^{18}F-FDG PET Is an Early Predictor of Overall Survival in Suspected Atypical Parkinsonism

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Early prognostic stratification is desirable in patients with suspected atypical parkinsonian syndromes (APSs) for optimal treatment and counseling. We investigated the prognostic value of imaging disease-specific metabolism patterns with ^{18}F-FDG PET compared with that of clinical diagnosis. **Methods:** Seventy-eight patients with suspected APS at study inclusion underwent a follow-up of up to 5.9 y after prospective ^{18}F-FDG PET imaging. Survival data were analyzed by Kaplan–Meier and Cox regression analyses according to diagnostic classifications provided by ^{18}F-FDG PET at baseline and clinical diagnoses after a median follow-up of 1 y after PET. **Results:** Forty-four of 78 patients were alive 4.7 ± 0.6 y after PET. Patients diagnosed with an APS by PET or 1-y clinical follow-up showed a significantly shorter median survival time (4.1 y, age-adjusted hazard ratios [HRs] = 3.8 for both classifiers) than those diagnosed with Lewy-body diseases (LBDs; majority Parkinson disease [PD]; median survival time not reached). Subgroup classifications of progressive supranuclear palsy/corticobasal degeneration (PSP/CBD) or multiple-system atrophy (MSA) by PET and clinical follow-up were associated with significantly shorter survival than PD. Age-adjusted mortality was significantly increased for PSP/CBD (HR = 5.2) and MSA (HR = 5.6) classified by PET, but for PSP/CBD only when diagnosed by clinical follow-up (HR = 4.5). Patients with a PET pattern suggestive of PD with dementia/dementia with Lewy bodies (PDD/DLB) exhibited a trend toward shorter survival than those with PD (P = 0.07), whereas patients classified as PDD/DLB by clinical follow-up did not (P = 0.65). **Conclusion:** ^{18}F-FDG PET is an early predictor of survival in patients with clinically suspected APS. Detection of cortical or subcortical hypometabolism by ^{18}F-FDG PET is an unfavorable predictor. Risk stratification by ^{18}F-FDG PET appears to be at least as predictive as the 1-y follow-up clinical diagnosis. This finding strongly supports the early inclusion of PET imaging in patient care.

Key Words: ^{18}F-FDG PET; survival; prognosis; parkinsonism; atypical parkinsonian syndrome

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Early differentiation between Parkinson disease (PD) and atypical parkinsonian syndromes (APSs; including multiple-system atrophy [MSA], progressive supranuclear palsy [PSP], and corticobasal degeneration [CBD]) is pursued for decisions on treatment strategies and prognostic counseling. APSs are characterized by a rapid progression to disability and death. According to clinical and clinicopathologic studies, MSA, PSP, and CBD share a comparably short survival time of about 7–8 y from symptom onset or less than 3–4 y from clinical diagnosis (*1–8*). Survival in PD is distinctly better: although some population-based studies did not find higher mortality (*9*), others convincingly demonstrated an increased age-adjusted mortality in PD (*10,11*). As in APS (*1,2,5,8*), higher age at onset is also associated with a higher PD mortality (*9,10*), but median survival time was still 10.3 y in a recent population-based cohort with a high average age of 70 y at diagnosis (*9*). The cumulative incidence of PD with dementia (PDD) increases with age and disease duration up to 80%–90% (*12*), being associated with a strong increase in mortality (*9–11*). In fact, the mean time span between onset of cognitive impairment and death appears to be only about 2–4 y (*12–14*).

Disease-specific patterns of regional cerebral glucose metabolism depicted by ^{18}F-FDG PET allow for an accurate differential diagnosis between PD and APS (*15–17*). Moreover, PDD is characterized by posterior cortical hypometabolism, which is also observed in a significant fraction of nondemented PD patients (*16*). Recent studies suggest that this pattern may herald the conversion from PD to PDD and thus the onset of rapid deterioration (*18*). Given the high concordance between PET and clinical diagnoses (80% for the aforementioned groups) (*16*), it may be expected that disease-specific PET patterns also carry prognostic information. However, this rationale is challenged by the limited accuracy of the clinical diagnosis compared with the diagnosis at autopsy (70%–75%) (*4,19–23*), which implies that the correctness of the diagnosis or prognosis given by PET is ill-defined (55%–95%).

