and in 98 (10%) MRI was equivocal. The majority of patients had a 3-T MRI (n = 609, 64%); 461 (76%) of those had a negative MRI. Among patients who received a 1.5-T MRI

TABLE 1 Patient demographics and characteristics

Characteristic	All	TLE	ETLE	Uncertain
n (%)	951	479 (50)	219 (23)	253 (27)
Female sex, *n* (%)	436 (46)	134 (28)	91 (42)	111 (44)
Children [<18 years], *n* (%)	33 (4)	16 (3)	14 (6)	3 (1)
Age at time of FDG-PET, years, median (IQR)	31 (22–40)	31 (22–41)	28 (20–37)	29 (21–40)
Age at time of epilepsy onset, years, median (IQR)	12 (6–18)	9 (4–16)	9 (4–14)	11 (6–16)
Duration of epilepsy, years, median (IQR)	16 (9–26)	18 (11–29)	16 (9–25)	15 (7–25)
Focal aware seizures, *n* (%)	529 (56)	317 (66)	96 (44)	116 (46)
Focal seizures with impaired awareness, *n* (%)	639 (67)	395 (83)	105 (48)	139 (55)
Focal to bilateral tonic–clonic seizures, *n* (%)	577 (61)	309 (65)	121 (55)	147 (58)
Localization of ictal EEG, *n* (%)				
Temporal	489 (51)	399 (83)	32 (15)	48 (19)
Extratemporal	264 (28)	35 (7)	133 (61)	96 (38)
Uncertain	182 (19)	39 (8)	49 (22)	94 (37)
NA	16 (2)	6 (1)	5 (2)	5 (2)
Presence of MRI lesion, *n* (%)				
Negative	578 (61)	249 (52)	134 (61)	195 (77)
Positive	275 (29)	180 (38)	62 (28)	33 (13)
Equivocal	98 (10)	50 (10)	23 (11)	25 (10)

Note: "Uncertain" indicates epilepsy of uncertain lobar origin.

Abbreviations: EEG, electroencephalogram; ETLE, extratemporal lobe epilepsy; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; IQR, interquartile range; MRI, magnetic resonance imaging; TLE, temporal lobe epilepsy.

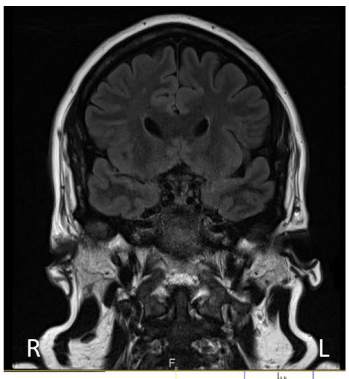
(n = 342, 36%), 117 (34%) had a negative MRI. These rates differed between centers, although those with the highest rates of 3-T MRI also had the highest rates of negative MRIs; the inverse relation was true for 1.5-T MRI (see Table S4).

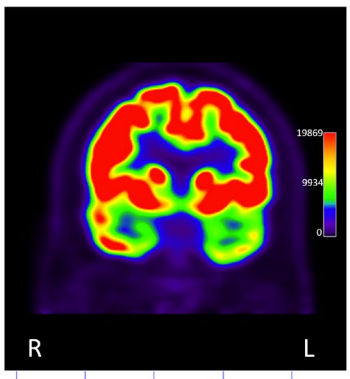
3.2 | Distribution of FDG-PET hypometabolism

FDG-PET demonstrated a distinct focal or regional hypometabolism in 587 (62%) patients. In the remaining patients, FDG-PET showed no hypometabolism, that is, FDG-PET was negative (n = 330, 35%), or diffuse hypometabolism (n = 34, 3%). Focal or regional hypometabolism on FDG-PET was seen in 316 of the negative MRI cases (56%), in 66 patients (68%) with equivocal MRI, and in 205 cases with positive MRI (79%; Figures S1 and S2). Significantly more patients with TLE (n = 371, 77%) had focal or regional hypometabolism than patients with ETLE (n = 123, 56%, $p < .001$) or those with uncertain lobar origin (n = 93, 37%, $p < .001$; see examples of accordant MRI and FDG-PET findings in Figure 2). Rates of focal and regional hypometabolism on FDG-PET were

FIGURE 2 Decision-making process in exemplary cases showing magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) results and seizure onset from scalp video-electroencephalographic (EEG) recordings (all EEG traces are in bipolar montage, 1s interval between blue lines, showing 16 s of EEG). (A) MRI-negative temporal lobe epilepsy (TLE) case (coronal fluid-attenuated inversion recovery [FLAIR] sequence, corresponding coronal FDG-PET and EEG trace), which illustrates that despite negative MRI, additional information by FDG-PET and as a second step intracranial EEG (iEEG) can lead to good postoperative outcome. (B) MRI-negative extratemporal lobe epilepsy case (transversal FLAIR, corresponding transversal FDG-PET, EEG trace with onset on contralateral side), which illustrates bilateral epilepsy; at some centers, further investigation with iEEG would have been undertaken, although in this case, considering psychosocial factors, the decision was made against that. (C) MRI equivocal TLE case (coronal T1, white arrows indicate a left temporal gray–white matter blurring, scalp EEG with sphenoidal electrodes [SP1]). In direct contrast to example case A, the postoperative outcome was unexpectedly bad; the most likely hypothesis is that a second seizure focus was missed due to the seemingly clear and concordant results. We do not have data to support this assumption, as the patient decided against further investigations. ILAE, International League Against Epilepsy; L, left; R, right

