\textsuperscript{18}F-FDG PET is an early predictor of overall survival in suspected atypical parkinsonism

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Running title: PET predicts survival in parkinsonism.
ABSTRACT

Early prognostic stratification is desirable in patients with suspected atypical parkinsonian syndromes (APS) for optimal treatment and counseling. We investigated the prognostic value of imaging disease-specific metabolism patterns with $^{18}$F-FDG PET compared to the clinical diagnosis.

Methods: Seventy-eight patients with suspected APS at study inclusion underwent a follow-up of up to 5.9 years 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 year after PET.

Results: Forty-four of 78 patients were alive at 4.7±0.6 years after PET. Patients diagnosed with an atypical parkinsonian syndrome (APS) by PET or 1-year clinical follow-up showed a significantly shorter median survival time (4.1 years, age-adjusted hazard ratios [HR]=3.8 for both classifiers) than those diagnosed with Lewy-body diseases (LBD; majority Parkinson’s disease, PD; median survival time not reached). Subgroup classifications of progressive supranuclear palsy/corticobasal degeneration (PSP/CBD) or multisystem 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 only for PSP/CBD 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 towards shorter survival than 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 $[^{18}\text{F}]$FDG-PET is
an unfavorable predictor. Risk stratification by $^{18}$F-FDG PET appears to be at least as predictive as the 1-year follow-up clinical diagnosis. This strongly supports the early inclusion of PET imaging into patient care.

**Key words:** $^{18}$F-fluorodeoxyglucose positron emission tomography, survival, prognosis, parkinsonism, atypical parkinsonian syndrome.
INTRODUCTION

Early differentiation between Parkinson’s disease (PD) and atypical parkinsonian syndromes (APS; including multiple system atrophy [MSA], progressive supranuclear palsy [PSP], and corticobasal degeneration [CBD]) is pursued for decisions on treatment strategies and prognostic counseling. APS are characterized by a rapid progression to disability and death. According to clinical and clinicopathological studies, MSA, PSP, and CBD share a comparably short survival of about 7-8 years from symptom onset or less than 3-4 years from clinical diagnosis (1-8). Survival in PD is distinctly better: While some population-based studies did not find higher mortality (e.g., 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 years in a recent population-based cohort with a high average age of 70 years 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 years (12-14).

Disease-specific patterns of regional cerebral glucose metabolism depicted by positron emission tomography with [18F]fluorodeoxyglucose ([18F-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 non-demented PD patients (16). Recent studies suggest that this pattern may herald the conversion from PD to PDD and thus rapid deterioration (reviewed in 18). Given the high concordance between PET and clinical diagnoses (about 80% for the aforementioned groups) (16), it may be expected that disease-specific PET patterns
also carry prognostic information. However, this rational is challenged by the limited accuracy of the clinical diagnosis compared to the diagnosis at autopsy (70-75%) (4, 19-23), which implies that the correctness of the diagnosis/prognosis given by PET is ill-defined at the moment (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 years after prospective $^{18}$F-FDG PET imaging. We compared the prognostic value of $^{18}$F-FDG PET performed at baseline and of the clinical diagnosis finalized after a median follow-up of 1 year.
**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 months (minimum 6 months) two board-certified neurologists specialized in movement disorders and blinded for aforementioned imaging results made the clinical diagnosis in accordance to consensus criteria (16, 24). Seventeen patients were excluded from the comparison of the prognostic values of 18F-FDG PET and 1-year follow-up diagnosis, because the latter indicated a diagnosis other than APS or Lewy body diseases (LBD; i.e., PD, PDD, and dementia with Lewy bodies [DLB]). Thus, 78 patients (n = 44 APS, n = 34 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 non-demented PD. Likewise, we also used a combined PSP/CBD diagnosis group for the present analyses given the uncertainty of differentiating between these two diseases by clinical or imaging findings. At time of imaging, there were no significant group differences in terms of sex, symptom duration, or Unified Parkinson's 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 (see Table 1).
Of note, several patients were diagnosed as PD by PET and/or 1-year clinical follow-up, opposed to the initial suspicion. Supplemental Table S1 summarizes individual clinical features prompting the initial suspicion (e.g., multifactorial gait disorder for example caused by vascular disease and polyneuropathy, response to levodopa only at high dose equivalents, tremor as a symptom with limited response to levodopa, 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 and/or the care-giving 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 the Schwab and England activities of daily living scale (ADL; range 0–100, with lower scores reflecting greater disease burden) (26).