Against this background, we investigated whether ^{18}F-FDG PET provides an early prediction of survival in patients with clinically suspected APS. Patients with suspected APS at study inclusion underwent a follow-up of up to 5.9 y after prospective ^{18}F-FDG PET imaging. We compared the prognostic value of ^{18}F-FDG PET performed at baseline with that of clinical diagnosis finalized after a median follow-up of 1 y.

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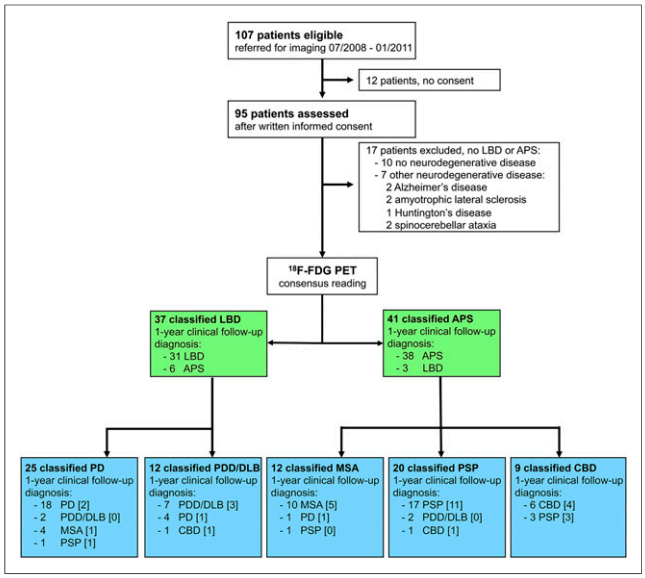

FIGURE 1. Study protocol and patient flow. Group of patients with LBD included patients with PD and patients with PDD/DLB. Patients with APS included subgroups of patients with MSA and PSP/CBD. Consensus readings of 2 investigators (unaware of clinical data) were used to classify patients by ^{18}F-FDG PET as either LBD or APS (green, first-level) and into LBD and APS subgroups (blue). One-year clinical follow-up diagnoses are given for comparison; numbers refer to number of patients; numbers in brackets refer to number of patients who died during extended follow-up.

MATERIALS AND METHODS

Study Design and Patients

The present study population has been reported before (*16*). Patient flow is summarized in Figure 1. Ninety-five of 107 patients referred for diagnostic imaging between July 2008 and January 2011 for clinically suspected, but not yet verified, early-stage APS (based on clinical symptoms and poor response to levodopa; Karnofsky score ≥ 40%) gave written informed consent.

After a median follow-up of 12 mo (minimum, 6 mo), 2 board-certified neurologists, specialized in movement disorders and unaware of the aforementioned imaging results, made the clinical diagnosis in accordance with consensus criteria (*16,24*). Seventeen patients were excluded from the comparison of the prognostic values of ^{18}F-FDG PET and 1-y follow-up diagnosis because the latter indicated a diagnosis other than APS or Lewy body diseases (LBDs); that is, PD, PDD, and dementia with Lewy bodies [DLB]). Thus, 78 patients (n = 44 for APS, n = 34 for LBD) were retained. Patients' characteristics are summarized in Table 1. As previously suggested (*16*), patients with the clinical diagnosis of PDD and DLB were allocated to a combined group (PDD/DLB), opposed to nondemented PD. Likewise, we also used a combined PSP/CBD diagnosis group for the present analyses, given the uncertainty of differentiating between these 2 diseases by clinical or imaging findings. At the time of imaging, there were no significant group differences in terms of sex, symptom duration, or Unified Parkinson Disease Rating Scale motor (part III) score. In line with the clinical diagnoses, APS patients showed higher Hoehn & Yahr (H&Y) scores than PD patients. Furthermore, PD patients were significantly younger than PDD/DLB patients, whereas PDD/DLB patients showed a significantly lower Mini-Mental State Examination (MMSE) score than PD and MSA patients (Table 1).

Of note, several patients were diagnosed as having PD by PET or 1-y clinical follow-up, as opposed to the initial suspicion. Supplemental Table 1 summarizes individual clinical features prompting the initial suspicion (e.g., multifactorial gait disorder caused by vascular disease and polyneuropathy, response to levodopa only at high-dose equivalents, tremor as a symptom with limited response to levodopa, and early onset comparable to MSA).

