Prognostic Criteria Development for Metastatic Well- or Moderately-Differentiated Neuroendocrine Tumors

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Abstract

Background: Neuroendocrine tumors (NET) are a unique subset of malignancies that share certain histologic, cytologic, and biochemical features. While tumor differentiation, staging, and Ki-67% are important factors in NET prognosis, no well-defined prognostic criteria exist for stage IV (metastatic) patients with well-differentiated/Ki-67 of <5% or moderately-differentiated/Ki-67 of 5-20% NET. As the five-year survival is only 67%, it is imperative to identify prognostic factors to aid in both choosing treatment timing and aggressiveness and stratifying patients for clinical trials. The aim of this research was to create a NET prognostic tool and correlate patient characteristics with tumor markers.

Methods: Adult patients with well-to-moderately differentiated metastatic NET treated at the Ohio State University (OSU) Comprehensive Cancer Center between 2000-2005 were included in this retrospective study. Gender, age and carcinoid syndrome at diagnosis, primary/metastatic tumor sites, treatments administered, and survival length were evaluated. Pathologic characteristics and tumor markers assessed at diagnosis and throughout the clinical course (≥3 years) were examined. Data is reported as median (range) unless otherwise noted.

Results: Fifty patients, 22 men and 28 women, were examined. Age at diagnosis was 54.5 years (25-84) and 48% of patients exhibited carcinoid syndrome features. The primary NET site was small bowel in 42%, pancreas in 18%, other locations in 14%, and unknown in 26%. Eighty-eight percent of tumors were well-differentiated while 12% were moderately-differentiated. Metastases were found in the liver in 92%, mesentery in 16%, and bone in 14% of patients. Twenty-two patients were alive at data analysis. Median survival was 85 months (12-129). Tumor markers and their relationship to clinical parameters, including survival, are under analysis.

Conclusion: The clinical characteristics and disease course of metastatic NET in our cohort demonstrates similarities and differences compared to published literature. Further investigation of these features may help elucidate the tools necessary for more accurate assessment of NET prognosis.

Introduction

- Despite having highly similar pathology upon microscopy, prognosis can vary widely amongst patients with metastatic well or moderately differentiated NETs. For a cohort of these patients, their cancer can be indolent and survival can be longer than 5 years while for the other cohort (~33%), cancer progress rapidly and survival can be less than 5 years.
- Variability in survival of such pts results in following challenges: 1) choosing the most appropriate timing and aggressiveness of treatment 2) interpreting 'stable disease' as a response to experimental drug in a setting of clinical trial.
- Thus there is a critical need to identify prognostic factors that help predict survival of patients who have metastatic well or moderately differentiated NETs.

Study Design

- Medical records were queried for demographic, clinical, biochemical, radiologic, and histological data on pts who were treated at the NET clinic at OSU Comprehensive Cancer Center (OSUCC) between 2000-2005 and had f/up for ≥3 years.
- All patients were demonstrated to have well or moderately differentiated NET upon pathologic review at the OSU Medical Center.
- Metastatic disease, according to radiologic or histologic examination, was present within 1 year of first visit at the OSUCC.
- Overall survival (OS) was determined from the date of start of therapy to death from any cause or the date of last observation. Patients still alive at last follow-up were censored. The median survival time and corresponding 2-sided 95% confidence interval (CI) were provided.