(A)





Decision-making

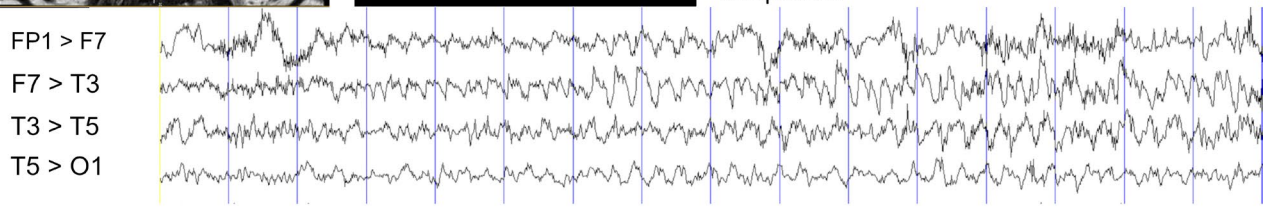
MRI negative; FDG-PET hypometabolism and EEG seizure onset left temporal
--> iEEG for language delineation and extent of resection --> left anterior temporal resection, sparing the hippocampus

Surgery outcome after 1 year

ILAE 1

Histopathology

unspecific



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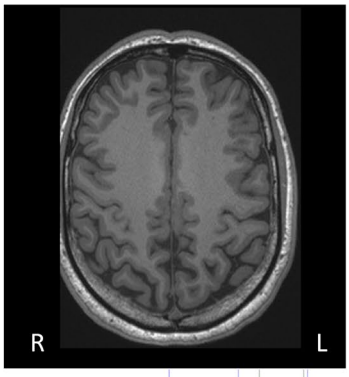
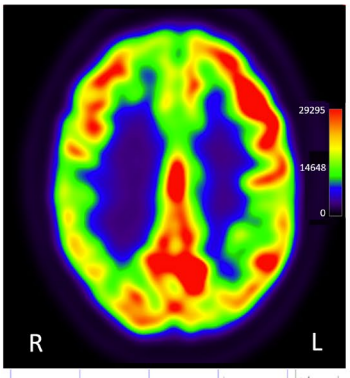
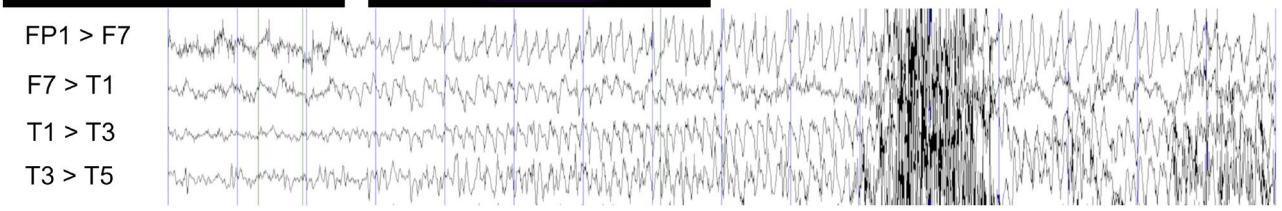


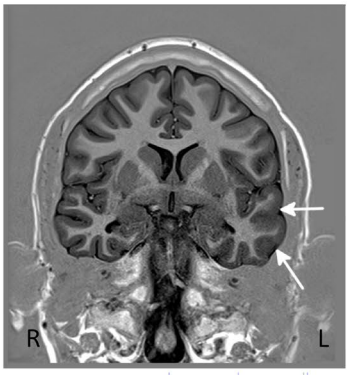


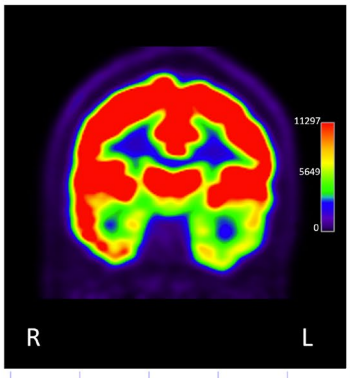
Decision-making

MRI negative, EEG with right and (as shown below) left frontal seizure onset, FDG-PET hypometabolism right frontal
--> because of bilateral epilepsy non-feasibility of surgery



(C)





