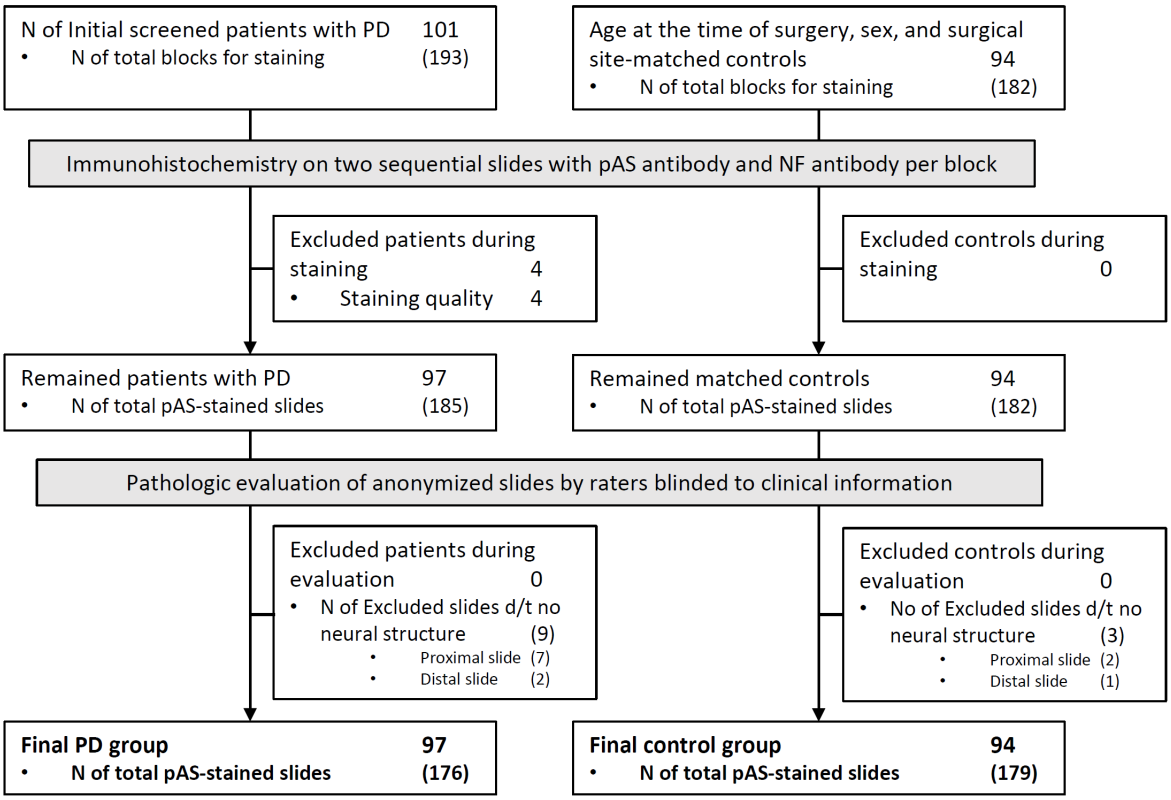