18F-FDG PET

PET scans were acquired and analyzed as described previously (16). In brief, PET scans were independently interpreted by two investigators with long-standing clinical experience in brain PET imaging who were blinded to clinical data. The investigators rated standardized transaxial and sagittal PET images and three-dimensional stereotactic surface projections (3D-SSP) depicting each individual’s cerebral 18F-FDG uptake (glucose metabolism) and its statistical deviation from a database of age-matched healthy controls (Neurostat/3D-SSP) (27). PET scans were interpreted in two consecutive levels using a-priori defined disease-specific patterns (16). The 1st-level decision entailed a classification of each scan as being indicative of either LBD or APS. On 2nd level, APS-positive scans were categorized as being 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 inter-rater agreement for 1st-level (LBD vs APS, Cohen’s kappa = 0.90) and 2nd-level classifications (MSA vs. PSP vs. CBD: Cohen’s kappa = 0.74; PDD/DLB-suggestive hypometabolism: Cohen’s 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 Corporation) and MedCalc (V11.6; 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-year clinical follow-up. In addition, we contemplated the subgroup of patients with congruent PET and 1-year 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 \( p < 0.05 \).

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 years (95% CI 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-year follow-up (final clinical diagnosis) and congruent cases.

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

Considering APS and LBD subgroup classifications (2nd-level decisions), Kaplan-Meier analyses indicated a 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 towards significance for PDD/DLB ($p=0.0715$, Chi$^2=3.2$) compared to those with a PET pattern compatible with PD (Figure 2D). Based on clinical diagnoses after 1-year 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 than patients with PD, whereas there was no significant difference in survival between PDD/DLB ($p=0.647$, Chi$^2=0.2$) and PD (Figure 2E). Median survival time was reached for PSP/CBD (3.86 years after PET for both classifications) and MSA (4.74 years for both classifications), while 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 very similar to those provided by PET alone (Figure 2F).

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

**Cox Proportional Hazards Model**

Age-adjusted hazard ratios (HR) for 1st-level and 2nd-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 (1st-level decision) with a HR of 3.81 for PET and 3.85 for 1-year follow-up (HR relative to LBD).

Regarding 2nd-level decisions, being classified as PSP/CBD by PET (HR=5.15; relative to PD) or by 1-year 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-year 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, aforementioned differences in HR between PET and 1-year follow-up diagnosis did not reach statistical significance (neither 1st nor the 2nd 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 each of the two classifiers alone (see Table 2).
Finally, when all 95 patients (including those 17 patients which had been excluded from the main analysis because of alternative clinical diagnoses, see Figure 1) were subjected to an intention-to-treat analysis of the prognostic value of PET, results remained essentially unchanged (see Table 2).

**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 (1st level), PET and the 1-year 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, which agrees with the current literature. Considering subgroup classifications (2nd level), PET tended to give a more differentiated prognostic stratification than the clinical follow-up diagnosis (see Figure 2D-F 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 year after the PET scan. A time span of 1 year (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 (e.g., 17), a systematic validation of PET classifications against post mortem 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 diagnoses as reference standard constitutes a central limitation of all previous diagnostic PET studies. The present study circumvents this limitation by focussing 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 post mortem 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 stage at time of PET as a marker of disease severity into multivariate analyses did only marginally affect the prognostic value of 18F-FDG PET (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 essentially did not alter the prognostic value of 18F-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 18F-FDG uptake of striatum, cerebellum, thalamus, 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 into models with visual PET pattern classifications (1st- or 2nd-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, pathological, genetic and biochemical features (29). Consequently, clinical distinction between PSP and CBD can be very 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 very similar and distinctive features are still 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, since the clinical distinction between PDD and DLB is controversial and metabolic patterns in PDD and DLB show only very subtle differences (if any) (34). Of note, a PET classification according to the presence of a PDD/DLB-suggestive hypometabolism does not only include patients with manifest PDD or DLB (as for clinical classification), but may also include a significant fraction of non-demented PD patients with probably increased risk of dementia and thus worse prognosis (reviewed in 18). Preceding posterior cortical hypometabolism at a non-demented stage has been described in patients who later converted to DLB (35) and PDD (36). Furthermore, patients with PD and mild cognitive impairment (PD-MCI), 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 the clinical diagnosis. On the other hand, using a combined clinical PDD/DLB classification may not be ideal for prognostic statements, since earlier studies suggest that overall survival from onset of dementia may be shorter in PDD than DLB (9, 12, 13). Taken together, a simple dichotomization probably does 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 finding to predicting survival in patients with LBD since no
comprehensive and standardized cognitive assessment was performed at study entry.