Decision-making

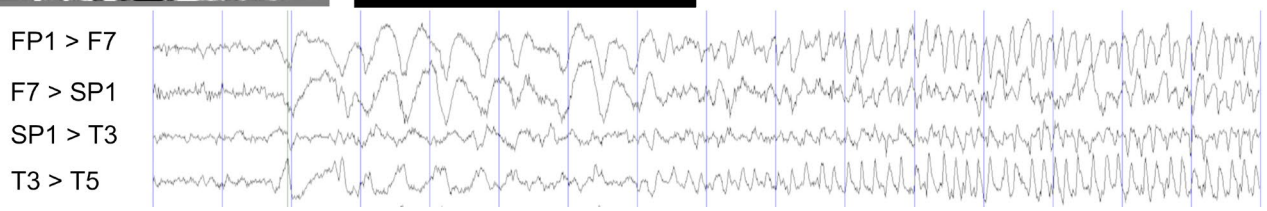
MRI equivocal with left temporal blurring, EEG seizure onset left temporo-mesial, FDG-PET hypometabolism left temporal
--> direct surgery with left anterior temporal resection.

Surgery outcome after 1 year

ILAE 5

Histopathology

Mesial temporal sclerosis



similar between those who had a 3-T MRI ($n = 365$, 60%) and 1.5-T MRI ($n = 222$, 65%; Table S4).

For comparison of MRI and FDG-PET results between those patients with mesial temporal sclerosis on histopathology and those with FCD, see Table S3.

3.3 | Concordance of FDG-PET with ictal EEG

FDG-PET was concordant with ictal EEG in 392 of all patients (63%). There was a significant difference in overall concordance rates between TLE ($n = 278$; 74%) and ETLE patients ($n = 72$, 56%, $p < .001$; Table 2).

3.4 | Utility of FDG-PET scan for decision-making

Overall, FDG-PET scans were considered to be useful in the decision-making in 396 patients (47%) of the 836 patients (excluding the comparison group of patients with positive MRI and concordant ictal EEG, $n = 115$, as explained in the Materials and Methods section). There was a significant difference in utility of FDG-PET comparing TLE versus ETLE (58% vs. 44%, $p = .001$; Table 3). Among the patients in whom FDG-PET was considered useful ($n = 396$), it led to the decision to recommend resection in 78 patients (20%) and helped to plan electrode placement in iEEG in another 187 cases (47%). Based upon the findings of FDG-PET, 131 patients (33%) were excluded from surgery because it was deemed not feasible (discordance with EEG and/or MRI [$n = 114$, 87%], diffuse hypometabolism discordant with EEG and/or MRI [$n = 17$, 13%]).

In half of the patients ($n = 440$, 53%), FDG-PET was not useful for the decision-making process, either because there was no hypometabolism present ($n = 330$, 40%) or further diagnostic investigations needed to be done, such as repeat video-EEG telemetry, repeat MRI, ictal single photon emission computed tomography (SPECT), magnetoencephalography/magnetic source imaging, or ictal SPECT ($n = 110$, 13%). One third of patients ($n = 91$, 34%), for whom either iEEG or surgery ($n = 265$) was suggested, declined to undergo the procedures (Table 3).

If focal or regional hypometabolism was shown on FDG-PET ($n = 490$), the odds of being recommended for resection increased threefold (OR = 3, 95% CI = 1.88–4.78, $p < .001$) and by almost 50% for selection for iEEG (OR = 1.6, 95% CI = 1.2–2.1, $p = .001$) compared to those individuals in whom there was a diffuse or no hypometabolism. Diffuse and absent hypometabolism increased the likelihood of nonfeasibility of surgery (OR = 2.6, 95% CI = 1.93–3.5, $p < .001$). When analyzing TLE and ETLE individually, focal and regional FDG-PET hypometabolism

TABLE 2 Concordance of FDG-PET and ictal EEG findings in patients with hypometabolism on FDG-PET

Concordance of FDG-PET and EEG	All	MRI−	MRI+	MRI~
Temporal lobe epilepsy, *n* (%)	376	180	158	38
Lobar concordance [localizing]	225 (60)	90 (50)	112 (71)	23 (61)
Hemispheric concordance [lateralizing]	53 (14)	30 (17)	18 (11)	5 (13)
Nonconcordant/nonlocalizing	94 (25)	57 (32)	27 (17)	10 (26)
NA	4 (1)	3 (2)	1 (1)	0
Extratemporal lobe epilepsy, *n* (%)	129	68	45	16
Lobar concordance [localizing]	43 (33)	28 (41)	10 (22)	5 (31)
Hemispheric concordance [lateralizing]	29 (22)	15 (22)	11 (24)	3 (19)
Nonconcordant/nonlocalizing	55 (43)	24 (35)	23 (51)	8 (50)
NA	2 (2)	1 (2)	1 (2)	0

Note: Lobar EEG-PET concordance included all patients in whom focal FDG-PET abnormalities (hypometabolism in one lobe) were concordant with ictal EEG. Additionally, some cases with regional FDG-PET abnormalities (hypometabolism in >1 lobe), where the hypometabolism extended into the directly adjacent regions, were labeled as having lobar concordance with ictal EEG (e.g., right temporoparietal hypometabolism with right temporal ictal EEG findings). Hemispheric EEG-PET concordance includes more extended hypometabolisms, as well as multifocal ones that were confined to one hemisphere. Of patients with uncertain lobar origin, n = 116 had a positive FDG-PET; n = 42 had EEG-PET concordance (localizing and lateralizing).