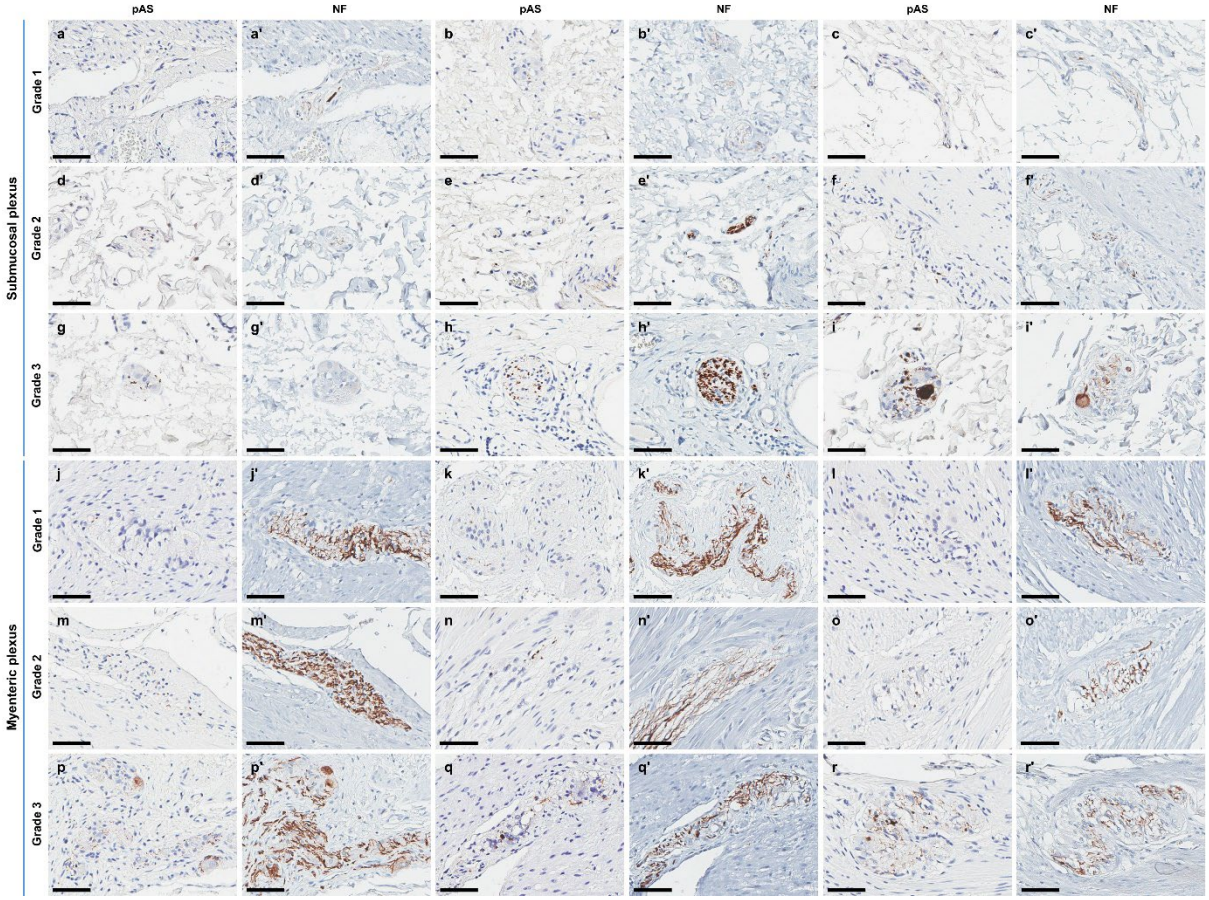
Supplementary Data

