

Predictors of low-to-high grade progression in pancreatic neuroendocrine tumors

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BACKGROUND

- Pancreatic neuroendocrine neoplasms are separated into grades defined by the Ki67 tumor proliferation index: <3% for G1, 3-20% for G2, and >20% for G3
- Low-to-high grade progression (from G1/2 to G3) occurs commonly over time and is an independent prognostic factor ^{1,2}

Research aims

- Determine the incidence of longitudinal progression to G3 in a single institutional cohort
- Characterize these patients along with their survival outcomes
- Assess whether any clinicopathologic characteristics predict grade progression

METHODS

- UCSF IRB-approved retrospective chart review

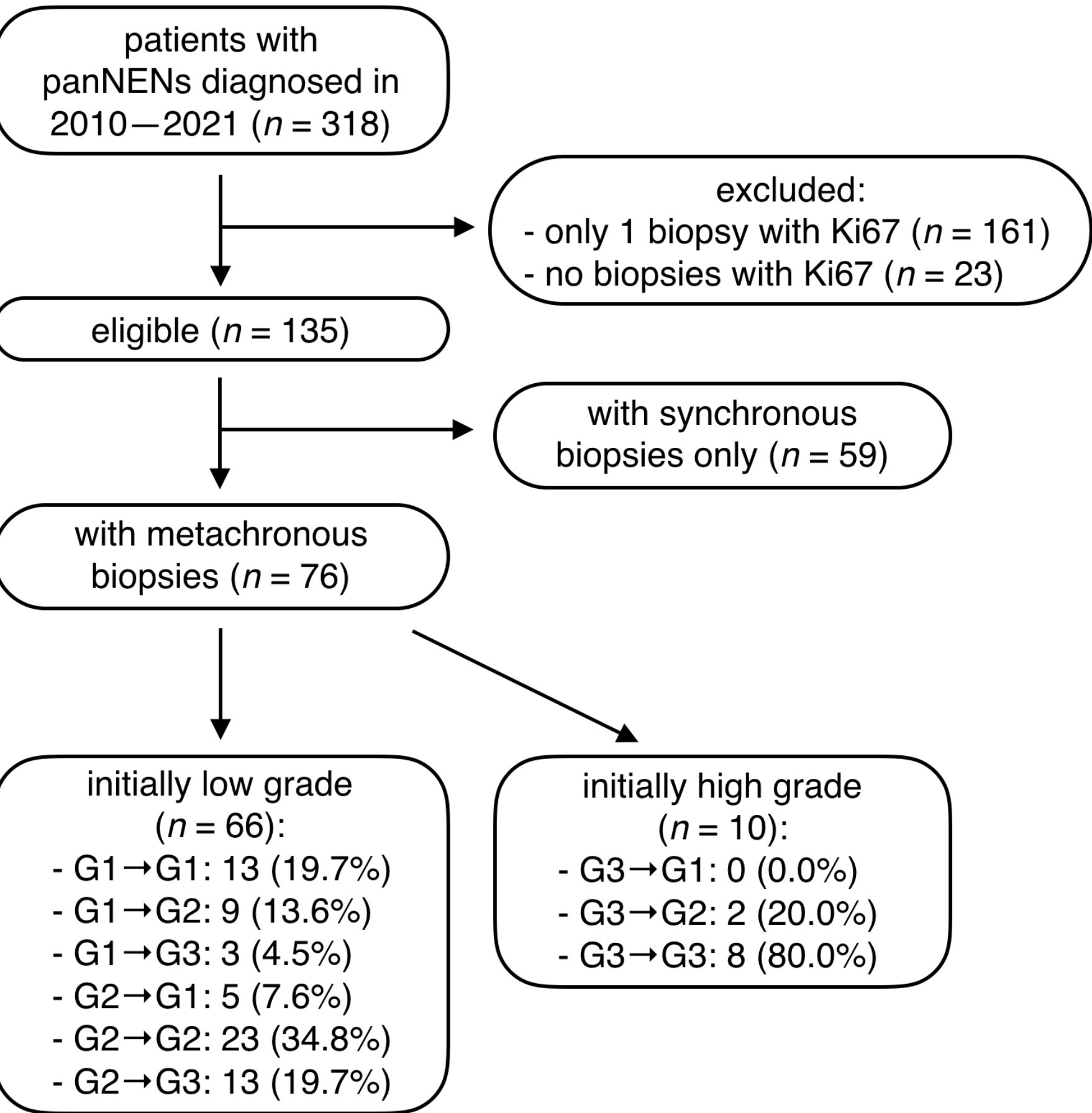


Figure 1. CONSORT flow diagram of study cohort

Characteristic by group	Total No. (%)	Low No. (%)	Low-to-high No. (%)	P value
No. of individuals	66 (100.0)	50 (75.8)	16 (24.2)	
Median follow-up time (yrs)	6.9	6.9	5.1	0.29
Age at diagnosis (yrs)				0.25
Range	22.7 - 76.5	22.7 - 76.5	37.3 - 71.5	
Median	52.4	50.6	56.3	
Ki67 at diagnosis (%)				0.12
Range	1.0 - 20.0	1.0 - 20.0	1.9 - 13.9	