Abbreviations: EEG, electroencephalography; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; MRI−, negative MRI; MRI~, equivocal MRI; MRI+, positive MRI; NA, not available.

TABLE 3 Utility of FDG-PET scans for decision-making in the different epilepsy subtypes

	All	TLE	ETLE	Uncertain
n[a]	836	382	205	249
FDG-PET not useful	440 (53)	160 (42)	115 (56)	165 (66)
FDG-PET useful [b] [for recommendation to resection/iEEG]	396 (47)	222 (58)	90 (44)	84 (34)
Direct surgery	78 (20)	70 (31)	8 (9)	0
iEEG	187 (47)	113 (51)	62 (69)	12 (14)
Nonfeasibility of surgery	131 (33)	39 (18)	20 (22)	72 (86)
Final decision outcome [in cases where FDG-PET was useful]	396	222	90	84
Direct surgery	57 (14)	51 (23)	6 (7)	0
Surgery after iEEG	63 (16)	40 (18)	23 (26)	0
Nonfeasibility of surgery	158 (40)	54 (24)	33 (37)	71 (85)
Patients declined iEEG/surgery	91 (23)	64 (29)	21 (23)	6 (7)
Improved with drugs[c]	13 (3)	6 (3)	1 (1)	6 (7)
Lost to follow-up	14 (4)	7 (3)	6 (7)	1 (1)

Abbreviations: EEG, electroencephalography; ETLE, extratemporal lobe epilepsy; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; iEEG, intracranial EEG; TLE, temporal lobe epilepsy.

[a] Patients with positive magnetic resonance imaging and concordant ictal EEG results ($n = 115$, 12%) were excluded, as FDG-PET had not been necessary for the decision-making process.

[b] Nonfeasibility.

[c] Some patients significantly improved under pharmacotherapy, therefore surgery/iEEG was postponed.

compared to no or diffuse hypometabolism did not increase the odds significantly of being selected for direct surgery (TLE: OR = 1.4, 95% CI = .8–2.4, $p = .29$; ETLE: OR = 2.9, 95% CI = .8–10.8, $p = .15$).

3.5 | Seizure outcome after epilepsy surgery

Epilepsy surgery was performed in 282 (30%) of all 951 patients included in this study and 168 (60%) of those had a good outcome (ILAE 1 + 2) 1 year after surgery (Table S2).

Two hundred eleven of the 479 TLE patients (44%) had epilepsy surgery and 134 (64%) had a good outcome 1 year after epilepsy surgery. In ETLE, 71 of the 219 patients (33%) underwent epilepsy surgery, half of whom ($n = 34$, 48%) had a good outcome 1 year after surgery.

3.6 | Temporal lobe epilepsy

In TLE, 120 (25%) patients had a *negative MRI but EEG-PET concordance* (Table 2). Overall, 47 of these patients (39%) underwent surgery, of whom 30 (65%) had a good 1-year postoperative outcome. Sixteen patients (70%) who went directly to surgery had a good outcome, as did 14 (58%) of those who needed iEEG (Figure 3).

Forty-four TLE patients (9%) had a *positive MRI and PET-MRI concordance* but discordant results between MRI and EEG; 27 of this group (62%) had surgery, with a good outcome in 23 (85%).

