Prognostic Value of TP53 and DAXX/ATRX Mutations in Pancreatic Neuroendocrine Neoplasms

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Background

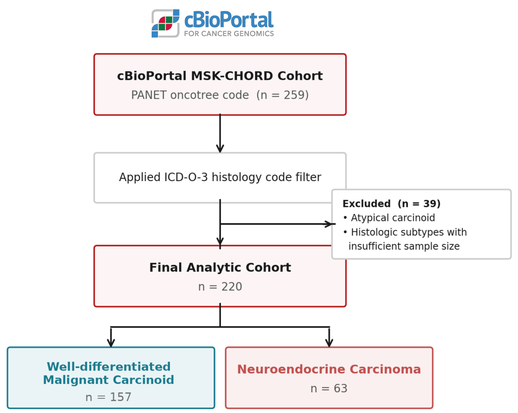
- Pancreatic neuroendocrine neoplasms (pNENs) are rare, heterogeneous tumors with rising incidence
- The 2022 WHO classification separates two fundamentally distinct tumor types with distinct prognoses and genomic landscapes:
  - **Well-differentiated pancreatic neuroendocrine tumors (pNETs)** *(historically known as malignant carcinoid tumors)*
  - **Poorly-differentiated neuroendocrine carcinomas (NEC)**
- **Genomic hallmarks differ by subtype:**
  - Well-differentiated pNETs: *MEN1*, *DAXX/ATRX* alterations
  - Poorly-differentiated NEC: *TP53*, *RB1* alterations
- Despite this, the **prognostic impact of specific mutations *within* each subtype,** particularly mutations characteristic of the opposing subtype, remains poorly characterized in large real-world cohorts.

Objective: To characterize the genomic landscape and independent prognostic significance of key somatic mutations in well-differentiated pNET (Malignant Carcinoid) and NEC, analyzed as distinct histologic subtypes using the MSK-CHORD cBioPortal cohort.

Methods

- Retrospective analysis using cBioPortal's MSK-CHORD cohort of pancreatic neuroendocrine neoplasms (*Jee J. et al. 2024*)
- Performed survival analyses and multivariable regression modeling using overall survival (OS) to assess genomic and clinical associations across the pNEN histologic subtypes as defined by ICD-O-3 histology codes

Figure 1. Cohort selection



*Grading, Ki-67, mitotic index, or differentiation status not available in cohort

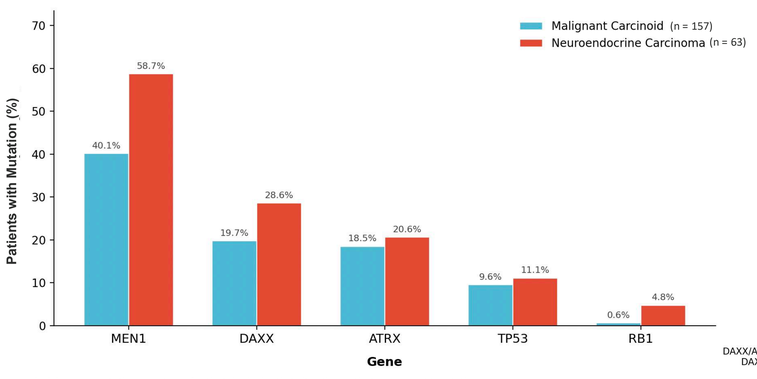
Results

Table 1. Baseline clinical and demographic characteristics by histologic subtype

Variable	Malignant Carcinoid (n=157)	NEC (n=63)	p-value
Age, median (IQR)	64.0 (54.0–72.0)	66.0 (56.5–73.0)	0.388
Sex			0.493
Male	87 (55.4%)	31 (49.2%)	
Female	70 (44.6%)	32 (50.8%)	
Race			0.144
White	125 (79.6%)	57 (90.5%)	
Black or African American	7 (4.5%)	3 (4.8%)	
Asian	10 (6.4%)	2 (3.2%)	
Other/Unknown	15 (9.6%)	1 (1.6%)	
Ethnicity			0.727
Non-Hispanic	141 (89.8%)	58 (92.1%)	
Hispanic or Latino	12 (7.6%)	3 (4.8%)	
Unknown	4 (2.5%)	2 (3.2%)	
Smoking History			**0.035**
Never	94 (59.9%)	39 (61.9%)	
Former/Current	55 (35.0%)	15 (23.8%)	
Unknown	8 (5.1%)	9 (14.3%)	
Stage			**0.009**
Stage I–III	94 (59.9%)	22 (34.9%)	
Stage I	36 (22.9%)	6 (9.5%)	
Stage II	26 (16.6%)	4 (6.3%)	
Stage III	5 (3.2%)	2 (3.2%)	
Unknown	27 (17.2%)	10 (15.9%)	
Stage IV	63 (40.1%)	41 (65.1%)	
Metastatic Burden			**0.003**
0 organ sites	35 (22.3%)	2 (3.2%)	
1 organ site	23 (14.6%)	10 (15.9%)	
2+ organ sites	99 (63.1%)	51 (81.0%)	
FGA, median (IQR)	0.3 (0.1–0.8)	0.5 (0.2–0.9)	**0.044**

FGA = Fraction Genome Altered. Metastatic burden: number of NLP-annotated tumor sites involved. p-values: Mann–Whitney U (continuous); χ^2 (categorical). Bold = $p < 0.05$.