Median	4.0	3.1	8.2	
Gender				1.00
Female	24 (32.4)	18 (36.0)	6 (37.5)	
Male	42 (56.8)	32 (64.0)	10 (62.5)	
Race				0.68
Black / African-American	3 (4.1)	3 (6.0)	0 (0.0)	
Asian / Pacific Islander	10 (13.5)	9 (18.0)	1 (6.3)	
White	44 (59.5)	32 (64.0)	12 (75.0)	
Hispanic	6 (8.1)	4 (8.0)	2 (12.5)	
Other	3 (4.1)	2 (4.0)	1 (6.3)	
Functional tumor				1.00
Yes	15 (20.3)	11 (22.0)	4 (25.0)	
No	51 (68.9)	39 (78.0)	12 (75.0)	
Stage at diagnosis				0.17
Localized	21 (28.4)	17 (34.0)	4 (25.0)	
Regional	13 (17.6)	12 (24.0)	1 (6.3)	
Distant	32 (43.2)	21 (42.0)	11 (68.8)	
DOTA-avid				1.00*
Yes	58 (78.4)	43 (86.0)	15 (93.8)	
No	5 (6.8)	4 (8.0)	1 (6.3)	
Unknown	3 (4.1)	3 (6.0)	0 (0.0)	
FDG-avid				0.33*
Yes	13 (17.6)	4 (8.0)	9 (56.3)	
No	5 (6.8)	3 (6.0)	2 (12.5)	
Unknown	48 (64.9)	43 (86.0)	5 (31.3)	
Sites of initial and subsequent biopsies				0.22
Primary → primary	13 (17.6)	11 (22.0)	2 (12.5)	
Primary → met	28 (37.8)	22 (44.0)	6 (37.5)	
Met → primary	4 (5.4)	4 (8.0)	0 (0.0)	
Met → met	22 (29.7)	13 (26.0)	9 (56.3)	
Reason for subsequent biopsy				0.008
Routine	37 (50.0)	33 (66.0)	4 (25.0)	
Suspicious clinical behavior	29 (39.2)	17 (34.0)	12 (75.0)	