Results: Patient Characteristics

Characteristic	N=50	%	Median	Range
Gender				
Male	22	44	-	-
Female	28	56	-	-
Age Distribution				
Age (years)	-	-	54	25-84
Age <60 years	32	64	-	-
Age ≥60 years	16	36	-	-
Primary Tumor Grade				
Well-differentiated	44	88	-	-
Moderately-differentiated	6	12	-	-
Primary Tumor Location				
Small Bowel	21	42	-	-
Pancreas	9	18	-	-
Other location	7	14	-	-
Unknown at dx	13	26	-	-
Metastases Location				
Liver	46	92	-	-
Mesentery	8	16	-	-
Bone	7	14	-	-
>1 Location	21	42	-	-
Carcinoid Syndrome at Diagnosis				
Present	23	46%	-	-
Absent	24	48%	-	-
Data Not Available	3	6%	-	-
Elevated Tumor Markers (Data only available in 34 of 50 pts)				
	N=34 total			
Calcitonin (≥100)	4	12%	4345	100-124000
Gastrin (≥123)	9	26%	419	133-6520
Neurotensin (≥100)	7	21%	109	103-276
Pancreatic polypeptide (≥500)	14	41%	1116	584-14000
Pancreastatin (≥135)	33	94%	1090	151-39600
Survival at follow-up				
Alive	22	44%	-	-
Expired	28	56%	-	-

Table 1.
Patient characteristics

- **Sample size = 250**
- **Data reported in 50 pts**
- **Data collection ongoing for rest of the group**

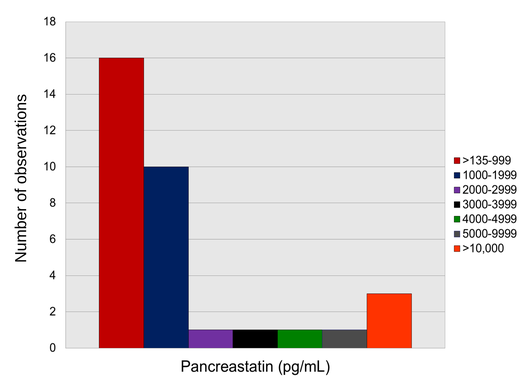

Figure 1. Histogram demonstrating the distribution of elevated pancreastatin levels at diagnosis (N=33).

Results: Variable Relationship with OS

		N	Censored	Median (weeks)	95% CI (weeks)	p-value
Bone metastatic	yes	7	2	56.0	26.0, NA	0.27
	no	42	20	94.5	60.0, NA	
Pancreatic primary	yes	9	2	58.0	12.0, NA	0.16
	no	41	20	91.0	56.0, NA	
Carcinoid syndrome	Yes	23	9	62.0	47.0, NA	0.17
	No	24	13	NA	61.0, NA	
Differentiation	Well	36	16	88.0	56.0, NA	0.70
	moderate	5	3	NA	31.0, NA	
Calcitonin (<100)	Normal	30	16	NA	60.0, NA	0.10
	Elevated	4	1	46.5	12.0, NA	
Gastrin (<122)	Normal	25	14	NA	52.0, NA	0.27
	Elevated	9	3	61.0	31.0, NA	
Neurotensin (<100)	Normal	27	13	91.0	49.0, NA	0.66
	Elevated	7	4	NA	31.0, NA	
Pancreatic Polypeptide (<500)	Normal	20	11	NA	50.0, NA	0.50
	Elevated	14	6	76.5	40.0, NA	
Pancreastatin (<3000) (Note: normal <135)	<3000	29	16	NA	60.0, NA	**0.02**
	≥3000	6	1	44.5	26.0, NA	
Age	<55	25	15	NA	76.0, NA	**0.01**
	≥55	25	7	52.0	47.0, 91.0	

Table 2. For each variable, the number of patients (N) in each group, the number of patients still alive (censored), the estimated median, 95% CI, and p-values are listed above. Overall survival (OS) was determined from the date of diagnosis to death or the date of last observation.

Conclusions & Future Directions

- Our data suggest that pancreastatin level and age at diagnosis may affect survival outcomes in patients with metastatic neuroendocrine tumors; however caution must be taken with interpreting the data due to the small sample size.
- The data presented herein are preliminary since we have evaluated only first 50 patients of planned cohort of 250 patients.
- The study is limited as about 50% of pts are alive in the cohort we examined to date. This resulted in lot of censored points when correlating different variable with survival.
- Whether or not additional variables will contribute to survival outcomes, and to what extent these factors contribute, will require expansion of the patient population to increase the statistical power of the cohort.
- We plan to acquire data for entire cohort of patients. As survival data matures, we plan to analyze the data.

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