For the purpose of the present study, a movement disorders specialist conducted a structured telephone interview with the patient, the caregiver, or the caregiving physician (as appropriate) in September 2014. The vital status and the need for long-term professional care were systematically recorded. Overall disease severity was assessed by the H&Y score (range, 1–5, with higher scores indicating greater impairment) (*25*). The level of functional independence was evaluated using

TABLE 1
Demographic Characteristics of Patient Groups According to the 1-Year Clinical Follow-up Diagnosis

Clinical diagnosis	F/M (n)	Age (y)	Symptom duration (y)	Clinical follow-up (mo)	H&Y score	UPDRS-III score	MMSE score
LBD	16/18	65.0 (13.7)	3.6 (2.5)	12.1 (6.2)	2.7 (1.2)*	29.8 (13.7)	26.4 (4.6)
PD	10/13	61.6 (14.6)†	4.1 (2.2)	10.8 (6.1)	2.5 (1.2)‡	28.7 (14.1)	28.2 (2.4)§
PDD/DLB	6/5	72.0 (8.4)c	2.3 (2.6)	14.6 (5.8)	3.1 (1.2)	32.0 (13.3)	22.9 (5.7)§
APS	23/21	67.9 (8.5)	3.3 (1.9)	11.3 (4.4)	3.5 (0.9)*	33.1 (14.8)	26.7 (3.6)
MSA	8/5	65.5 (7.1)	3.5 (2.0)	9.6 (3.1)	3.5 (0.7)‡	33.3 (15.6)	28.4 (1.7)§
PSP/CBD	15/16	68.9 (8.9)	3.2 (1.8)	12.1 (4.7)	3.5 (1.0)‡	33.0 (14.7)	26.0 (4.0)

*Wilcoxon test LBD vs. APS, P = 0.002.

†ANOVA across subgroups, P = 0.029, post hoc Tukey-Kramer honestly significant difference test indicated significantly higher age in PDD/DLB than in PD (P < 0.05).

‡Kruskal–Wallis test across subgroups, P = 0.071, post hoc Wilcoxon test indicated significantly higher H&Y score in MSA (corrected P = 0.03) and PSP/CBD (corrected P = 0.01) than in PD.

§ANOVA across subgroups, P = 0.0009, post hoc Tukey-Kramer honestly significant difference test indicated significantly lower MMSE in PDD/DLB than in PD and MSA (P < 0.05).

UPDRS-III = Unified Parkinson Disease Rating Scale, part III (motor score).

Data are given as mean value followed by SD in parentheses, except for sex (F/M). Clinical follow-up refers to time between PET imaging and clinical diagnosis; other data refer to time of PET imaging, except MMSE: scores were available in 67 patients, in 23 patients only at follow-up. In the latter, 17 patients still showed normal scores (≥27). Availability of MMSE data did not differ between patient groups (P > 0.1).

TABLE 2
Survival Data

Diagnosis	Diagnosed by…	*n*	Patients who died (*n*)	All patients: Median follow-up (y)	2-y survival (%)	4-y survival (%)	Median survival (y)	Age-adjusted HR
LBD	PET	37	9 (24)	4.79 (4.20–5.38)	97	84	Not reached [not reached]*	1 (reference) [1 (reference)]*
	1-y follow-up	34	7 (21)	4.62 (4.13–5.11)	94	85	Not reached	1 (reference)
	Congruent cases	31	6 (19)	4.79 (4.08–5.50)	97	87	Not reached	1 (reference)
PD	PET	25	4 (16)	4.58 (4.40–4.76)	100	96	Not reached [not reached]*	1 (reference) [1 (reference)]*
	1-y follow-up	23	4 (17)	4.50 (4.11–4.89)	91	91	Not reached	1 (reference)
	Congruent cases	18	2 (11)	4.50 (4.05–4.95)	100	100	Not reached	1 (reference)
PDD/DLB	PET	12	5 (42)	5.04 (4.40–5.68)	92	58	Not reached [not reached]*	2.01 (0.54–7.56) [1.77 (0.59–5.26)]*
	1-y follow-up	11	3 (27)	5.04 (4.24–5.84)	100	73	Not reached	1.05 (0.24–4.69)
	Congruent cases	7	3 (43)	5.27 (4.86–5.68)	100	57	Not reached	2.33 (0.39–14.02)
APS	PET	41	25 (61)	4.56 (4.26–4.86)	85	54	4.13 (3.34–4.24) [4.16 (3.26–4.74)]*	3.81 (1.74–8.30)† [3.39 (1.71–6.71)]*†
	1-y follow-up	44	27 (61)	4.77 (4.46–5.08)	89	55	4.13 (3.47–4.29)	3.85 (1.67–8.87)†
	Congruent cases	38	24 (63)	4.77 (4.37–5.17)	87	53	4.05 (3.35–4.25)	5.19 (2.07–13.03)†
PSP/CBD	PET	29	19 (66)	4.77 (4.30–5.24)	86	48	3.86 (3.19–4.23) [3.86 (2.9–4.68)]*	5.15 (1.74–15.18)‡ [4.07 (1.71–9.72)]*‡
	1-y follow-up	31	21 (68)	4.91 (4.54–5.28)	87	48	3.86 (3.24–4.23)	4.46 (1.53–12.99)‡
	Congruent cases	27	19 (70)	4.91 (4.57–5.25)	85	44	3.49 (3.08–4.15)	7.36 (1.72–31.56)‡
MSA	PET	12	6 (50)	4.51 (3.88–5.14)	83	67	4.74 (3.05–4.67) [4.74 (3.00–4.74)]*	5.64 (1.54–20.67)‡ [4.94 (1.57–15.58)]*‡
	1-y follow-up	13	6 (46)	4.51 (4.10–4.92)	92	69	4.74 (3.48–4.84)	2.80 (0.79–9.88)
	Congruent cases	10	5 (50)	4.51 (4.12–4.90)	90	70	4.74 (3.21–4.73)	6.57 (1.25–34.47)‡