Table 1. Cohort demographic, clinical, and pathologic characteristics

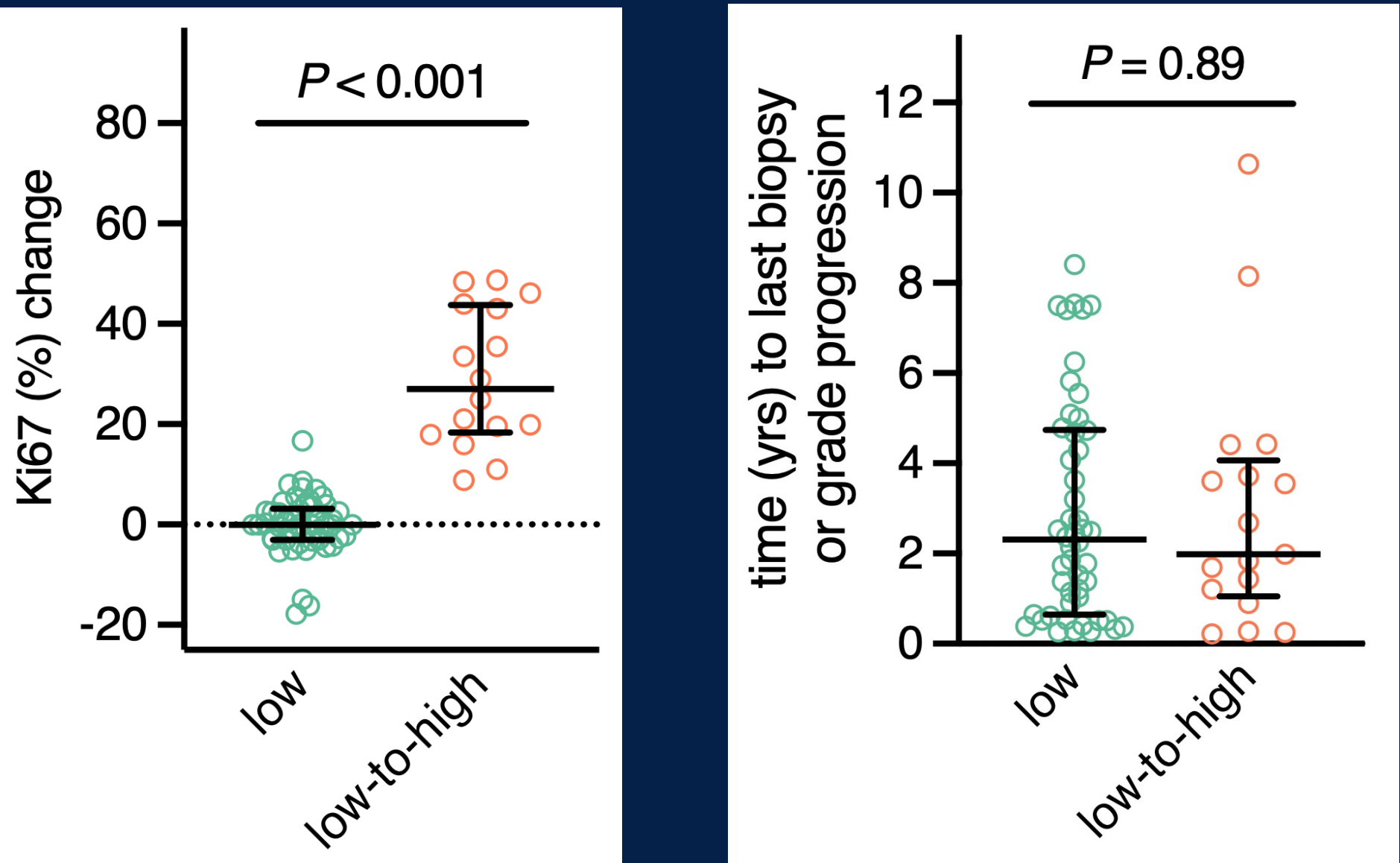


Figure 2. Ki67 changes and time elapsed between serial biopsies for G1/2 patients who remained low grade vs those who progressed to G3

