



¹Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; ²Department of Environmental Health, ³Department of Biostatistics, Harvard School of Public Health

INTRODUCTION

Purpose:

- The clinical course of neuroendocrine (NET) patients remains poorly defined.
- We evaluated clinical outcomes and prognostic factors in 853 NET patients enrolled in a large, prospective outcomes study.

Characteristics of NET

- Incidence** ~ 5.25 /100,000
 - Diagnosis is increasing
- Prevalence estimated at >100,000**
- Often pursue indolent course**
- Hormone-secreting**
- Common subtypes:
 - Carcinoid** – small bowel is most common site
 - Pancreatic Endocrine tumor**

METHODS

Patient population

- Case recruitment at the Dana-Farber Cancer Institute (DFCI) from 2003-2009
- 853 cases diagnosed 1958-2009
 - 190 pancreatic NET
 - 321 small bowel carcinoid
 - 342 other carcinoid
- Clinical information recorded from time of initial diagnosis
 - updated at 6-month intervals following study enrollment

Statistics:

- Kaplan-Meier plot with the log-rank test
- Prognostic factors evaluated by **Cox proportional hazards regression analysis** adjusting for
 - age, sex (M, F=ref)
 - metastasis at initial diagnosis (M0=fully resected=ref, M1- metastatic)
 - tumor subtype (small bowel, pancreatic NET, other carcinoid=ref)
 - histologic grade (unknown, poor, moderate, well=ref)
 - octreotide treatment (Y/N=ref)
- Subgroups of Small Bowel Carcinoids and Pancreatic NET also analyzed separately

Table 1: Baseline Characteristics of the patient population

	All patients (N=853) ^a	Small Bowel Carcinoid (N=321)	Pancreatic NET (N=190)
Age at Dx	54 yrs (13.2- 86.4)	57 yrs (26.6-86.4)	53 yrs (13-85.8)
Gender M/ F	396 (46%), 457 (54%)	162 (50.5%), 159 (49.5%)	93 (49%), 97 (51%)
Stage M0 /M1	375 (44.1%), 476 (55.9%)	118 (36.9%), 202 (63.1%)	67 (35.4%), 122 (64.6%)
Grade of Differentiation			
Well	750 (87.9%)	312 (97.2%)	167 (87.9%)
Moderate	47(5.5%)	5 (1.6%)	9 (4.74%)
Poor	30 (3.5%)	1 (0.3%)	10 (5.26%)
Unknown	26 (3.1%)	3 (0.9%)	4 (2.11%)
Octreotide Treatment (Y/N)	393 (46%), 460 (53.9%)	186 (58%), 135(42%)	90 (47%), 100 (53%)

a. Includes small bowel carcinoid (37.6%), pancreatic NET(22%) and other carcinoid (lung(8.4%), appendix (5.7%), <5%: stomach, colon, rectum, anus, thorax, larynx, heart, thyroid and unknown primary sites)

Table 2: Baseline Survival Characteristics of the patient population

	All patients (N=853)	Small Bowel Carcinoid (N=321)	Pancreatic NET (N=190)
Total Deaths	210 (24.6%)	56 (17.4%)	66 (34.7%)
Overall median survival (range)	12.83 yrs (2.2mo-42.1yrs)	15.09 yrs (64days -18.03yrs)	7.88 yrs (67days- 34.88yrs)
Median F/U	4.45yrs (3days- 51.13yrs)	4.60 yrs (50days-42.13yrs)	5.05 (58days-22.18yrs)
Metastases	607 (71.2%)	240 (74.8%)	157 (82.6%)
Disease Free survival	244 (65.1%)	80 (67.8%)	32 (47.8%)
Stage M0 median time to recurrence (95%CI)	7.92yrs (6.88, 9.00)	9.00yrs (5.50, 11.10)	4.55yrs (2.96, 7.25)
Stage M1 median survival (95%CI)	7.58yrs (5.98, 9.64)	12.51yrs (8.87, 17.16)	4.71yrs (3.93, 9.51)

Figure 1. Kaplan-Meier curve for overall survival

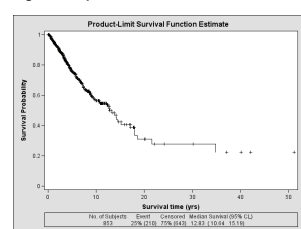


Figure 2. Overall survival for resected (M0) vs. metastatic (M1) patients

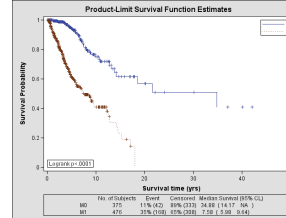
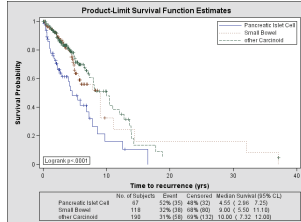
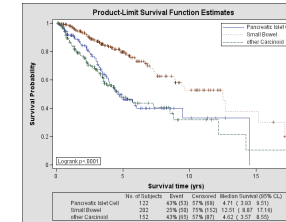


Figure 3. Disease free survival for resected patients (M0) by subtype (small bowel carcinoid vs other carcinoid vs pancreatic NET)



Patients with resected pancreatic tumor most likely to recur (median 4.5 yrs), adjusted HR= 2.21 (1.43, 3.43) p=0.0004

Figure 4. Overall survival for M1 patients by subtype (small bowel carcinoid vs other carcinoid vs pancreatic NET)



Patients with small bowel tumor and metastasis most likely to survive (median 12.5 yrs), adjusted HR=0.34 (0.23, 0.51) p<0.0001

RESULTS

Clinical characteristics of all patients

- Follow-up time = initial diagnosis to death or last known follow up
 - Median F/U= 4.45 years
 - 80% at 8.63 yrs
 - 95% at 17.7 yrs
- 210 (24.6%) deaths occurred
- 46% male, 54% female
- 44% M0, 55.9% M1
- Median OS** for the entire cohort was 12.8 yrs.