*Results from intention-to-treat analyses comprising all 95 patients who gave their consent to participate.
†Significant predictor of shorter survival for first-level classification.
‡Significant predictor of shorter survival for second-level classification.
Data in parentheses are percentage or 95% confidence interval. All time specifications refer to time since PET imaging. Two- and 4-y survival rates were estimated by Kaplan–Meier analyses (Fig. 2). Median follow-up was determined by reverse Kaplan–Meier method. Age-adjusted HRs were estimated by Cox proportional hazards analyses including first-level (LBD as reference) and second-level (PD as reference) diagnostic classifications as predictor variables.

the Schwab and England activities-of-daily-living scale (range, 0–100, with lower scores reflecting greater disease presence) (*26*).

^{18}F-FDG PET

PET scans were acquired and analyzed as described previously (*16*). In brief, PET scans were independently interpreted by 2 investigators with long-standing clinical experience in brain PET imaging who were unaware of the clinical data. The investigators rated standardized transaxial and sagittal PET images and 3-dimensional stereotactic surface projections (3D-SSP) depicting each individual's cerebral ^{18}F-FDG uptake (glucose metabolism) and its statistical deviation from a database of age-matched healthy controls (Neurostat/3D-SSP; Department of Radiology, University of Washington) (*27*). PET scans were interpreted in 2 consecutive levels using a priori–defined disease-specific patterns (*16*). The first-level decision entailed classifying each scan as indicative of either LBD or APS. On a second level, APS-positive scans were categorized as indicative of MSA, PSP, or CBD. In addition, LBD-positive scans were rated for PDD/DLB-suggestive hypometabolism of posterior cortical areas (i.e., absent: no or only mild and scattered areas of posterior cortical hypometabolism; present: larger, confluent posterior cortical areas of significant hypometabolism). As previously described (*16*), both investigators reached a high to very high interrater agreement for first-level (LBD vs. APS, Cohen $\kappa = 0.90$) and second-level classifications (MSA vs. PSP vs. CBD: Cohen $\kappa = 0.74$; PDD/DLB-suggestive hypometabolism: Cohen $\kappa = 0.82$). Thus, after both investigators rated all scans independently, a consensus was reached in discrepant cases for subsequent analyses.

Statistics

The software packages SPSS (version 21; IBM Corp.) and MedCalc (version 11.6; MedCalc Software) were used for statistical analyses. Survival times from PET imaging onward were calculated using Kaplan–Meier analyses based on classifications given by PET and 1-y clinical follow-up. In addition, we contemplated the subgroup of

patients with congruent PET and 1-y follow-up clinical diagnoses (group with highest diagnostic confidence). Log-rank tests were applied to compare survival distributions across diagnostic subgroups. Cox proportional hazards regression analyses were performed to assess the prognostic value of the different classifiers (categorical predictors). Age was included as continuous covariate. Results were considered significant if the P value was less than 0.05.

