



**INTRODUCTION**

**Background:**

- Studies show that Chromogranin A (CgA) and Alkaline Phosphatase (ALP) have prognostic significance for the presence of neuroendocrine tumors and metastasis respectively.

**Chromogranin A**

- A glycoprotein precursor to a number of functional peptides and hormones
- Secreted from neurosecretory vesicles of NET cells
- **Alkaline Phosphatase**
- Combination of several isoenzymes found in the liver, bone, kidney, and intestinal lining
- Can indicate the presence of bone and/or liver metastases

**Objectives:**

- To evaluate CgA and ALP in 363 patients with metastatic NET enrolled in a large, prospective outcomes study
- To analyze NET subgroups

**METHODS**

**Patient population**

- Case recruitment at the Dana-Farber Cancer Institute (DFCI) from 2003-2010
- Clinical information recorded from time of initial diagnosis
  - updated at 6-month intervals following study enrollment

**Statistics:**

- Elevated Chromogranin A or Alkaline Phosphatase
  - single measurement collected after time of metastatic diagnosis
  - Classified as a binary variable based on laboratory specification of elevated value
    - elevated Alk Phos. >126U/L
    - elevated CgA >36.4 ng/ml or >225ng/ml, measuring different subunits of the CgA protein
- Kaplan-Meier plot with the log-rank test
- **Cox proportional hazards regression analysis** adjusting for
  - Age, Sex, Stage, Tumor subtype (ileal carcinoid, pancreatic NET, other NET=ref), Histologic grade
  - modeled as time varying to account for variable time to test from time of diagnosis

**I. Population Characteristics**

**Table 1. Characteristics of the patient population**

	All patients (N=363) <sup>a</sup>
<b>Age at Dx</b>	56 yrs (13.2- 84.2)
<b>Gender</b>	
M	188 (53.6%)
F	175 (48.2%)
<b>Race</b>	
Caucasian	343 (95%)
Non-Caucasian	19 (5%)
<b>Grade of Differentiation</b>	
Well	319 (87.9%)
Moderate	17 (4.68%)
Poor	12 (3.31%)
Unknown	15 (4.13%)
<b>Tumor Type</b>	
Ileal Carcinoid	172 (47.4%)
Pancreatic NET	88 (24.3%)
Other NET <sup>a</sup>	103 (28.3%)

a. Other NET includes lung (14), appendix (3), unknown primary carcinoid (66), <5%: stomach, colon, rectum, anus, thorax, larynx, heart, thyroid

**Table 3. Time to Test from metastatic diagnosis**

Biomarker	Median	Mean	Range
<b>CgA</b>	3.1 months	1.3 years	0 to 14.5 yrs
<b>ALP</b>	2 months	1.1 years	0 to 14.5 yrs

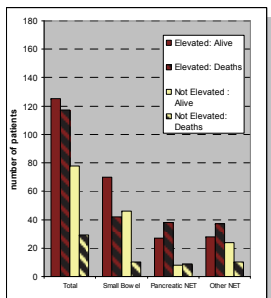
Half the patients tested within 3 months of their diagnosis of metastasis but there was a large range for the other half. Therefore time dependent modeling was necessary to account for this.

**Table 4. Elevated CgA and ALP among Tumor types**

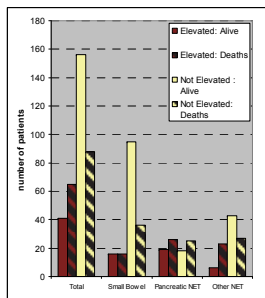
	All	Ileal Carcinoid	Pancreatic NET	Other NET
<b>CgA Elevated (N/Y)</b>	N=349 (69% Elevated), Deaths=146	N=168 (66% E), Deaths=52	N=82 (79% E), Deaths=47	N=99 (66% E), Deaths=47
<b>AlkPhos Elevated (N/Y)</b>	N=350 (30% E), Deaths=153	N=163 (20% E), Deaths=52	N=88 (51% E), Deaths=50	N=99 (29% E), Deaths=50

At the end of Follow-up, patients with:

- Small Bowel Carcinoid had the highest number and percentage of patients still alive with an Elevated CgA
- Other NET had the lowest number and percentage of patients still alive with an Elevated ALP.