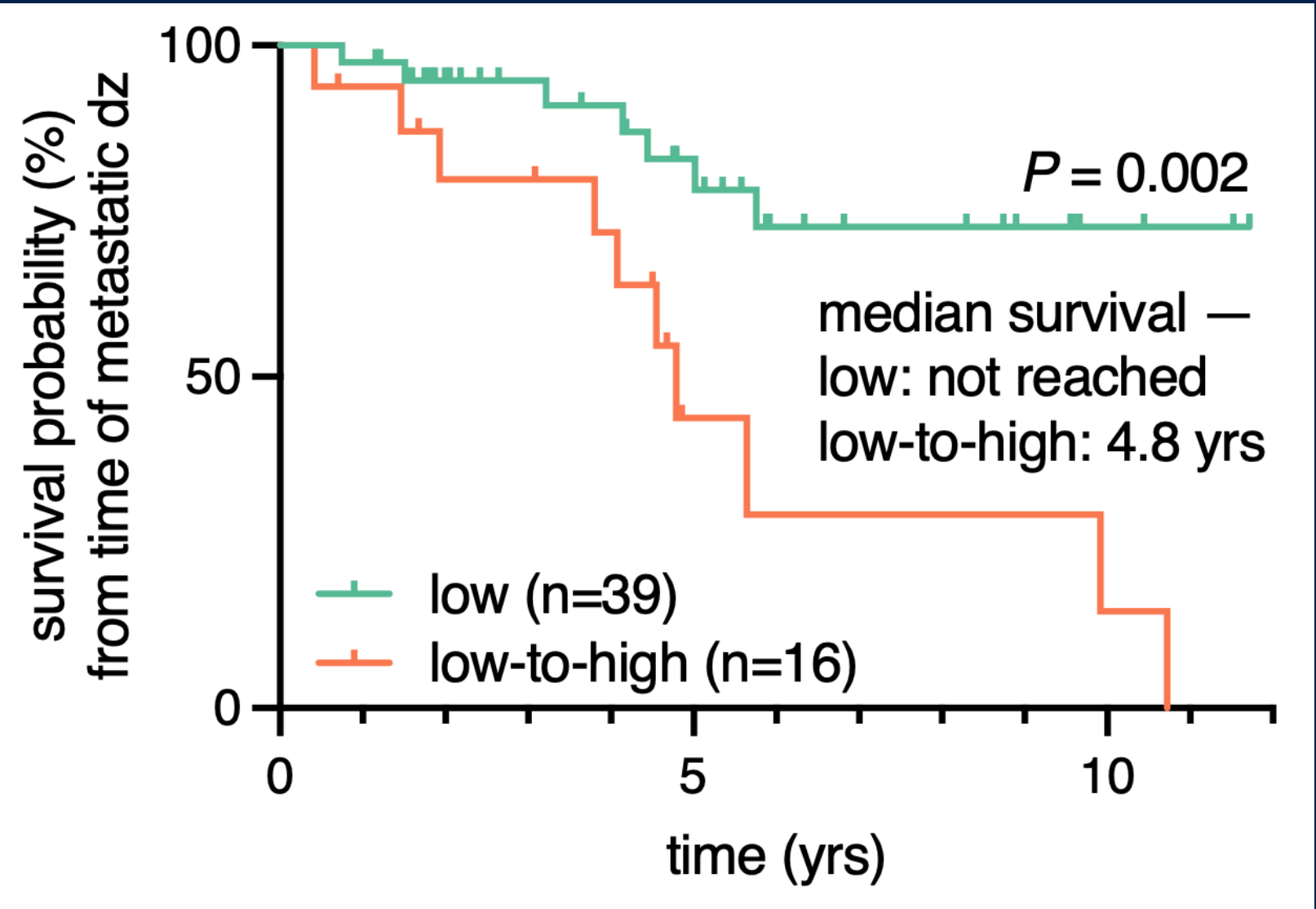


Figure 3. Kaplan-Meier curves for survival from time of metastatic disease for low vs low-to-high grade patients