Table of contents



Supplementary Figure 1. Selection process. Abbreviations: N, number; PD, Parkinson's disease; pAS, phosphorylated alpha-synuclein; NF, neurofilament.



Supplementary Figure 2. Additional images for each grade of AS accumulation of the neural structures within the submucosa and muscularis propria. a-r All images were assigned the same grade by all raters: grade 0 (negative), grade 1 (sparse), grade 2 (moderate), and grade 3 (frequent). The dotted circle-shaped staining (p, lower right) represents one of the frequently observed staining patterns in the intestinal wall, potentially indicating pAS accumulation in neural processes adjacent to ganglion cells. **a'-r'** NF immunostaining in adjacent sections confirms the presence of neuronal cells. Scale bar: 60 µm. Abbreviations: AS, alpha-synuclein; pAS, phosphorylated AS; NF, neurofilament.

Supplementary Table 1. Individual data and results

ID	Group (1=PD, 0=Control)	Sex	Age at symptom onset (yrs)	Age at diagnosis (yrs)	Age at the final follow-up visit (yrs)	Age at surgery (yrs)	Duration from onset to diagnosis (yrs)	Duration from onset to the final follow-up visit (yrs)	Duration from onset to surgery (yrs)	Duration from surgery to the final follow-up visit (yrs)	Clinical diagnosis	HY stage	Surgery category (1=stomach, 2=colorectal, 3=esophagus, 4=others)	Surgery	pAS result final	distal pAS	distal pAS, mucosa-submucosa	distal pAS, muscularis	distal pAS, serosa	distal NF	proximal pAS	proximal pAS, mucosa-submucosa	proximal pAS, muscularis	proximal pAS, serosa	proximal NF
1	1	F	71	74	84	74	3	13	3	10	PD		1	STG	**1**	X	X	X	X	X	3	3	3	3	1
2	1	M	74	77	78	76	3	4	2	2	PD		1	TG	**1**	3	3	1	0	1	3	0	3		1
3	1	M	73	73	83	74	0	10	1	9	PD		1	DG	**0**	0	0	0	0	1	0	0	0	0	1
4	1	M	69	70	76	76	1	7	7	0	PD		1	STG	**1**	1	1	1	0	1	2	1	2		1
5	1	M	71	74	81	76	3	10	5	5	PD		1	DG	**1**	3	3	2	2	1	2	1	2	0	1
6	1	M	69	69	72	71	0	3	2	1	PD		1	TG	**1**	X	X	X	X	X	2	2	2	1	1
7	1	M	57	59	73	62	2	16	5	11	PD		1	TG	**1**	2	0	2	0	1	3	0	3	0	1
8	1	M	57	63	75	68	6	18	11	7	PD		1	DG	**1**	2	1	2		1	2	1	2	0	1
9	1	F	65	67	78	73	2	13	8	5	PD		1	DG	**1**	3	2	3	0	1					0
10	1	M	64	67	78	75	3	14	11	3	PD		1	TG	**1**	3	3	2	3	1					0
11	1	M	75	75	80	71	0	5	-4	9	PD		2	Miles	**1**					0	1	0	1	0	1
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13	1	F	66	66	73	69	0	7	3	4	PD		2	RHC	**0**	0	0	0	0	1	0	0	0		1
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47	1	F	68	68	75	75	0	7	7	0	PD	3.5	1	PPPD	**1**	X	X	X	X	X	2	0	2	0	1
48	1	F	72	73	84	74	1	12	2	10	PD		1	STG	**1**	3	2	3	1	1	X	X	X	X	X
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68	1	M	58	65	74	68	7	16	10	6	PD		1	STG	**1**	2	0	2		1	X	X	X	X	X
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78	1	F	57	57	65	62	0	8	5	3	PD		2	RHC	**1**	1	0	1	0	1	0	0	0	0	1
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85	1	F	64	65	78	69	1	14	5	9	PD	2.5	1	DG	**1**	3	1	3	0	1	3	3	3	2	1
86	1	F	72	73	86	84	1	14	12	2	PD	3	2	AR	**1**	3	1	3		1	2	2	2	2	1
87	1	F	68	69	80	73	1	12	5	7	PD	2	2	AR	**0**	0	0	0		1	0	0	0	0	1
88	1	F	58	58	66	62	0	8	4	4	PD	3	1	DG	**1**	3	3	3		1	2	2			1
89	1	M	64	65	75	71	1	11	7	4	PD	2.5	1	DG	**1**	3	2	3	1	1	2	0	2	1	1
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91	1	M	79	82	82	82	3	3	3	0	PD	3	1	DG	**1**	3	3	3	0	1					0
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108	0	F			61	54				7	NC		2	LHC	**0**	0	0	0	0	1	0	0	0	0	1
109	0	F			75	69				6	NC		2	LHC	**0**	0	0	0	0	1	0	0	0	0	1
110	0	M			81	72				9	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
111	0	F			61	54				7	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
112	0	M			77	72				5	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
113	0	F			77	67				10	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
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116	0	F			70	62				8	NC		2	RHC	**0**					0	0	0	0	0	1
117	0	F			82	75				7	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
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125	0	F			80	70				10	NC		2	RHC	**0**	0	0	0		1	0	0	0	0	1
126	0	F			79	74				5	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
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137	0	F			81	73				8	NC		1	STG	**0**	0	0	0	0	1	0	0	0	0	1
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139	0	M			76	70				6	NC		1	STG	**0**	0	0	0	0	1	0	0	0	0	1
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143	0	F			80	74				6	NC		1	TG	**0**	0	0	0	0	1	0	0	0	0	1
144	0	M			86	78				8	NC		1	TG	**0**	0	0	0	0	1	0	0	0	0	1

