

## B-2

# Upregulation of Immune Signaling Pathways Differentiates Metastatic from Localized Pancreatic Neuroendocrine Tumors

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**BACKGROUND:** Metastases may be present at diagnosis of pancreatic neuroendocrine tumors (PNETs), which is associated with decreased overall survival. Furthermore, the high heterogeneity of PNETs makes treatment particularly difficult. Here we aimed to determine whether there is differential expression of immune system genes between localized and metastatic PNETs.

**METHODS:** Bulk RNA sequencing was performed on samples of sporadic well-differentiated primary PNETs resected from 2000-2016 at our institution. Differentially expressed genes were compared between localized and metastatic tumors. Immunohistochemistry was used for validation.

**RESULTS:** 22 primary tumors were sequenced: 15 localized and 7 metastatic [to liver (n=5) or to lymph nodes (n=2)]. Patients were demographically similar. The Ki67 proliferation index was higher in metastatic tumors, although not statistically significant [median 10 (range 4-20) vs 4 (1-10),  $p=0.055$ ]. There were 188 genes that were significantly differentially expressed ( $FDR < 0.05$ ) between localized and metastatic PNETs: 64 upregulated and 124 downregulated genes. A gene set enrichment analysis indicated several pathways involved in immune and inflammatory responses (i.e. T cell recruitment and signaling) that were significantly upregulated in metastatic tumors (all  $FDR < 0.05$ ). Additionally, immunohistochemical analysis showed high expression of CD3+ T cells more frequently in metastatic lesions compared to localized tumors (57% vs 0%,  $p=0.026$ ).

**CONCLUSION:** Upregulation of immune and inflammatory system specific pathways appears to be associated with metastatic PNETs as compared to localized tumors. Further investigation into the specific tumor immune microenvironment of metastatic PNETs is warranted to analyze its role in disease progression and identify potential therapeutic targets.