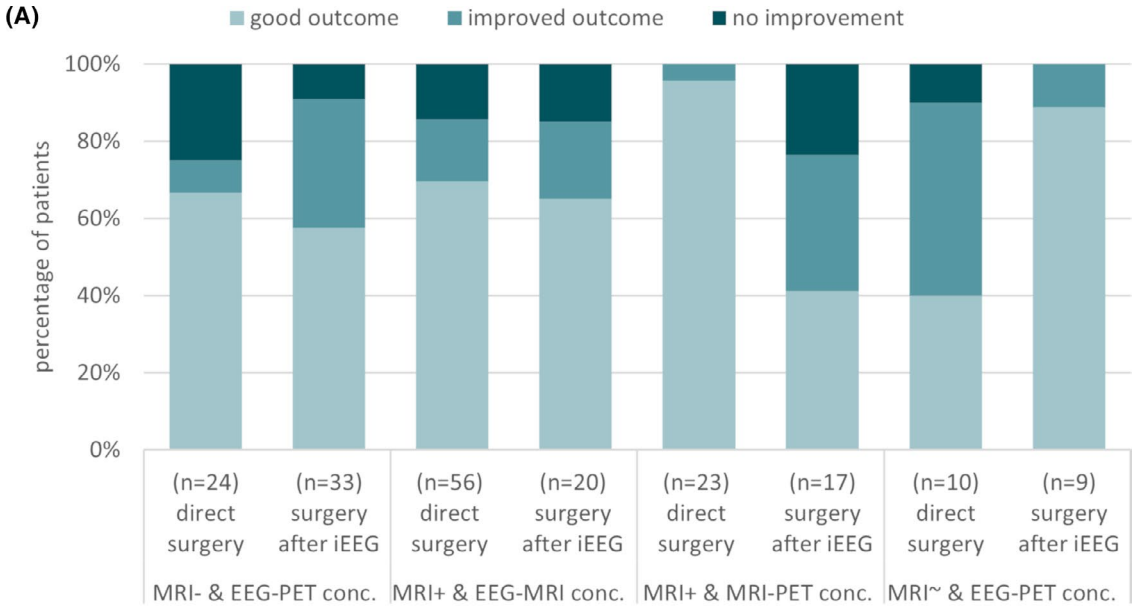
Ninety-seven TLE patients (20%) had a *positive MRI and EEG-MRI concordance*. In this group of patients, we report the results irrespective of concordance with their FDG-PET findings. Overall, 68 patients (70%) with a *positive MRI and EEG-MRI concordance* had surgery, of whom 46 patients (68%) had a good outcome 1 year after resection. A comparable percentage of patients had a good outcome after direct surgery ($n = 37$, 69%) and surgery after iEEG ($n = 9$, 64%).

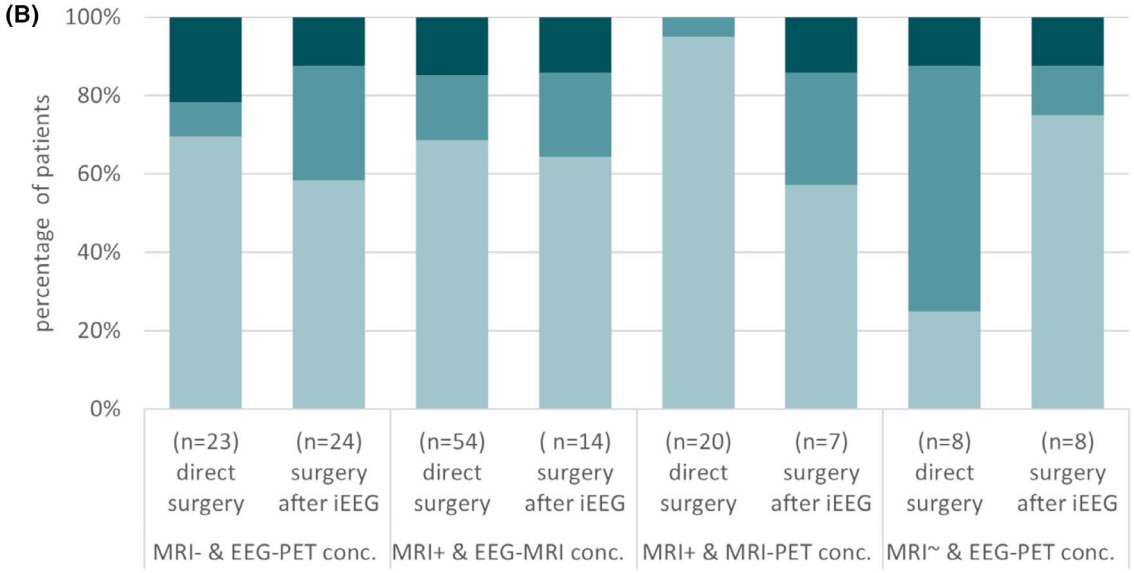
Twenty-eight TLE patients (6%) had an *equivocal MRI and EEG-PET concordance*; 16 patients (57%) in this subgroup had surgery, half of whom ($n = 8$, 50%) had a good 1-year outcome. An equal number of patients went directly to surgery or iEEG before surgery ($n = 8$ each).

Seventeen TLE patients (4%) had an equivocal MRI and concordance of all three diagnostic modalities (EEG, MRI, FDG-PET); 13 of these had surgery, and six (46%) had a good outcome.

3.7 | Group comparisons within TLE patients for outcome after epilepsy surgery

Comparing TLE patients who underwent surgery with *negative MRI and EEG-PET concordance* ($n = 47$) to


(A)
good outcome
improved outcome
no improvement
percentage of patients
100%
80%
60%
40%
20%
0%
(n=24) direct surgery
(n=33) surgery after iEEG
(n=56) direct surgery
(n=20) surgery after iEEG
(n=23) direct surgery
(n=17) surgery after iEEG
(n=10) direct surgery
(n=9) surgery after iEEG
MRI- & EEG-PET conc.
MRI+ & EEG-MRI conc.
MRI+ & MRI-PET conc.
MRI~ & EEG-PET conc.


