Incidence, Survival and Prevalence of Neuroendocrine Tumors Versus Neuroblastoma in Children and Young Adults: Nine SEER Registries, 1975-2004

University of Iowa Neuroendocrine Tumor Program

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Introduction

- Neuroendocrine tumors arise from the diffuse neuroendocrine system and can occur in almost any endocrine or non-endocrine tissue (Modlin, 2006).
- Classification as a neuroendocrine tumor (NET) is based primarily on histology showing clear cells, together with positive immunohistochemistry for chromogranin A, synaptophysin and neuron specific enolase. Differentiation and proliferation are reliable prognostic biomarkers (Faggiano, 2008).
- Patients who are diagnosed with neuroendocrine tumors often have a multi-year history of symptoms prior to identification of the malignancy with average lag period of 8-10 years (Vinik A & Mattari AR, 1989). Thus, a 29-year old adult diagnosed as having a neuroendocrine tumor may well have been an adolescent when the first symptoms occurred.
- Literature reports suggest that as many as 10 percent of these children and young adults have metastatic disease at presentation (Corpron, 1995 ; Ladd, 2006; Khanna G, 2008; Broaddus, 2003; O'Dorisio, 2008; Parham, 2001; Spunt, 2000). This disturbing observation is due in part to the wide distribution of the diffuse neuroendocrine system, the multiple histologic diagnoses associated with neuroendocrine tumors and delays in diagnosis.
- The rationale for comparing the incidence, survival and prevalence rates for neuroendocrine tumors and neuroblastoma in the 0-29 year age group comes from similarities in wide distribution, wide variations in aggressiveness from benign to highly malignant, together with their shared biomarkers namely chromogranin, synaptophysin, VMAT1/2, and somatostatin receptors.

Methods

- Data were obtained from the 9 standard SEER registries for diagnosis years of 1975 to 2004 using SEER*Stat software (version 6.4.4; 6.5.1) with histology codes based on ICD-O-3
- Observed survival rates and survival case listing files for neuroendocrine tumors and neuroblastoma were obtained by using the SEER*Stat software; only actively followed cases of known age were selected.
- Thirty-year limited duration prevalence rates for NET and neuroblastoma as of January 1, 2005, were obtained by selecting cases of malignant behavior and known age while excluding death certificate and autopsy only cases using the SEER*Stat software. Prevalence counts were based on cancer prevalence proportions from SEER 9 registries and US population based on the average of 2004 and 2005 population estimates from the US Bureau of the Census.

Results

Table 1: Distribution of malignant neuroendocrine tumors by 5-digit morphology code, ages 0-29, 9 Standard SEER Registries, 1975-2004

ICD-0-3 codes	Count (n=975)	Incidence Rate* (per million)	Lower 95% CI	Upper 95% CI
8240/3: Carcinoid tumor, malignant	497	1.4	1.3	1.5
8510/3: Medullary carcinoma, NOS	203	0.5	0.5	0.6
8041/3: Small cell carcinoma, NOS	104	0.3	0.2	0.4
8246/3: Neuroendocrine carcinoma	88	0.2	0.2	0.3
8245/3: Adenocarcinoid tumor	21	0.1	0	0.1
8700/3: Pheochromocytoma	17	0.1	0	0.1
8680/3: Paraganglioma, malignant	13	0	0	0.1
Others: 8013/3: Large cell neuroendocrine carcinoma; 8044/3: Small cell carcinoma, intermediate cell; 8045/3: Combined small cell carcinoma; 8244/3: Composite carcinoid; 8247/3: Merkel cell carcinoma; 8693/3: Extra-adrenal paraganglioma, malignant	11	0	0	0
8241/3: Enterochromaffin cell carcinoid	8	0	0	0
8042/3: Oat cell carcinoma	7	0	0	0
8243/3: Goblet cell carcinoid	6	0	0	0

ICD-O-3 = International Classification of Diseases for Oncology, 3rd Edition
*Rates are age-adjusted to the 2000 US standard population; Confidence intervals (Tiwari mod) are 95% for rates.