CONCLUSION

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

Dr. Hellwig received research support from GE Healthcare. Prof. Dr. Weiller serves as a consultant for Pierre Fabre. Prof. Dr. Dr. Meyer receives research support from GE Healthcare and Piramal Life Sciences. Dr. Buchert receives research support from Piramal Life Sciences. Prof. Dr. Vach serves as a consultant for the Nordic Institute for Chiropractice and Clinical Biomechanics, Odense, Denmark, the Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark. Dr. Amtage, Dr. Tüschler, Dr. Spehl, Dr. Frings, Prof. Dr. Weber, and Dr. Rijntjes declare no conflicts of interest.

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Figure 1: Study protocol and patient flow

The group of patients with a Lewy body disease (LBD) included patients with Parkinson’s disease (PD) and patients with PD with dementia or dementia with Lewy bodies (PDD/DLB). Patients with an atypical parkinsonian syndrome (APS) included subgroups of patients with multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Consensus readings of two investigators (blinded for clinical data) were used to classify patients by $^{18}$F-FDG PET as either LBD or APS (green; 1st level) and into the LBD and APS subgroups (blue). One-year clinical follow-up diagnoses are given for comparison, numbers refer to the number of patients, numbers in brackets refer to the number of patients died during the extended follow-up.
**Figure 2: Kaplan-Meier Survival Plots.**

Survival rates were estimated using Kaplan-Meier analyses for 1st level (A-C) and 2nd level (D-F) diagnostic classifications according to PET, 1-year 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).
### Table 1: Demographic characteristics of patient groups according to the 1-year clinical follow-up diagnosis

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Sex (female/male)</th>
<th>Age (years)</th>
<th>Symptom duration (years)</th>
<th>Clinical follow-up (months)</th>
<th>H&amp;Y stage</th>
<th>UPDRS-III score</th>
<th>MMSE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBD</td>
<td>16/18</td>
<td>65.0 (13.7)</td>
<td>3.6 (2.5)</td>
<td>12.1 (6.2)</td>
<td>2.7 (1.2)</td>
<td>29.8 (13.7)</td>
<td>26.4 (4.6)</td>
</tr>
<tr>
<td>PD</td>
<td>10/13</td>
<td>61.6 (14.6)</td>
<td>4.1 (2.2)</td>
<td>10.8 (6.1)</td>
<td>2.5 (1.2)</td>
<td>28.7 (14.1)</td>
<td>28.2 (2.4)</td>
</tr>
<tr>
<td>PDD/DLB</td>
<td>6/5</td>
<td>72.0 (8.4)</td>
<td>2.3 (2.6)</td>
<td>14.6 (5.8)</td>
<td>3.1 (1.2)</td>
<td>32.0 (13.3)</td>
<td>22.9 (5.7)</td>
</tr>
<tr>
<td>APS</td>
<td>23/21</td>
<td>67.9 (8.5)</td>
<td>3.3 (1.9)</td>
<td>11.3 (4.4)</td>
<td>3.5 (0.9)</td>
<td>33.1 (14.8)</td>
<td>26.7 (3.6)</td>
</tr>
<tr>
<td>MSA</td>
<td>8/5</td>
<td>65.5 (7.1)</td>
<td>3.5 (2.0)</td>
<td>9.6 (3.1)</td>
<td>3.5 (0.7)</td>
<td>33.3 (15.6)</td>
<td>28.4 (1.7)</td>
</tr>
<tr>
<td>PSP/CBD</td>
<td>15/16</td>
<td>68.9 (8.9)</td>
<td>3.2 (1.8)</td>
<td>12.1 (4.7)</td>
<td>3.5 (1.0)</td>
<td>33.0 (14.7)</td>
<td>26.0 (4.0)</td>
</tr>
</tbody>
</table>

Abbreviations: H&Y, Hoehn & Yahr stage; MMSE, Mini-Mental State Examination; UPDRS-III, Unified Parkinson’s Disease Rating Scale, part III (motor score); for additional abbreviations see Figure 1.