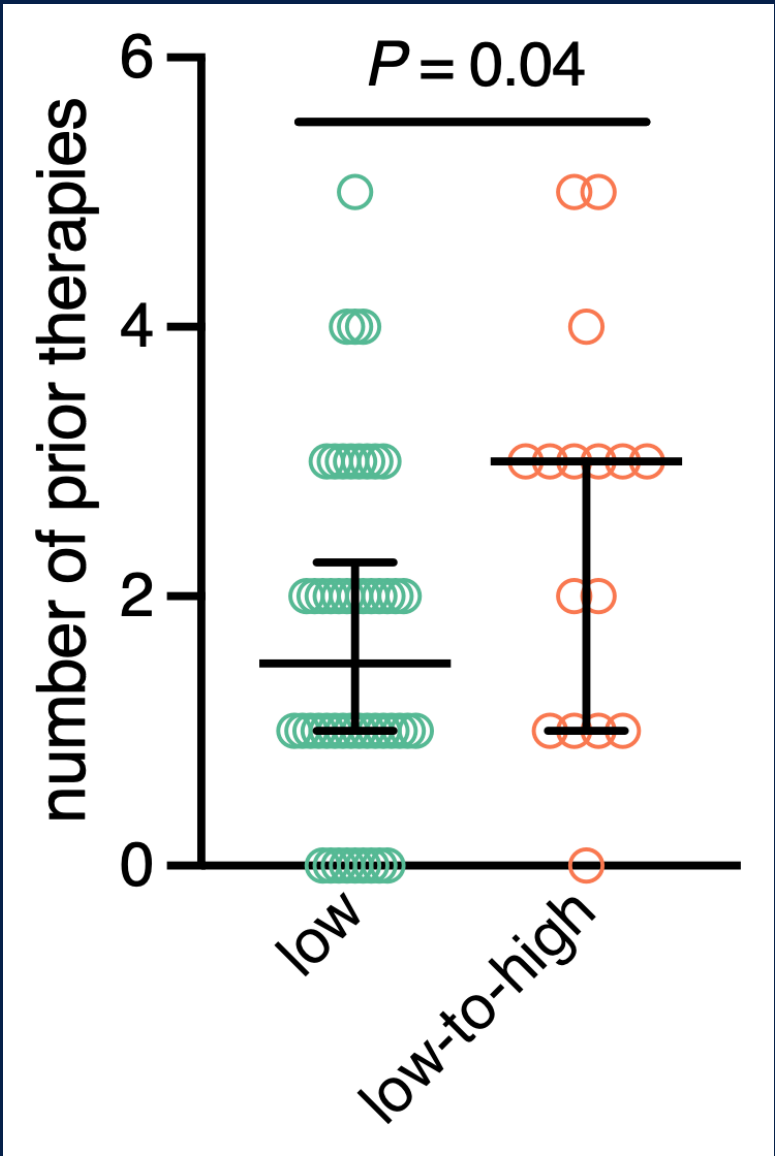


Figure 4. Number of therapies received prior to last biopsy for low grade patients, and prior to grade progression for low-to-high grade patients

Treatment by group	Total No. (%)	Low No. (%)	Low-to-high No. (%)	P value
No. of individuals	66 (100.0)	50 (75.8)	16 (24.2)	
Somatostatin analogue				0.27
Yes	36 (54.5)	25 (50.0)	11 (68.8)	
No	30 (45.5)	25 (50.0)	5 (31.3)	
Surgery				1.00
Yes	34 (51.5)	26 (52.0)	8 (50.0)	
No	32 (48.5)	24 (48.0)	8 (50.0)	
Chemotherapy				1.00
Yes	18 (27.3)	11 (22.0)	7 (43.8)	
No	48 (72.7)	39 (78.0)	9 (56.3)	
Targeted therapy				0.09
Yes	14 (21.2)	8 (16.0)	6 (37.5)	
No	52 (78.8)	42 (84.0)	10 (62.5)	
Immunotherapy				1.00
Yes	1 (1.5)	0 (0.0)	1 (6.3)	
No	65 (98.5)	50 (100.0)	15 (93.8)	
Radiation therapy				0.35
Yes	9 (13.6)	4 (8.0)	5 (31.3)	
No	57 (86.4)	46 (92.0)	11 (68.8)	
Peptide receptor radionuclide therapy				0.003
Yes	5 (7.6)	0 (0.0)	5 (31.3)	
No	61 (92.4)	50 (100.0)	11 (68.8)	
Liver-directed therapy				0.46
Yes	12 (18.2)	8 (16.0)	4 (25.0)	
No	54 (81.8)	42 (84.0)	12 (75.0)	