Results

Figure 1: Distribution of 975 neuroendocrine tumors by primary site, ages 0-29 years, 9 Standard SEER Registries, 1975-2004

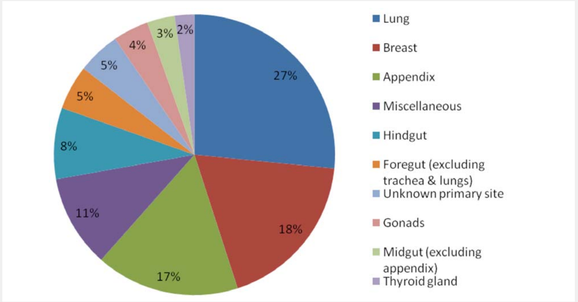

Table 2: Frequency & incidence rates for malignant neuroendocrine tumors, common sites & morphologies, 0-29 years, 9 Standard SEER Registries, 1975-2004

All Sites	Most Common Histology Codes	Count (n=975)			Incidence Rate * (per million)		
		Total	Males	Females	Total	Males	Females
Lung	8240/3: Carcinoid tumor, malignant	224	91	133	0.6	0.5	0.8
Breast	8510/3: Medullary carcinoma, NOS	179	0	179	0.5	0	1
Appendix	8240/3: Carcinoid tumor, malignant	124	39	85	0.4	0.2	0.5
Hindgut	8240/3: Carcinoid tumor, malignant	74	26	48	0.2	0.1	0.3
Miscellaneous	8041/3: Small cell carcinoma, NOS	52	17	35	0.1	0.1	0.2
Midgut (excluding appendix)	8240/3: Carcinoid tumor, malignant	38	19	19	0.1	0.1	0.1
Gonads	8041/3: Small cell carcinoma, NOS	27	0	27	0.1	0	0.2
Thyroid gland	8510/3: Medullary carcinoma, NOS	20	8	12	0.1	0	0.1
Foregut (excluding trachea & lungs)	8246/3: Neuroendocrine carcinoma	7	3	4	0	0	0

ICD-O-3 = International Classification of Diseases for Oncology, 3rd Edition
*Rates are age-adjusted to the 2000 US standard population.

Table 3: 5-year observed survival rates for malignant neuro-endocrine tumors, common sites and morphologies, 0-29 years, 9 Standard SEER Registries, 1975-2004

Primary Site-labeled	ICD-0-3 Histology Code	Alive at start	Observed survival rate* (%)	95% confidence interval	
				Lower limit	Upper limit
Appendix	8240/3: Carcinoid tumor, malignant	121	100.0	100.0	100.0
Hindgut	8240/3: Carcinoid tumor, malignant	69	100.0	100.0	100.0
Thyroid gland	8510/3: Medullary carcinoma, NOS	20	100.0	100.0	100.0
Lungs	8240/3: Carcinoid tumor, malignant	220	96.6	94.1	99.2
Midgut (excluding appendix)	8240/3: Carcinoid tumor, malignant	25	91.1	79.1	103.1
Breast	8510/3: Medullary carcinoma, NOS	175	80.8	74.9	86.7
Foregut (excluding lungs & trachea)	8246/3: Neuroendocrine carcinoma	26	46.7	25.7	67.7
Miscellaneous	8041/3: Small cell carcinoma, NOS	36	21.6	7.9	35.3
Gonads	8041/3: Small cell carcinoma, NOS	27	20.2	4.52	35.88

*Survival rates are unadjusted

Table 4: Comparing frequency and incidence rates for neuro-endocrine tumors versus neuroblastoma by demographic and tumor characteristics, 0-29 years, 9 Standard SEER Registries, 1975-2004.

Variables		Neuroendocrine Tumors		Neuroblastoma	
		Count	Incidence Rate* (per million)	Count	Incidence Rate* (per million)
Age Groups	< 05 yrs	5	0.0	1320	24.9
	05-09 yrs	6	0.1	117	2.2
	10-14 yrs	47	0.9	35	0.7
	15-19 yrs	126	2.3	25	0.5
	20-24 yrs	249	4.5	14	0.3
	25-29 yrs	542	9.2	17	0.3
Stage**	Localized	447	1.2	194	0.6
	Regional	217	0.6	311	1.0
	Distant	100	0.3	772	2.4
	Unstaged	93	0.3	246	0.8
	Blank***	117	0.3	5	0