Overall survival and disease free survival of resected (M0) patients

- Median OS** was not reached
- 5-yr OS was 94%
- 5-yr DFS was 65%
- Median time to recurrence** was 7.9 yrs
 - 9 yrs for small bowel carcinoid
 - 4.6 yrs for pancreatic NET**
 - 10 yrs for other carcinoid

Overall survival of metastatic (M1) patients

- Median OS** was 7.6 yrs
 - 12.5 yrs for small bowel carcinoid
 - 4.7 yrs for pancreatic NET
 - 4.6 yrs for other carcinoid

Prognostic Factors for resected patients

Higher risk of recurrence: Older age, male gender, pancreatic primary site, and poor histologic grade were significantly associated

Prognostic Factors for metastatic patients

Overall survival and survival since metastasis: The same factors were associated with shorter survival but

- Pancreatic origin is no longer significant
- Small bowel origin is protective**

Octreotide treatment

Suggested improved survival for patients since time of metastasis

- M1: adjusted HR = 0.83, p=0.29
- M0 + M1: adjusted HR = 0.78, p=0.12

DISCUSSION

- Strengths**
 - Large cohort of neuroendocrine cases
 - Long follow-up
 - 25% events occurred
- Limitations**
 - Observational study
 - Conclusions on treatment may be confounded by time of administration
 - Restricted to metastatic only to address this

Table 3. Prognostic Factors for resected and metastatic patients at diagnosis – adjusted HR (95%CI) for overall survival (Deaths=210/853)

Variable	Statistics			Hazard ratio and 95% CI
	Hazard ratio	Lower limit	Upper limit	
Age at Diagnosis	1.04	1.03	1.05	<0.0001
Stage	5.75	3.96	8.36	<0.0001
Male	1.44	1.10	1.90	0.009
Pancreatic	1.12	0.81	1.56	0.486
Small bowel	0.37	0.25	0.53	<0.0001
Moderate grade	2.07	1.26	3.41	0.004
Poor grade	4.69	2.86	7.70	<0.0001
Unknown grade	1.21	0.66	2.21	0.539

Table 4. Prognostic Factors for resected patients at initial diagnosis (M0) – adjusted HR (95%CI) for overall survival (Deaths= 42/375) and time to recurrence (Metastases=131/375)

Group by Outcome	Variable	Statistics			Hazard ratio and 95% CI	
		Hazard ratio	Lower limit	Upper limit		
DFS	Age at Diagnosis	1.02	1.00	1.03	0.009	
	Male	1.42	1.01	2.01	0.047	
	Pancreatic	2.21	1.43	3.43	<0.0001	
	Small bowel	1.19	0.77	1.86	0.433	
	Moderate grade	3.73	2.15	6.48	<0.0001	
	Poor grade	6.01	1.85	19.51	0.003	
	Unknown grade	1.41	0.50	3.93	0.516	
	OS	Age at Diagnosis	1.03	1.00	1.05	0.045
		Male	1.27	0.69	2.33	0.445
		Pancreatic	1.33	0.64	2.75	0.440
Small bowel		0.48	0.19	1.22	0.124	
Moderate grade		2.36	0.95	5.88	0.065	
Poor grade		10.96	2.42	49.50	0.002	
Unknown grade		1.36	0.29	6.34	0.694	

Table 5. Prognostic Factors for all patients with metastatic disease (M0+M1) – adjusted HR (95%CI) for survival since time of metastasis (Deaths = 207/607)

Variable	stage	Statistics			Hazard ratio and 95% CI
		Hazard ratio	Lower limit	Upper limit	
Age at Diagnosis	M0+M1	1.04	1.03	1.05	<0.0001
Male	M0+M1	1.41	1.07	1.87	0.016
Pancreatic	M0+M1	0.99	0.71	1.39	0.967
Small bowel	M0+M1	0.37	0.25	0.53	<0.0001
Moderate grade	M0+M1	1.76	1.06	2.90	0.028
Poor grade	M0+M1	3.82	2.30	6.33	<0.0001
Unknown grade	M0+M1	0.93	0.49	1.76	0.825
Octreotide	M0+M1	0.78	0.57	1.06	0.115
Stage	M0+M1	1.73	1.19	2.52	0.004

CONCLUSIONS

- Pancreatic primary site increases the risk for recurrence after resection**
- Small Bowel primary site increases the chances for survival after metastasis compared to other carcinoid**
- Octreotide may be associated with improved survival after metastasis**
- Tumor recurrences, when they occur, may develop more than 5 years after initial diagnosis.**