Data are given as mean value (standard deviation). Clinical follow-up refers to the time between PET imaging and clinical diagnosis; other data refer to the 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). a Wilcoxon test LBD vs APS, p=0.002. b Kruskal-Wallis test across subgroups, p=0.071, post hoc Wilcoxon test indicated a significant higher H&Y for MSA (p_corrected=0.03) and PSP/CBD.
\( p_{\text{corrected}} = 0.01 \) compared to PD. \(^c\)Analysis of variance (ANOVA) across subgroups, \( p = 0.029 \), post hoc Tukey-Kramer honestly significant difference (HSD) test indicated significant higher age in PDD/DLB compared to PD \( (p < 0.05) \). \(^d\)ANOVA across subgroups, \( p = 0.0009 \), post hoc Tukey-Kramer HSD test indicated significant lower MMSE in PDD/DLB compared to PD and MSA \( (p < 0.05) \).
Table 2: Survival Data

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnosed by ...</th>
<th>N</th>
<th>Patients died</th>
<th>N (%)</th>
<th>Median (95% CI) Follow-up (years)</th>
<th>2-Year Survival (%)</th>
<th>4-Year Survival (%)</th>
<th>Median (95% CI) Survival (years)</th>
<th>Age-adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBD PET</td>
<td></td>
<td>37</td>
<td>9 (24)</td>
<td>4.79 (4.20 - 5.38)</td>
<td>97</td>
<td>84</td>
<td>Not reached</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>1-year follow-up</td>
<td></td>
<td>34</td>
<td>7 (21)</td>
<td>4.62 (4.13 – 5.11)</td>
<td>94</td>
<td>85</td>
<td>Not reached</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>congruent cases</td>
<td></td>
<td>31</td>
<td>6 (19)</td>
<td>4.79 (4.08 – 5.50)</td>
<td>97</td>
<td>87</td>
<td>Not reached</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>PD PET</td>
<td></td>
<td>25</td>
<td>4 (16)</td>
<td>4.58 (4.40 – 4.76)</td>
<td>100</td>
<td>96</td>
<td>Not reached</td>
<td>1 (reference)</td>
<td></td>
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<tr>
<td>1-year follow-up</td>
<td></td>
<td>23</td>
<td>4 (17)</td>
<td>4.50 (4.11 – 4.89)</td>
<td>91</td>
<td>91</td>
<td>Not reached</td>
<td>1 (reference)</td>
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<tr>
<td>congruent cases</td>
<td></td>
<td>18</td>
<td>2 (11)</td>
<td>4.50 (4.05 – 4.95)</td>
<td>100</td>
<td>100</td>
<td>Not reached</td>
<td>1 (reference)</td>
<td></td>
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<tr>
<td>PDD/DLB PET</td>
<td></td>
<td>12</td>
<td>5 (42)</td>
<td>5.04 (4.40 – 5.68)</td>
<td>92</td>
<td>58</td>
<td>Not reached</td>
<td>2.01 (0.54 – 7.56)</td>
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<tr>
<td>1-year follow-up</td>
<td></td>
<td>11</td>
<td>3 (27)</td>
<td>5.04 (4.24 – 5.84)</td>
<td>100</td>
<td>73</td>
<td>Not reached</td>
<td>1.05 (0.24 – 4.69)</td>
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<tr>
<td>congruent cases</td>
<td></td>
<td>7</td>
<td>3 (43)</td>
<td>5.27 (4.86 – 5.68)</td>
<td>100</td>
<td>57</td>
<td>Not reached</td>
<td>2.33 (0.39 – 14.02)</td>
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</tbody>
</table>
### Table 1: Survival Analysis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>PET</th>
<th>Follow-up</th>
<th>N</th>
<th>N (%)</th>
<th>Median (Min - Max)</th>
<th>4-year Survival (95% CI)</th>
<th>5-year Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APS</strong></td>
<td></td>
<td>1-year</td>
<td>41</td>
<td>25 (61)</td>
<td>4.56 (4.26 – 4.86)</td>
<td>4.13 (3.34 – 4.24)</td>
<td>3.81 (1.74 – 8.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>follow-up</td>
<td>85</td>
<td>54</td>
<td></td>
<td>[4.16 (3.26 – 4.74)]</td>
<td>[3.39 (1.71 - 6.71)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>38</td>
<td>24 (63)</td>
<td>4.77 (4.37 – 5.17)</td>
<td>4.05 (3.35 – 4.25)</td>
<td>5.19 (2.07 – 13.03)</td>
</tr>
<tr>
<td><strong>PSP/CBD</strong></td>
<td></td>
<td>1-year</td>
<td>29</td>
<td>19 (66)</td>
<td>4.77 (4.30 – 5.24)</td>
<td>3.86 (3.19 – 4.23)</td>
<td>5.15 (1.74 – 15.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>follow-up</td>
<td>86</td>
<td>48</td>
<td></td>
<td>[3.86 (2.9 – 4.68)]</td>
<td>[4.07 (1.71 – 9.72)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27</td>
<td>19 (70)</td>
<td>4.91 (4.57 – 5.25)</td>
<td>3.49 (3.08 – 4.15)</td>
<td>7.36 (1.72 – 31.56)</td>
</tr>
<tr>
<td><strong>MSA</strong></td>
<td></td>
<td>1-year</td>
<td>12</td>
<td>6 (50)</td>
<td>4.51 (3.88 – 5.14)</td>
<td>4.74 (3.05 – 4.67)</td>
<td>5.64 (1.54 – 20.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>follow-up</td>
<td>83</td>
<td>67</td>
<td></td>
<td>[4.74 (3.00 – 4.74)]</td>
<td>[4.94 (1.57 – 15.58)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13</td>
<td>6 (46)</td>
<td>4.51 (4.10 – 4.92)</td>
<td>4.74 (3.48 – 4.84)</td>
<td>2.80 (0.79 – 9.88)</td>
</tr>
</tbody>
</table>