Figure 2. Somatic mutation prevalence by histologic subtype



Each bar represents the percentage of patients harboring that alteration; patients may carry ≥1 mutation.

Figure 3. 5-year OS by TP53 mutation status in malignant carcinoid tumors

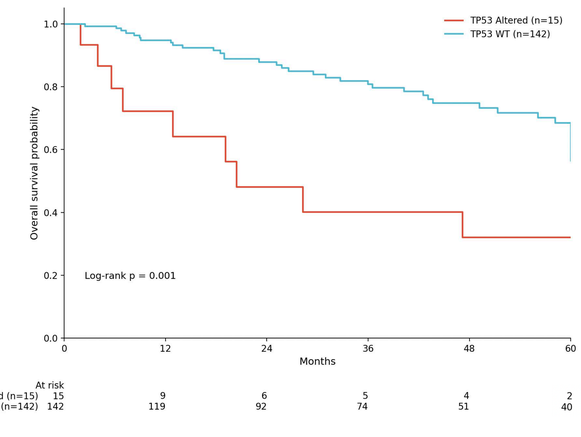


Figure 4. TP53 mutations associated with worse OS in malignant carcinoid

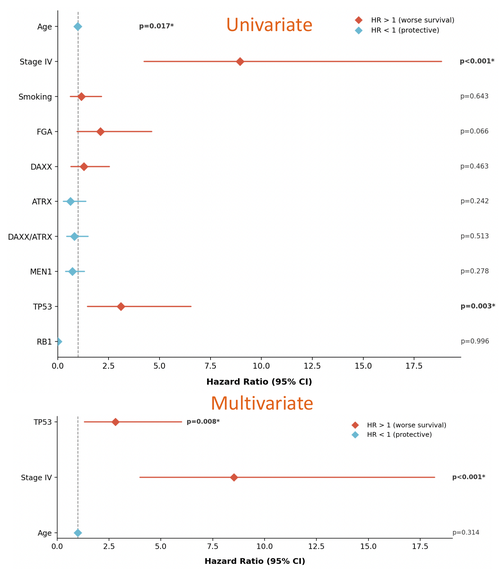


Figure 5. 5-year OS by DAXX/ATRX mutation status in NEC tumors

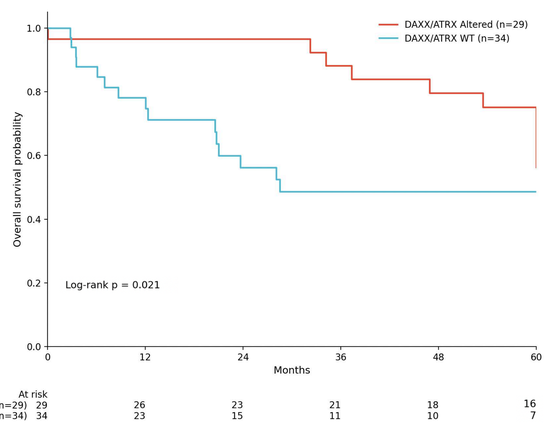
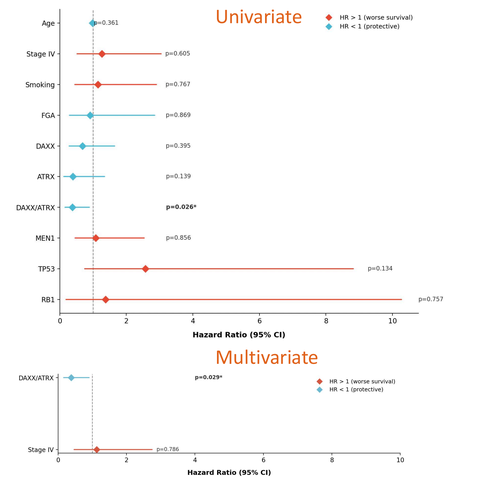


Figure 6. DAXX/ATRX mutations associated with improved OS in NEC



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Conclusions

- **NEC presented with significantly more advanced disease than Malignant Carcinoid** including more Stage IV disease, higher metastatic burden, and increased genomic instability.
- **TP53 alteration was independently associated with worse overall survival in Malignant Carcinoid after stage adjustment**, suggesting genotype captures prognostic information not reflected by histology alone.
- **DAXX/ATRX alteration was independently associated with improved OS in NEC,** identifying a molecularly distinct subgroup with a favorable survival signal.
- **Molecular profiling may complement conventional clinicopathologic staging as a prognostic tool in pNENs.**
- Independent validation in larger cohorts is warranted with additional pathologic detail including tumor grade, Ki-67 index, and surgical resection status.