# C-48

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

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### BACKGROUND

Pancreatic neuroendocrine neoplasms (panNENs) are heterogeneous, with grade (G) defined by Ki67 proliferation index (<3% G1, 3-20% G2, >20% G3) or mitotic rate. The G3 NEN subgroup is further divided into well differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NEC). Grade progression can occur over time, with low-to-high grade progression (L-to-H; G1/2 to G3) the most clinically relevant form. It is associated with shorter overall survival (OS) and occasional dedifferentiation into NEC. However, little is known about the timeframe over which L-to-H occurs or what drives this change, adding uncertainty to individual clinical management and complexity to use of archived biopsies for clinical trial inclusion.

### METHODS

We conducted a retrospective review of patients with stage I-IV G1-3 panNENs diagnosed between 2010-2021 and identified from an IRB-approved NET database. Patients with at least two serial tumor biopsies (with Ki67 staining) over 3 months apart were eligible.

### RESULTS

Of 318 cases, 76 patients (23.9%) had metachronous tumor biopsies with Ki67 staining (median follow-up 6.8 yr), and 66/76 (86.8%) were initially diagnosed with low grade NET (median Ki67 4.6%, range 1.0-20.0%). Of these, 23/66 (34.8%) showed grade progression, with 16/66 (24.4%) demonstrating L-to-H. Over a median 2.3 years, L-H patients experienced a median Ki67 increase of 27.0% to a median subsequent Ki67 of 31.0% (range 21.0-60.0%). In comparison, N=50 low-to-low (L-to-L) patients were diagnosed as low grade and remained so upon serial biopsy, with a median Ki67 change of 0% between serial biopsies a median 2.3 years apart. L-to-H patients were more likely to display heterogeneity on DOTA PET imaging ($P$=0.003), receive more lines of therapy prior to subsequent biopsy ($P$=0.04), and have a change in disease behavior trigger a biopsy ($P$=0.008), more often via percutaneous techniques rather than surgical resection ($P$=0.02). Time to serial biopsy, median follow-up, sex, race, functional status and stage at diagnosis did not differ significantly between groups. L-to-H was associated with worse OS from metastatic disease than L-to-L ($P$=0.002).

## CONCLUSIONS

In patients with G1/2 panNET undergoing serial biopsies, 24.4% demonstrated L-to-H. Clinicians should be aware of the potential for L-to-H over time, particularly if the patient is heavily pretreated, or has heterogeneous uptake on DOTA PET scan or suspicious clinical behavior. Our findings highlight the potential limitations associated with use of archival tissue for clinical trial eligibility. Additional work is needed to understand the molecular mechanisms underlying L-to-H, optimal therapy, and incidence in extrapancreatic NETs.

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