All time specifications refer to the time since PET imaging. 2- and 4-year survival rates were estimated by Kaplan-Meier analyses (see also Figure 2). Median follow-up was determined by the reverse Kaplan Meier method. Age-adjusted HR were estimated by Cox proportional hazards analyses including 1st level (LBD as reference) and 2nd level (PD as reference) diagnostic classifications as predictor variables: a,bsignificant predictors of shorter survival for 1st and 2nd level classifications, respectively. Results from intention to treat analyses comprising all 95 patients who gave their consent to participate.

Abbreviations: 95% CI, 95% confidence interval; for additional abbreviations see Figure 1.
Table 3: Characteristics of patients with discrepant PET and 1-year follow-up clinical diagnoses

<table>
<thead>
<tr>
<th>1-year follow-up diagnosis</th>
<th>PET diagnosis</th>
<th>Vital status</th>
<th>Disease duration</th>
<th>H&amp;Y stage</th>
<th>ADL score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>MSA</td>
<td>dead</td>
<td>3.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PD</td>
<td>PDD/DLB</td>
<td>alive</td>
<td>7.7</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>PD</td>
<td>PDD/DLB</td>
<td>alive</td>
<td>8.2</td>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>PD</td>
<td>PDD/DLB</td>
<td>alive</td>
<td>5.2</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>PD</td>
<td>PDD/DLB</td>
<td>dead</td>
<td>4.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MSA</td>
<td>PD</td>
<td>alive</td>
<td>5.2</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>MSA</td>
<td>PD</td>
<td>alive</td>
<td>12.2</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>MSA</td>
<td>PD</td>
<td>dead</td>
<td>5.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PDD/DLB</td>
<td>PD</td>
<td>alive</td>
<td>6.0</td>
<td>2.5</td>
<td>90</td>
</tr>
<tr>
<td>PDD/DLB</td>
<td>PD</td>
<td>alive</td>
<td>5.4</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>PSP/CBD</td>
<td>PD</td>
<td>alive</td>
<td>7.2</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>PSP/CBD</td>
<td>PD</td>
<td>dead</td>
<td>5.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PDD/DLB</td>
<td>PSP/CBD</td>
<td>alive</td>
<td>5.3</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>PDD/DLB</td>
<td>PSP/CBD</td>
<td>alive</td>
<td>7.2</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>PSP/CBD</td>
<td>PDD/DLB</td>
<td>dead</td>
<td>8.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PSP/CBD</td>
<td>MSA</td>
<td>alive</td>
<td>8.1</td>
<td>3</td>
<td>90</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activity of daily living; H&Y, Hoehn & Yahr stage; for additional abbreviations see Figure 1. Patients were grouped into three categories (see table segments): favorable 1-year 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.
18F-FDG PET is an early predictor of overall survival in suspected atypical parkinsonism

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