* Rates are age-adjusted to the 2000 US standard population.
** One additional case involved the prostate and was staged as localized/regional
*** "The SEER Program strives to make all L/R/D stage variables consistent for all cancer sites for the appropriate years. However, there are certain site/year combinations where this is not possible" (http://seer.cancer.gov/seerstat/variables/seer/yr1973_2005/lrd_stage/)

Table 5: Observed survival rates for malignant neuroendocrine tumors, common sites and morphologies, 0-29 years, 9 Standard SEER Registries, 1975-2004

Primary Site-Labeled	ICD-0-3 Histology Code	Alive at Start			5-yr Observed Survival Rate* (%)		
		Total	Male	Female	Total	Male	Female
Appendix	8240/3: Carcinoid tumor, malignant	121	38	83	100.0	100.0	100.0
Hindgut	8240/3: Carcinoid tumor, malignant	69	25	44	100.0	100.0	100.0
Thyroid gland	8510/3: Medullary carcinoma, NOS	20	8	12	100.0	100.0	100.0
Lungs	8240/3: Carcinoid tumor, malignant	220	91	129	96.6	98.7	95.1
Midgut (excluding appendix)	8240/3: Carcinoid tumor, malignant	36	18	18	84.9	83.0	86.9
Breast	8510/3: Medullary carcinoma, NOS	175	0	175	80.8	0.0	80.8
Foregut (excluding lungs & trachea)	8246/3: Neuroendocrine carcinoma	7	3	4	70.10	33.3	100.0
Miscellaneous	8041/3: Small cell carcinoma, NOS	52	17	35	20.7	11.8	24.9
Gonads	8041/3: Small cell carcinoma, NOS	27	0	27	20.2	0.0	20.2

*Survival rates are unadjusted

Table 6: Observed survival rates for neuroendocrine tumors versus neuroblastoma by demographic and tumor characteristics variables, 0-29 years, 9 Standard SEER Registries, 1975-2004

Variables		Neuroendocrine Tumors		Neuroblastoma	
		Alive at Start	5-yr Observed Survival Rate* (%)	Alive at Start	5-yr Observed Survival Rate* (%)
Year Diagnosed	1975 to1979	191	83.0	204	45.3
	1980 to 1984	138	80.2	235	45.1
	1985 to 1989	153	78.8	238	53.9
	1990 to 1994	149	68.8	257	66.6
	1995 to 1999	134	72.7	277	63.9
	2000 to 2004	183	85.1	292	73

*Survival rates are unadjusted

Results cont.

Table 7: 30-year limited prevalence data for neuroendocrine tumors versus neuroblastoma as of January 1, 2005, 0-29 year old persons at diagnosis, entire US population

Variables		Neuroendocrine Tumors Estimated Prevalence Count		Neuroblastoma Estimated Prevalence Count	
		Male	Female	Male	Female
Age Groups in Years	0-9	0	0	1851	1722
	10-19	152	162	1892	1459
	20-29	636	866	999	1079
	30-39	863	1282	146	172
	40-49	580	1505	21	21
	50-59	236	962	0	10
Total	0-59	2467	4777	4909	4463
Grand Total		7244		9372	

Conclusions

- Lungs, breast, and appendix are the most common sites for malignant NETs, accounting for 62% of all NETs in young people <30 yrs of age.
- Small cell neuroendocrine carcinoma, occurring most often in the ovaries, is associated with only a 20% 5-year survival rate.
- The incidence of malignant NETs is almost double in females as compared to males, with exception of adenocarcinoid tumor and paraganglioma.
- At least 10% of malignant NETs in children and young adults present as "distant" stage, thus supporting the past literature reports.
- While survivorship has significantly increased for neuroblastoma during the past 30 years, young people diagnosed with NETs have shown a more variable survival pattern with no linear trend.
- NETs constitute an unrecognized cancer threat comparable to neuroblastoma in both number of affected persons and disease severity.

Future Directions

- Establish centers of excellence for diagnosis and treatment of children and young adults, especially adolescent females with neuroendocrine tumors.
- Educate pediatric endocrinologists, oncologists, gastroenterologists and adolescent medicine specialists in the diagnosis of neuroendocrine tumors.
- Develop specific treatment regimens for young people with NET of the breast and ovaries.

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