145	0	M			71	66				5	NC		1	TG	**0**	0	0	0	0	1	0	0	0	0	1
146	0	M			84	76				8	NC		1	STG	**0**	0	0	0	0	1	0	0	0	0	1
147	0	M			78	71				7	NC		1	STG	**0**	0	0	0	0	1	0	0	0	0	1
148	0	F			89	77				12	NC		2	RHC	**0**	0	0	0	0	1	0	0	0		1
149	0	F			77	67				10	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
150	0	F			80	72				8	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
151	0	M			68	62				6	NC		1	TG	**0**	0	0	0		1	0	0	0	0	1
152	0	M			78	73				5	NC		1	DG	**0**	0	0	0	0	1	0	0	0	0	1
153	0	F			84	77				7	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
154	0	M			87	78				9	NC		1	STG	**0**	0	0	0	0	1	X	X	X	X	X
155	0	M			87	82				5	NC		1	DG	**1**	3	3	2	1	1	3	2	3	0	1
156	0	M			78	66				12	NC		2	LHC	**0**	0	0	0		1	0	0	0	0	1
157	0	M			73	66				7	NC		1	DG	**0**	0	0	0		1	0	0	0	0	1
158	0	M			85	72				13	NC		2	RHC	**0**	0	0	0	0	1					0
159	0	M			83	74				9	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
160	0	F			81	69				12	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
161	0	M			97	88				9	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
162	0	M			79	68				11	NC		1	STG	**0**	0	0	0		1	0	0	0	0	1
163	0	M			90	82				8	NC		2	RHC	**0**	0	0	0	0	1	0	0	0		1
164	0	M			85	73				12	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
165	0	M			76	70				6	NC		1	STG	**0**	0	0	0	0	1	0	0	0	0	1
166	0	M			91	78				13	NC		1	STG	**0**	0	0	0	0	1	0	0	0	0	1
167	0	F			86	74				12	NC		1	STG	**0**	0	0	0	0	1	X	X	X	X	X
168	0	F			88	83				5	NC		2	total colec	**0**	0	0	0	0	1	0	0	0	0	1
169	0	M			70	63				7	NC		2	subtotal c	**0**	0	0	0	0	1	0	0	0	0	1
170	0	F			82	73				9	NC		1	STG	**0**	X	X	X	X	X	0	0	0	0	1
171	0	F			78	66				12	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
172	0	F			72	62				10	NC		2	LHC	**0**	0	0	0	0	1	0	0	0	0	1
173	0	M			82	71				11	NC		1	STG	**0**	0	0	0	0	1	0	0	0	0	1
174	0	M			81	70				11	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
175	0	F			82	72				10	NC		1	DG	**0**	0	0	0	0	1	0	0	0	0	1
176	0	M			79	72				7	NC		1	STG	**1**	2	2	2	2	1	2	1	2	1	1
177	0	M			88	79				9	NC		1	STG	**0**	0	0	0	0	1	0	0	0	0	1
178	0	M			81	71				10	NC		2	RHC	**0**	0	0	0	0	1	0	0	0	0	1
179	0	M			80	69				11	NC		1	STG	**0**	0	0	0	0	1	0	0	0	0	1
180	0	F			90	84				6	NC		2	RHC	**0**	0	0	0	0	1	0	0	0		1
181	0	F			80	73				7	NC		2	RHC	**0**	0	0	0	0	1					0
182	0	M			67	62				5	NC		1	DG	**1**	3	3	3		1	3	2	3	3	1
183	0	M			76	71				5	NC		1	STG	**0**	0	0	0	0	1	0	0	0	0	1
184	0	M			83	73				10	NC		2	RHC	**0**	0	0	0		1	0	0	0	0	1
185	0	M			87	82				5	NC		1	STG	**0**	X	X	X	X	X	0	0	0	0	1
186	0	F			85	76				9	NC		1	STG	**0**	0	0	0	0	1	0	0	0	0	1
187	0	M			81	68				13	NC		2	AR	**0**	0	0	0	0	1	0	0	0	0	1
188	0	M			81	76				5	NC		1	TG	**0**	0	0	0	0	1	0	0	0	0	1
189	0	M			82	77				5	NC		1	DG	**1**	3	3	3	3	1	3	3	3	0	1
190	0	M			90	82				8	NC		1	STG	**1**	1	1	1		1	2	2	2	0	1
191	0	F			65	60				5	NC		1	DG	**0**	0	0	0	0	1	0	0	0	0	1