(B)
percentage of patients
100%
80%
60%
40%
20%
0%
(n=23) direct surgery
(n=24) surgery after iEEG
(n=54) direct surgery
(n=14) surgery after iEEG
(n=20) direct surgery
(n=7) surgery after iEEG
(n=8) direct surgery
(n=8) surgery after iEEG
MRI- & EEG-PET conc.
MRI+ & EEG-MRI conc.
MRI+ & MRI-PET conc.
MRI~ & EEG-PET conc.

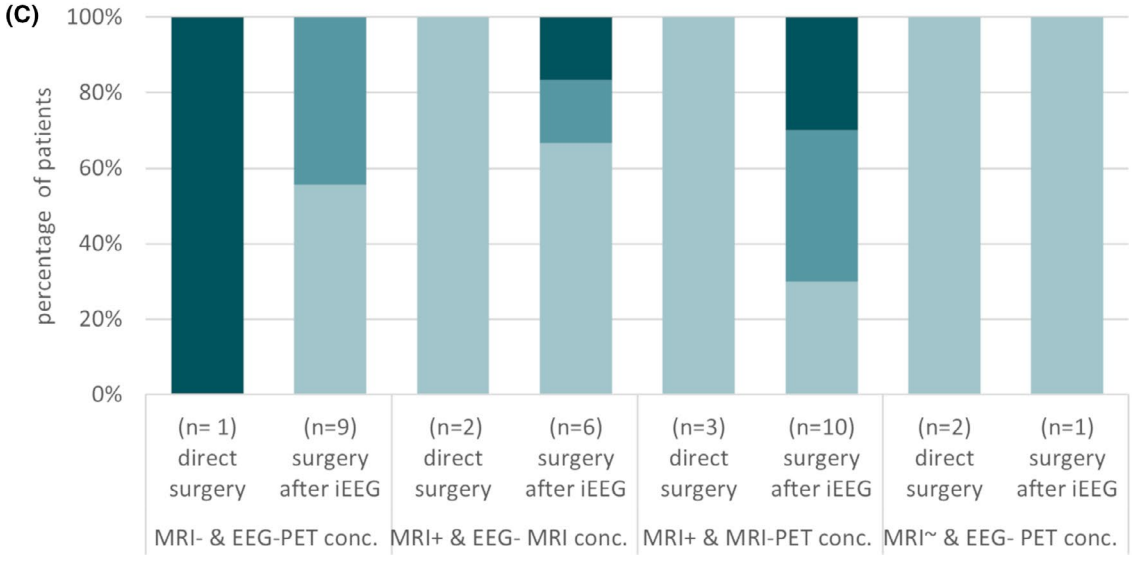

(C)
percentage of patients
100%
80%
60%
40%
20%
0%
(n= 1) direct surgery
(n=9) surgery after iEEG
(n=2) direct surgery
(n=6) surgery after iEEG
(n=3) direct surgery
(n=10) surgery after iEEG
(n=2) direct surgery
(n=1) surgery after iEEG
MRI- & EEG-PET conc.
MRI+ & EEG- MRI conc.
MRI+ & MRI-PET conc.
MRI~ & EEG- PET conc.

FIGURE 3 Epilepsy surgery outcome. (A–C) Epilepsy surgery outcome across all subgroups. (A) overall outcome, (B) temporal lobe epilepsy (TLE), (C) extratemporal lobe epilepsy (ETLE). Good outcome: International League Against Epilepsy (ILAE) 1 and 2; improved outcome: ILAE 3 and 4; no improvement: ILAE 5 and 6. In this subgroup analysis, we disregarded cases with no hypometabolism on 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and/or nonconcordance between FDG-PET and all other tests (overall: $n = 90$, 10%; TLE: $n = 53$, 11%; ETLE: $n = 37$, 17%). EEG, electroencephalography; EEG-MRI conc., concordance between ictal EEG results and epileptogenic focus on MRI; EEG-PET conc., concordance between ictal EEG results and FDG-PET hypometabolism; iEEG, intracranial EEG recordings; MRI, magnetic resonance imaging; MRI−, negative MRI; MRI~, equivocal MRI; MRI+, positive MRI; MRI-PET conc., concordance between positive MRI and PET, but no concordance with EEG; PET, positron emission tomography

those with *positive MRI and EEG-MRI concordance* ($n = 68$), there was no significant difference in good outcome 1-year after surgery in the overall group ($n = 30$, 65% vs. $n = 46$, 68%; Figure 3). There was also no significant difference in overall seizure outcome comparing cases with *positive MRI and EEG-MRI concordance* to those with *equivocal MRI and EEG-PET concordance* ($n = 8/16$, 68% vs. 50%).

3.8 | Extratemporal lobe epilepsy

Forty-three ETLE patients (20%) had a *negative MRI and concordance between EEG and FDG-PET* (Table 2); 10 of these patients had surgery, and half of those ($n = 5$) had a good outcome from surgery.