Study Approval

All procedures were approved by the local ethics committee. Written informed consent was obtained from all participants. The initial study was registered at the German Clinical Trials Register (DRKS00003613).

RESULTS

Survival Analyses

A total of 34 patients died during follow-up; 44 patients were still alive at final contact. Median follow-up duration was 4.77 y (95% confidence interval, 4.44–5.10; estimated by the reverse Kaplan–Meier method (*28*)). Table 2 summarizes the survival data for diagnostic classifications provided by PET, 1-y follow-up (final clinical diagnosis), and congruent cases.

As depicted in Figures 2A–2C, patients diagnosed with APS showed a significantly shorter survival than those with a diagnosis of LBD (first-level decision). In fact, diagnostic classification by PET, 1-y follow-up, or consensus thereof (69/78, or 88.5% of patients) yielded similar median survival durations (PET and 1-y follow-up, 4.13 y; consensus, 4.05 y) after time of PET imaging in APS, whereas median survival time was not reached in LBD (APS vs. LBD, all $P < 0.001$).

Considering APS and LBD subgroup classifications (second-level decisions), Kaplan–Meier analyses indicated significantly worse survival of patients with PET metabolism patterns suggestive of PSP/CBD ($P < 0.0005$, $\chi^2 = 14.4$) or MSA ($P < 0.01$, $\chi^2 = 7.5$) and a trend toward significance for PDD/DLB ($P = 0.0715$, $\chi^2 = 3.2$) when compared with those having a PET pattern compatible with PD (Fig. 2D). Based on clinical diagnoses after 1-y follow-up, patients with PSP/CBD ($P < 0.001$, $\chi^2 = 11.0$) or MSA ($P < 0.05$, $\chi^2 = 4.6$) also showed a significantly worse survival rate than patients with PD, whereas there was no significant difference in survival between PDD/DLB ($P = 0.647$, $\chi^2 = 0.2$) and PD (Fig. 2E). Median survival time was reached for PSP/CBD (3.86 y after PET for both classifications) and MSA (4.74 y for both classifications); median survival time was not reached for PDD/DLB (Table 2). Interestingly, survival curves of patients with congruent PET and clinical classifications (62/78, or 79.5% patients) were similar to those of patients with PET alone (Fig. 2F).

Table 3 gives an overview of survival data of patients with discrepant PET and follow-up clinical diagnoses. Albeit vital status and neurologic performance at last contact (given by H&Y score or activities-of-daily-living scale) suggest correct prognostic classification by either PET or follow-up clinical diagnosis in some cases, no clear pattern is apparent given the limited number of discrepant cases.

Cox Proportional Hazards Model

Age-adjusted hazard ratios (HRs) for first- and second-level classifications as predictors for overall survival are also given in Table 2. Regression analyses indicated a significantly higher age-adjusted mortality for patients classified as APS (first-level decision), with an HR of 3.81 for PET and 3.85 for 1-y follow-up (HR relative to LBD).

Regarding second-level decisions, being classified as PSP/CBD by PET (HR = 5.15; relative to PD) or by 1-y follow-up (HR = 4.46) was associated with significantly increased mortality. In contrast, a diagnosis of MSA was a significant predictor of worse age-adjusted survival only for PET (HR = 5.64) but not for 1-y follow-up (HR = 2.80). The age-adjusted HR for patients with a PDD/DLB-suggestive hypometabolism on PET (HR = 2.01) tended to be higher than the HR for patients clinically diagnosed with PDD/DLB (HR = 1.05), but neither group exhibited a statistically significant higher age-adjusted mortality than PD. In direct comparisons, the aforementioned differences in HR between PET and 1-y follow-up diagnosis did not reach statistical significance (neither first- nor second-level). As may be expected (highest diagnostic confidence), a congruent PET and clinical classification was consistently associated with a higher age-adjusted HR than for either of the 2 classifiers alone (Table 2).

Finally, when all 95 patients (including the 17 patients excluded from the main analysis because of alternative clinical diagnoses (Fig. 1)) were subjected to an intention-to-treat analysis of the prognostic value of PET, results remained essentially unchanged (Table 2).