Supplementary Table 2. Clinical characteristics of patients and matched controls in UGI subgroup

Characteristic	Patients with PD (N=55)	Controls (N=53)	*p*-value
Sex, No. (%)			
Male	36 (65.5)	40 (75.5)	0.254
Female	19 (34.5)	13 (24.5)	
Age, mean (SD), y			
At surgery	71.1 (6.3)	70.8 (6.1)	0.767
At the final follow-up visit	75.9 (7.2)	77.9 (6.7)	0.145
At symptom onset	66.9 (8.4)		
At diagnosis	68.6 (8.3)		
Duration, mean (SD), y			
Onset to surgery	4.2 (4.6)		
Onset to diagnosis	1.7 (1.7)		
Onset to the final follow-up visit	9.0 (4.7)		
Surgery to the final follow-up visit	4.8 (3.2)	7.1 (2.0)	<0.001
Frequency of patients who underwent surgery before the symptom onset, No. (%)	6 (10.9)		
HY stage at the year of surgery (available in 18 patients, No. (%)			
1	3 (5.5)		
2	3 (5.5)		
2.5	8 (14.5)		
3	4 (7.3)		
Surgical site, No. (%)			
Stomach	53 (96.4)	53 (100)	0.496
Esophagus	2 (3.6)	0	

Abbreviations: UGI, upper gastrointestinal tract; PD, Parkinson's disease; HY, Hoehn and Yahr.

Supplementary Table 3. Clinical characteristics of patients and matched controls in LGI subgroup

Characteristic	Patients with PD (N=42)	Controls (N=41)	*p*-value
Sex, No. (%)			
Male	21 (50.0)	20 (48.8)	0.912
Female	21 (50.0)	21 (51.2)	
Age, mean (SD), y			
At surgery	70.8 (7.7)	71.0 (7.6)	0.899
At the final follow-up visit	75.6 (6.8)	79.5 (7.6)	0.016
At symptom onset	66.7 (7.2)		
At diagnosis	68.6 (7.7)		
Duration, mean (SD), y			
Onset to surgery	4.1 (5.3)		
Onset to surgery	1.9 (3.0)		
Onset to diagnosis	8.9 (4.8)		
Onset to the final follow-up visit	4.8 (4.0)	8.5 (2.6)	<0.001
Frequency of patients who underwent surgery before the symptom onset, No. (%)	6 (14.3)		
HY stage at the year of surgery (available in 11 patients), No. (%)			
1	1 (2.4)		
2	4 (9.5)		
2.5	1 (2.4)		
3	5 (11.9)		
Surgical site, No. (%)			
[1]RLGI	12 (28.6)	33 (80.5)	
[2]LLGI	30 (71.4)	6 (14.6)	<0.001
[3]others	0	2 (4.9)	

[1]RLGI includes surgical specimens acquired by right hemi-colectomy.

[2]LLGI includes surgical specimens acquired by anterior resection, lower anterior resection, ultra-lower anterior resection, Miles' operation, Hartmann's operation, or left hemi-colectomy.

[3]others include surgical specimens acquired by total colectomy and subtotal colectomy.

Abbreviations: LGI, lower gastrointestinal tract; PD, Parkinson's disease; GI, gastrointestinal; UGI, upper GI tract; LGI, lower GI tract; RLGI, right LGI; LLGI, left LGI.

Supplementary Table 4. Differences of AS accumulation layer by layer in the intestinal wall between patients with PD and controls

Region	Layer	Patients with PD		Controls		*p*-value
		Total No.	AS+, No. (%)	Total No.	AS+, No. (%)	
Entire GI tract						
	Full layer	97	73 (75.3)	94	8 (8.5)	<0.001
	Mucosa / submucosa	96	45 (46.9)	94	5 (5.3)	<0.001
	Muscularis	96	72 (75.0)	94	8 (8.5)	<0.001
	Serosa	87	31 (35.6)	92	6 (6.5)	<0.001
UGI (stomach+esophagus)						
	Full layer	55	46 (83.6)	53	8 (15.1)	<0.001
	Mucosa / submucosa	54	35 (64.8)	53	5 (9.4)	<0.001
	Muscularis	54	45 (83.3)	53	8 (15.1)	<0.001
	Serosa	47	20 (42.6)	53	6 (11.3)	<0.001
LGI (colon+rectum)						
	Full layer	42	27 (64.3)	41	0	<0.001
	Mucosa / submucosa	42	10 (23.8)	41	0	0.001
	Muscularis	42	27 (64.3)	41	0	<0.001
	Serosa	40	11 (27.5)	39	0	<0.001

Abbreviations: PD, Parkinson’s disease; AS, alpha-synuclein; GI, gastrointestinal; UGI, upper GI tract; LGI, lower GI tract.