Twenty-two ETLE patients (10%) had a *positive MRI and PET-MRI concordance*; 13 (59%) had surgery, with a good outcome in six (46%).

In the ETLE group, only small numbers of patients had *equivocal MRI and EEG-PET concordance* ($n = 8$) or *positive MRI and concordant ictal EEG* ($n = 4$). Three patients (38%) with equivocal and eight patients (57%) with positive MRI had surgery, of whom all three patients with equivocal and six of eight with positive MRI had a good 1-year outcome.

4 | DISCUSSION

In this multicenter study, we present the largest published dataset of consecutive patients with DRE, who underwent FDG-PET scans as part of their presurgical workup, to date. By including patients from the daily clinical practice from representative epilepsy centers around the world and not applying advanced image analysis, as well as by using a variety of different MRI and PET scanners, we present real-world data from a heterogeneous group of patients with epilepsy.

Some previous studies have examined postsurgical seizure outcomes of patients with positive MRIs, negative MRIs, or equivocal MRIs who underwent FDG-PET as part of their presurgical evaluations, but most of those are single-center series with limited sample sizes.[20,23,25–27,35] Here, we provide data on the usefulness of FDG-PET as part of the evaluation for resective epilepsy surgery in almost 1000 patients from four established epilepsy centers from three continents representing a large and diverse population. Our data confirm that FDG-PET is highly sensitive for presurgical localization of the seizure onset zone. Overall, focal or regional hypometabolism in the FDG-PET scan was detected in 62% of the patients. In TLE, FDG-PET scans showed focal or regional hypometabolism in 77% of patients, and in ETLE in 56% of patients. This correlates well with previous studies, where FDG-PET has been found to provide localizing information in 60%–90% of patients with TLE and in 30%–60% of patients with ETLE.[16,27,36,37]

Although FDG-PET is quite effective in inferring the localization of the seizure onset zone, it often shows an area of hypometabolism with a greater extent than the actual seizure focus as demonstrated by EEG and MRI.[38,39] In epilepsy, FDG hypometabolism reflects the degree of cerebral dysfunction that may be due to loss of synaptic inputs.[40] The extent of removal of brain structures with FDG-PET hypometabolism has been found to correlate with the seizure outcome following temporal lobe resection.[41] Thus, the presence of an FDG-PET scan abnormality can be used to tailor placements for iEEG electrodes.

In our study, among those who were selected for surgery, there was no statistically significant difference in outcome among TLE patients with negative MRI compared to positive MRI. One year after surgery, 65% of TLE patients with *negative MRI but EEG-PET concordance* had no disabling seizures compared to 68% of TLE patients with *positive MRI and EEG concordance*. Some previous studies have demonstrated that patients with hypometabolism on FDG-PET concordant with EEG benefit from surgery as much as patients with hippocampus sclerosis identified on MRI. However, in those previous studies, good outcome of epilepsy surgery was on average 75%–84% in the MRI-negative group and 74%–86% in the MRI-positive group, which was higher than observed in our study.[19,20,25,42] However, these studies presented selected cohorts and not all consecutive patients with FDG-PET as we have done here. The outcome shown in this study is in line with results from the most recent Cochrane review on epilepsy surgery,

showing a good outcome (ILAE 1 + 2) in 64%.[43] Beyond that, the results of our study provide evidence that TLE patients with equivocal MRI are also good surgical candidates, although postsurgical outcome (50% seizure-free) is slightly less favorable than in patients with positive MRI (68%).

Conclusions for ETLE are limited by small numbers; 50% of patients with *negative MRI and EEG-PET concordance* had no disabling seizures after surgery and another 40% had a relevant improvement (ILAE 3 + 4) with a reduction in seizure frequency of >50%, which in this group of ETLE patients overall still means a relevant advantage compared to 2%–4% of seizure freedom with ASMs alone.[2] There is less literature on the role of FDG-PET in MRI-negative cases with ETLE compared to TLE. Overall, in the absence of positive MRI findings, seizure outcome is generally less favorable in ETLE due to lack of a distinct focus that can be resected.[44,45] Two studies have shown that in patients with nonlesional ETLE, focal hypometabolism on FDG-PET is a significant positive indicator of postoperative seizure freedom when used as a means of secondary diagnostic imaging.[16,23] In recent years, there have been relevant advances in the detection of FCD in ETLE patients with negative MRI through coregistration of FDG-PET and MRI.[24] In ETLE patients with FCD, the surgical outcome is as favorable as in patients with TLE.