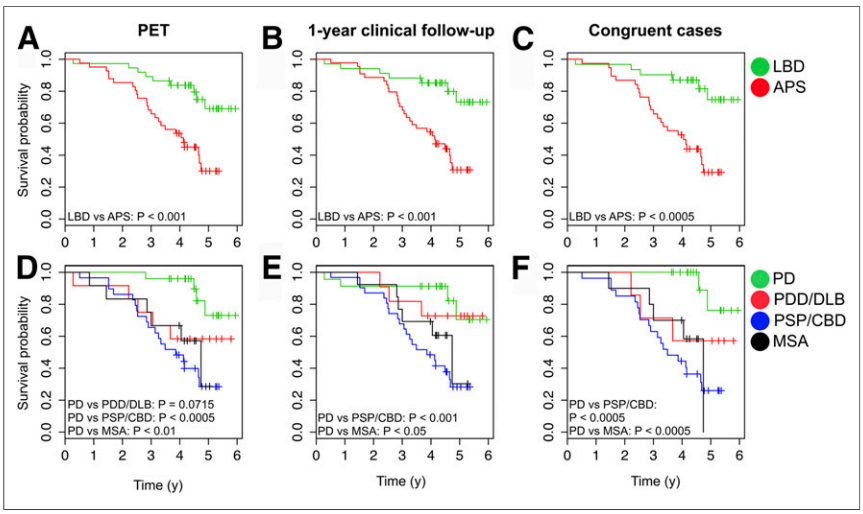

FIGURE 2. Kaplan–Meier survival plots. Survival rates were estimated using Kaplan–Meier analyses for first-level (A–C) and second-level (D–F) diagnostic classifications according to PET, 1-y clinical follow-up, and congruent classifications thereof ($n = 78$; except C, $n = 69$, and F, $n = 62$). P values for survival differences are given, if $P < 0.1$ (log-rank tests).

DISCUSSION

The present study demonstrates that ^{18}F-FDG PET is a powerful predictor of overall survival in patients with clinically suspected early-stage APS. Regarding the distinction between LBD and APS (first-level), PET and the 1-y follow-up clinical diagnosis yielded a virtually identical prediction of overall survival. Median survival time was significantly shorter in patients classified as APS by PET or clinical follow-up, a finding that agrees with the current literature. Considering subgroup classifications (second-level), PET tended to give a more differentiated

TABLE 3
Characteristics of Patients with Discrepant PET and 1-Year Follow-up Clinical Diagnoses

1-y follow-up diagnosis	PET diagnosis	Vital status	Disease duration	H&Y score	ADL
PD	MSA	Dead	3.5	—	—
PD	PDD/DLB	Alive	7.7	5	40
PD	PDD/DLB	Alive	8.2	4	90
PD	PDD/DLB	Alive	5.2	4	50
PD	PDD/DLB	Dead	4.2	—	—
MSA	PD	Alive	5.2	5	20
MSA	PD	Alive	12.2	5	20
MSA	PD	Dead	5.7	—	—
PDD/DLB	PD	Alive	6.0	2.5	90
PDD/DLB	PD	Alive	5.4	4	20
PSP/CBD	PD	Alive	7.2	4	80
PSP/CBD	PD	Dead	5.2	—	—
PDD/DLB	PSP/CBD	Alive	5.3	5	20
PDD/DLB	PSP/CBD	Alive	7.2	3	60
PSP/CBD	PDD/DLB	Dead	8.0	—	—
PSP/CBD	MSA	Alive	8.1	3	90

ADL = activities-of-daily-living scale.

Patients were grouped into 3 categories (see the 3 shaded/unshaded table sections): favorable 1-y follow-up clinical diagnosis (i.e., PD) but unfavorable PET diagnosis (i.e., PDD/DLB, MSA, or PSP/CBD), favorable PET diagnosis but unfavorable clinical diagnosis, and unfavorable clinical and PET diagnoses.

prognostic stratification than the clinical follow-up diagnosis (Figs. 2D–2F and Table 2). This finding is corroborated by a similar prognostic stratification achieved in patients with congruent PET and clinical classifications (consensus with highest confidence). Overall, these are remarkable results if one considers that the clinical diagnosis was finalized after a median follow-up of 1 y after the PET scan. A time span of 1 y (or 25% of remaining life expectancy) typically corresponds to a relevant disease progression in APS, which would be expected to translate into a higher diagnostic and prognostic clinical confidence.