Supplementary Table 5. Differences of AS accumulation layer by layer in the intestinal wall and location of marginal blocks

Block	Layer	PD Patients		Controls		*p*-value
		Total N	AS+ (%)	Total N	AS+ (%)	
One or more in both blocks						
	Full layer	97	73 (75.3%)	94	8 (8.5%)	<0.001
	Mucosa / submucosa	96	45 (46.9%)	94	5 (5.3%)	<0.001
	Muscularis	96	72 (75.0%)	94	8 (8.5%)	<0.001
	Serosa	87	31 (35.6%)	92	6 (6.5%)	<0.001
Proximal block only						
	Full layer	84	51 (60.7%)	88	8 (9.1%)	<0.001
	Mucosa / submucosa	83	26 (31.3%)	88	5 (5.7%)	<0.001
	Muscularis	78	50 (64.1%)	88	8 (9.1%)	<0.001
	Serosa	66	20 (30.3%)	79	3 (3.8%)	<0.001
Distal block only						
	Full layer	91	62 (68.1%)	91	7 (7.7%)	<0.001
	Mucosa / submucosa	91	38 (41.8%)	91	5 (5.5%)	<0.001
	Muscularis	86	58 (67.4%)	91	7 (7.7%)	<0.001
	Serosa	69	21 (30.4%)	80	4 (5.0%)	<0.001

Abbreviations: PD, Parkinson’s disease; AS, alpha-synuclein.

Supplementary Table 6. Differences of AS accumulation layer by layer in the intestinal wall and location of marginal blocks in UGI subgroup

Block	Layer	PD Patients		Controls		*p*-value
		Total No.	AS+, No. (%)	Total No.	AS+, No. (%)	
One or more in both blocks						
	Full layer	55	46 (83.6)	53	8 (15.1)	<0.001
	Mucosa / submucosa	54	35 (64.8)	53	5 (9.4)	<0.001
	Muscularis	54	45 (83.3)	53	8 (15.1)	<0.001
	Serosa	47	20 (42.6)	53	6 (11.3)	<0.001
Proximal block only						
	Full layer	45	33 (73.3)	49	8 (16.3)	<0.001
	Mucosa / submucosa	44	21 (47.7)	49	5 (10.2)	<0.001
	Muscularis	39	32 (82.1)	49	8 (16.3)	<0.001
	Serosa	32	13 (40.6)	48	3 (6.3)	<0.001
Distal block only						
	Full layer	50	40 (80.0)	51	7 (13.7)	<0.001
	Mucosa / submucosa	50	29 (58.0)	51	5 (9.8)	<0.001
	Muscularis	49	39 (79.6)	51	7 (13.7)	<0.001
	Serosa	36	11 (30.6)	45	4 (8.9)	0.013

Abbreviations: AS, alpha-synuclein; UGI, upper gastrointestinal tract; PD, Parkinson’s disease.

Supplementary Table 7. Differences of AS accumulation layer by layer in the intestinal wall and location of marginal blocks in LGI subgroup

Block	Layer	PD Patients		Controls		*p*-value
		Total No.	AS+, No. (%)	Total No.	AS+, No. (%)	
One or more in both blocks						
	Full layer	42	27 (64.3)	41	0	<0.001
	Mucosa / submucosa	42	10 (23.8)	41	0	0.001
	Muscularis	42	27 (64.3)	41	0	<0.001
	Serosa	40	11 (27.5)	39	0	<0.001
Proximal block only						
	Full layer	39	18 (46.2)	39	0	<0.001
	Mucosa / submucosa	39	5 (12.8)	39	0	0.055
	Muscularis	39	18 (46.2)	39	0	<0.001
	Serosa	34	7 (20.6)	31	0	0.012
Distal block only						
	Full layer	41	22 (53.7)	40	0	<0.001
	Mucosa / submucosa	41	9 (22.0)	40	0	0.002
	Muscularis	37	19 (51.4)	40	0	<0.001
	Serosa	33	10 (30.3)	35	0	<0.001

Abbreviations: AS, alpha-synuclein; LGI, lower gastrointestinal tract; PD, Parkinson’s disease.