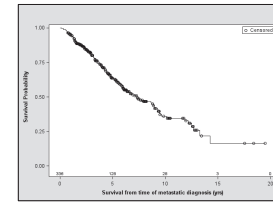
**Figure 3a. Distribution of patient outcomes with Elevated vs not elevated levels of CgA**



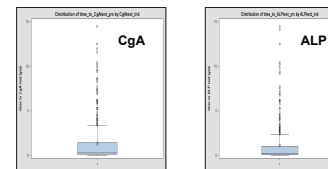
**Figure 3b. Distribution of patient outcomes with Elevated vs not elevated levels of ALP**

**Table 2. Survival Characteristics from time of diagnosis**

<b>Median F/U (range)</b>	5.94yrs (9 mo- 19.5yrs)
<b>Total Deaths<sup>a</sup></b>	155 (42.7%)
<b>Overall median survival (range)</b>	7.32 yrs (1.2 mo-15.19yrs)



**Figure 1. Overall Survival since metastatic diagnosis**



**Figures 2 a & b. Time to Test from metastatic diagnosis**

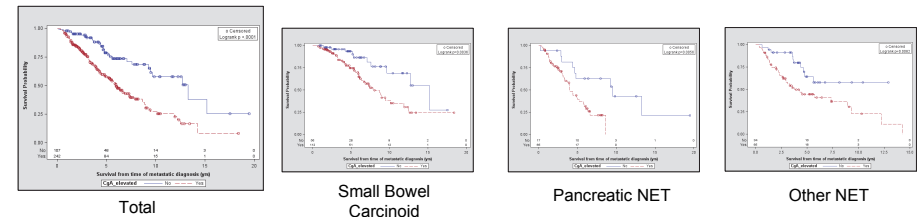
**RESULTS**

**II. Chromogranin A – Prognostic Value**

**Table 5. Median time to survival and adjusted Hazard Ratios<sup>a</sup> (time-varying model) for survival since metastatic diagnosis, by CgA value**

CgA Elevated (N/Y)	All	Small Bowel Carcinoid	Pancreatic NET	Other NET
<b>Median time to survival (years, 95%CI), log-rank p)</b>	N 13.27 (9.51, -) Y 5.98 (5.04, 7.3), p<0.0001	N 15.2 (9.64, -) Y 7.85 (6.33, 10.14), p=0.004	N 9.51 (4.37, -) Y 3.99 (3.32, 5.76), p=0.006	N not reached Y 3.79 (2.66, 8.93), p=0.008
<b>Hazard ratio (95% CI)</b>	4.36 (2.88, 6.60) p=3.8E-12	4.30 (2.13, 8.68) p=4.68E-08	4.63 (1.85, 11.61) p=0.001	5.22 (2.53, 10.75) p=7.47E-06

a. adjusting for age at diagnosis, gender, indicator variables of tumor type and grade of differentiation



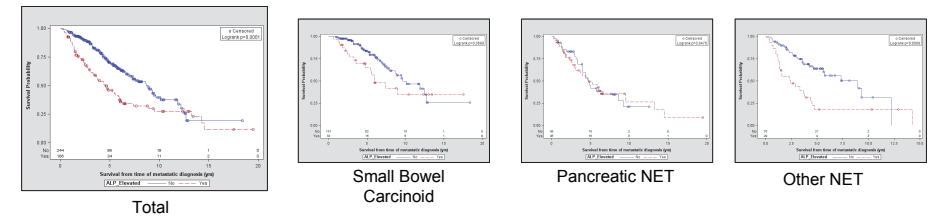
**Figures 4 (a-d): Overall survival for metastatic patients by CgA level (from time of diagnosis of metastatic disease)**

**III. Alkaline Phosphatase - Prognostic Value**

**Table 6. Median time to survival and adjusted Hazard ratios<sup>a</sup> (time-varying model) since metastatic diagnosis, by ALP value**

ALP Elevated (N/Y)	All	Small Bowel Carcinoid	Pancreatic NET	Other NET
<b>Median time to survival (years, 95%CI), log-rank p)</b>	N 8.87 (7.07, 9.64) Y 4.51 (3.27, 5.93), p=0.0001	N 9.64 (7.85, 12.70) Y 5.96 (3.57, -), p=0.07	N 4.82 (3.93, 8.62) Y 4.71 (2.99, 9.51), p=0.94	N 8.93 (4.62, 12.19) Y 2.41 (1.35, 3.79), p=0.0009
<b>Hazard Ratio (95%CI)</b>	2.40 (1.70, 3.40) p=7.96E-07	2.26 (1.24, 4.11) p=0.008	1.42 (0.77, 2.63) p=0.26	4.68 (2.61, 8.40) p=2.27E-07

a. adjusting for age at diagnosis, gender, indicator variables of tumor type and grade of differentiation



**Figures 5 (a-d): Overall survival for metastatic patients by ALP level (from time of diagnosis of metastatic disease)**

**Conclusions**

**Elevated Chromogranin A and elevated Alkaline phosphatase are significantly associated with shorter survival in patients with advanced NET, using a time-varying model**

**Subgroup analysis:**

- **Elevated Chromogranin A is significantly associated with shorter survival in all NET subgroups**
- **Elevated Alkaline Phosphatase is a strong predictor of shorter survival in patients with non-pancreatic NET**