To our knowledge, this study is the first to compare the prognostic value of PET and clinical diagnosis. Except for few individual cases (*17*), a systematic validation of PET classifications against postmortem histopathology has not been accomplished. Considering the limited accuracy of clinical diagnosis of about 70%–75% for PD (*19–21*) or APS (even worse for CBD) (*4,20,22,23*), the use of clinical diagnosis as the reference standard constitutes a central limitation of all previous diagnostic PET studies. The present study circumvents this limitation by focusing on prognosis and selecting the most important, hard clinical endpoint. Thereby we demonstrate that PET is a prognostic marker on its own. However, the good agreement between the disease-specific survival data of the present PET study and earlier postmortem studies also provides indirect support to the notion that metabolic patterns are valuable means for differential diagnosis (*2–5,7,13*).

Of note, we included only patients with an uncertain initial diagnosis because PET would be most useful in these patients, who represent an often-encountered initial clinical dilemma. Thus, albeit we have access to an early PET scan, we do not have access to a proper initial clinical diagnosis. Given the lack of an initial clinical diagnosis, we explored the possible prognostic value of general disease severity (not shown in detail): including the H&Y score at time of PET in multivariate analyses as a marker of disease severity affected the prognostic value of ^{18}F-FDG PET only marginally (HR = 3.4, 4.5, and 5.0 for APS, PSP/CBD, and MSA, respectively). Similarly, dysphagia or the presence of falls during the first year had little effect on the prognostic value of ^{18}F-FDG PET (HR = 3.7, 5.1, and 5.5 for APS, PSP/CBD, and MSA, respectively). In addition, we tried to enhance our prediction models by including regional PET analyses (normalized ^{18}F-FDG uptake of striatum, cerebellum, thalamus, and major lobes, as well as the frontal/parietooccipital uptake ratio). Relative regional metabolism of cerebellum; striatum; and frontal, temporal, and parietal lobes predicted survival at least at trend level ($P < 0.1$). However, when regional variables were included in models with visual PET pattern classifications (first- or second-level), only visual PET classifications and age remained significant predictors of survival.

We contemplated a combined PSP/CBD group. PSP and CBD are considered to belong to the same disease spectrum, with several common clinical, pathologic, genetic, and biochemical features (*29*). Consequently, clinical distinction between PSP and CBD can be challenging, with frequent misdiagnoses in both directions (*4,30*). Likewise, PET imaging patterns in patients with the clinical diagnoses of PSP and CBD may be similar, and distinctive features are still a matter of debate (*31–33*). Of note, median survival time in PSP and CBD were not significantly different (neither for PET nor for clinical diagnosis). We also used a combined PDD/DLB grouping because the clinical distinction between PDD and DLB is controversial, and metabolic patterns in PDD and DLB show only subtle differences, if any (*34*). Of note, a PET classification according to the presence of a PDD/DLB-suggestive hypometabolism may include not only patients

with manifest PDD or DLB, as for clinical classification, but also a significant fraction of nondemented PD patients who are probably at increased risk of dementia and thus have a worse prognosis (*18*). Preceding posterior cortical hypometabolism at a nondemented stage has been described in patients who later converted to DLB (*35*) and PDD (*36*). Furthermore, patients with PD and mild cognitive impairment, who are at increased risk of dementia, exhibit decreased cortical metabolism similar to that seen in PDD (*18*). Therefore, if a dichotomization between PD and PDD/DLB is pursued, PET may be expected to provide a better prognostic stratification than clinical diagnosis is able to. On the other hand, using a combined clinical PDD/DLB classification may not be ideal for prognostic statements, as earlier studies suggest that overall survival from onset of dementia may be shorter in PDD than DLB (*9,12,13*). Taken together, these findings suggest that a simple dichotomization may not take full advantage of the combined prognostic potential of PET and clinical findings. We did not attempt to unravel the contributions of clinical diagnosis, cognitive status, and PET findings to predicting survival in patients with LBD since no comprehensive and standardized cognitive assessment was performed at study entry.

CONCLUSION

^{18}F-FDG PET is a powerful predictor of overall survival in patients with clinically suspected early-stage APS. Detection of cortical or subcortical hypometabolism by ^{18}F-FDG PET is an unfavorable predictor. Risk stratification by ^{18}F-FDG PET appears to be at least as predictive as the 1-y follow-up clinical diagnosis. This finding strongly supports the early inclusion of PET imaging in patient care to aid decisions on treatment strategies, clinical trial participation, and prognostic counseling.

DISCLOSURE

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