Table 2. Treatment data for the cohort

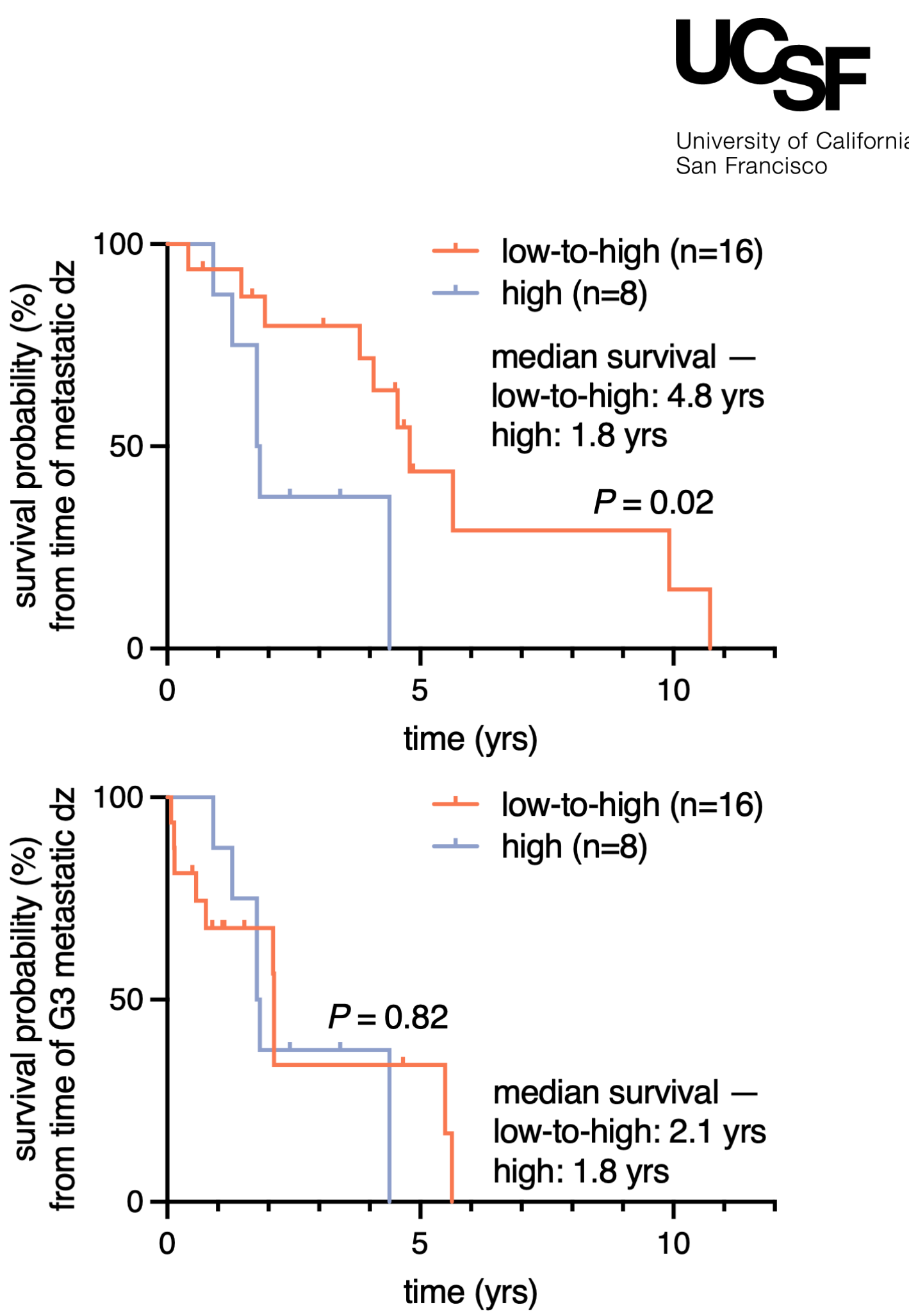


Figure 5. Survival outcomes of low-to-high grade progressors vs patients with de novo G3 panNET

CONCLUSIONS

- 16/66 (24%) low grade panNET patients experienced grade progression to G3, with a median Ki67 increase of 27.0% over 2.0 yrs
- Patients who underwent low-to-high grade progression experienced worse survival than low grade patients
- Suspicious clinical behavior, increased number of prior therapies, and prior PRRT point towards which patients warrant histological reassessment during their disease course
- Additional questions: What molecular features (e.g. mutations, patterns of gene expression or epigenetic changes) are associated with panNET before vs after grade progression? Are findings similar in extrapancreatic NET?

ACKNOWLEDGEMENTS

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REFERENCES

- ¹ Panzuto, et al. *PLoS One* (2017)
- ² Botling, et al. *Neuroendocrinology* (2020)