Our results show that FDG-PET influenced decision-making in 47% of patients, with a significant difference between TLE and ETLE patients (58% and 44%). The presence of hypometabolism on FDG-PET increased the odds of being selected for direct surgery threefold and was not associated with the likelihood of subsequent iEEG. In three previous studies, FDG-PET data influenced presurgical decision-making in 53%,[27] 58%,[46] and 71% of cases.[36] In the latter study, nonconsecutive patients were included, and different selection criteria for the patients who underwent FDG-PET might have been the reasons for a relatively higher usefulness of FDG-PET.[30] Our study also showed that the presence of hypometabolism on FDG-PET reduced the likelihood of having further investigations. In another study, it was also observed that there was no difference in surgical outcome in patients who had or had not undergone iEEG.[42] On the other hand, patients with *equivocal MRI and EEG-PET concordance* benefited from iEEG; in our study, a significantly higher rate of patients from this subgroup were free of disabling seizures when they had undergone surgery after iEEG compared to direct surgery (89% vs. 40%).

We found an overall low rate of surgeries in our cohort ($n = 282$, 30%); this was particularly the case in patients with *negative MRI and EEG-PET concordance*. Here, twice as many patients as in the other subgroups did not move on to surgery (62% with TLE and 77% of those with ETLE), despite the overall good outcome after surgery shown here and in previous studies.[19,20,25] A contributing factor may be that a higher proportion of these patients declined the recommendation for direct surgery or iEEG (36% with TLE and 33% with ETLE). Overall rates of patients who declined the given recommendation of surgery or iEEG in our study (27%) are in line with the literature, where rates of 20%–50% are reported.[47–49] Additionally, epilepsy cases become increasingly complex with only 50% of patients undergoing surgery after presurgical assessment.[47,50]

There are limitations to our study. Although this is a multicenter study including data from four different countries from three continents and including consecutive cases, thereby avoiding selection bias (e.g., preselecting patients with a particular epilepsy syndrome or histopathology), the study design was retrospective. Furthermore, even though this is the largest cohort of FDG-PET in presurgical assessment of epilepsy patients to date, some groups, in particular those with ETLE, are small. Because only a small group of patients were younger than 18 years, the data from this study are not generalizable to a pediatric population. As not all patients underwent surgery or iEEG to determine the final correct localization of the seizure focus, the true localizing value of FDG-PET could be flawed. Additionally, the visual image analysis used in this study is subjective, and some reduction and asymmetry in intensity is seen even in the temporal lobes of healthy volunteers.[51] Furthermore, multiple MRI and PET scanners from different manufacturers with different software and hardware were used over the course of the acquisition of the FDG-PET scans in the different centers over different periods of time. As we did not harmonize the data or perform comparisons between the four sites, several causes of bias could have been introduced. In addition, there may be inter- and intrareader variability in the MRI, FDG-PET, and EEG interpretations among the different sites. Lesions may have been missed, particularly on 1.5-T MRI, therefore possibly increasing the false negative rate at the different centers. However, in our study, patients who had a 3-T MRI had a higher rate of negative MRIs ($n = 461$, 76%) compared to patients who had a 1.5-T MRI ($n = 117$, 34%). Additionally, rates of focal and regional hypometabolism on FDG-PET were similar between those who had a 3-T MRI ($n = 365$, 60%) and 1.5-T MRI ($n = 222$, 65%).

Although two of the four sites in this study used semiquantitative analysis in their assessment of FDG-PET, this type of analysis is not as in-depth as SPM, and two sites used visual assessment alone. Given the variability in data interpretation and a lack of a standard definition of hypometabolism, this could be seen as a limitation of our multicenter approach. All data review was performed by

experienced professionals with an understanding of the appearance of hypometabolism in the image data. The use of a subjective opinion by experts in the field is a reasonable approach for this retrospective multicenter study, and this represents a real-world situation. Furthermore, we did not use computerized methods of PET data analysis, such as SPM or SPM analysis using asymmetry indices. Other authors have previously shown that these methods can increase the diagnostic yield of FDG-PET.[35,52,53] Drzezga and colleagues showed in patients with ETLE that by using such techniques, the sensitivity of FDG-PET can be increased by 30%.[54]

All FDG-PET scans were performed interictally, and no seizures were reported during, before, or after the FDG-PET scans by any of the participating sites. However, none of the patients had EEG recordings during the FDG-PET scans. Furthermore, we did not consider areas of hypermetabolism in our analysis. Therefore, subclinical seizures may have occurred, and we cannot exclude that ictal FDG-PET studies were performed.

Overall, there was a small number of patients with surgery and seizure freedom in different groups. Hence, differences may not be significant and should be interpreted with caution.

5 | CONCLUSIONS AND CLINICAL IMPLICATIONS

Our multicenter study in close to 1000 epilepsy patients pooled data across three continents. It supports the findings of previous studies that FDG-PET is especially useful in patients with negative and equivocal MRIs and is an accurate noninvasive method in the clinical decision-making in patients referred for epilepsy surgery evaluation. If FDG-PET findings are congruent with ictal EEG, patients are good surgical candidates, with postsurgical outcomes comparable to those patients with positive MRI; thus, surgery can be recommended in those MRI-negative or equivocal cases.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. We used the STROBE cohort reporting guidelines.[55]

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