Supplementary Table 8. Differences of clinical characteristics between UGI and LGI subgroups in patients with PD and AS accumulation in the GI tract

Characteristic	Patients with PD and AS+		*p*-value
	UGI (N=46)	LGI (N=27)	
Sex, No. (%)			
Male	30 (65.2)	15 (55.6)	0.412
Female	16 (34.8)	12 (44.4)	
Age, mean (SD), y			
At surgery	70.6 (5.7)	72.7 (8.1)	0.195
At the final follow-up visit	75.4 (6.5)	76.7 (6.6)	0.426
At symptom onset	65.6 (7.5)	67.8 (7.6)	0.243
At diagnosis	67.5 (7.6)	70.1 (8.2)	0.170
Duration, mean (SD), y			
Onset to surgery	5.0 (4.3)	4.9 (5.9)	0.980
Onset to diagnosis	1.8 (1.7)	2.3 (3.7)	0.521
Onset to the final follow-up visit	9.8 (4.5)	8.9 (4.7)	0.427
Surgery to the final follow-up visit	4.8 (3.2)	4.0 (3.7)	0.309
Frequency of patients who underwent surgery before the symptom onset, No. (%)	4 (8.7)	4 (14.8)	0.457
HY stage at the year of surgery (available in 22 patients), No. (%)			
1	2 (4.3)	1 (3.7)	0.242
2	3 (6.5)	2 (7.4)	
2.5	7 (15.2)	0	
3	3 (6.5)	4 (14.8)	

Abbreviations: PD, Parkinson's disease; AS, alpha-synuclein; GI, gastrointestinal; UGI, upper GI tract; LGI, lower GI tract; HY, Hoehn and Yahr.

Supplementary Table 9. Differences of clinical characteristics between controls with and without AS accumulation in the GI tract

Characteristic	Control		*p*-value
	AS+ (N=8)	AS− (N=86)	
Sex, No. (%)			
Male	7 (87.5)	53 (61.6)	0.251
Female	1 (12.5)	35 (38.4)	
Age, mean (SD), y			
At surgery	72.1 (8.0)	70.7 (6.7)	0.581
At the final follow-up visit	78.4 (8.4)	78.6 (7.0)	0.951
Duration from surgery to the final follow-up visit, mean (SD), y	6.3 (1.2)	7.9 (2.4)	0.072
Surgical site, No. (%)			
UGI	8 (100)	45 (52.3)	0.009
LGI	0	41 (47.7)	

Abbreviations: AS, alpha-synuclein; GI, gastrointestinal; UGI, upper GI tract; LGI, lower GI tract.

Supplementary Table 10. Frequency of AS accumulation in the discretized subgroups of duration from symptom onset to surgery in patients with PD

Duration of onset to surgery (years)	N of patients with PD	Entire GI tract		*p*-value	UGI		*p*-value	LGI		*p*-value
		AS+, No. (%)	AS−, No. (%)	0.017	AS+, No. (%)	AS−, No. (%)	0.062	AS+, No. (%)	AS−, No. (%)	0.281
before symptom onset	12	8 (66.7)	4 (33.3)		4 (66.7)	2 (33.3)		4 (66.7)	2 (33.3)	
0–5	48	31 (64.6)	17 (35.4)		22 (78.6)	6 (21.4)		9 (45.0)	11 (55.0)	
6–10	26	23 (88.5)	3 (11.5)		14 (93.3)	1 (6.7)		9 (81.8)	2 (18.2)	
≥11	11	11 (100)	0		6 (100)	0		5 (100)	0	

Abbreviations: PD, Parkinson's disease; AS, alpha-synuclein; GI, gastrointestinal; UGI, upper GI tract; LGI, lower GI tract.