

# Alkaline Phosphatase Predicts Survival in Patients with Metastatic Neuroendocrine Tumors

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The clinical course of patients with metastatic neuroendocrine tumors is highly variable. While some patients experience an indolent clinical course over many years, other patients may rapidly succumb to their disease. Little is known about prognostic factors in these patients, making decisions regarding their management more difficult.

We performed a retrospective analysis of 137 patients with metastatic neuroendocrine tumors referred to our institution for treatment. Potential prognostic factors were evaluated using multivariate survival analysis. The median overall survival of patients in our cohort was 6.0 years, although the range of survival times was broad (48 days to 23.4 years). Alkaline phosphatase levels above normal were predictive of shorter survival in both univariate and multivariate analysis. Elevated chromogranin A levels were also associated with shorter survival in univariate analysis; in a multivariate analysis, however, this correlation was no longer significant. There was no association between survival and gender, primary tumor site, or presence or absence of carcinoid syndrome. Elevated alkaline phosphatase is a robust adverse prognostic factor for survival in patients with metastatic neuroendocrine tumors and may be superior to chromogranin A in this setting. Close monitoring of alkaline phosphatase levels may be useful when considering initiation or changes of therapy in patients with metastatic neuroendocrine tumors.

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**KEY WORDS:** neuroendocrine tumor; carcinoid tumor; chromogranin; alkaline phosphatase; prognostic factor; survival.

Neuroendocrine tumors (NETs) are generally characterized by relatively slow growth rates and the capacity to synthesize and secrete polypeptide products with specific hormonal activity. Metastatic NETs typically follow an

indolent clinical course, and expectant observation may be recommended in asymptomatic patients. As these tumors progress, however, they may cause both morbidity and mortality due to the overproduction of specific amines and peptides. The use of somatostatin analogues to control symptoms of the carcinoid syndrome as well as other states of hormonal excess has significantly improved quality of life for such patients and has improved survival times compared to historical controls (1). Unfortunately, somatostatin analogues only rarely result in tumor regression; furthermore, over time, their efficacy in controlling the symptoms of hormonal secretion may decline (2–8). Patients who do not respond or become refractory to somatostatin analogues may pursue a number of other treatment options, including resection of hepatic

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metastases, chemoembolization, and, in some cases, administration of  $\alpha$ -interferon or systemic chemotherapy. Some asymptomatic patients may also consider treatment as a way to prevent or delay the onset of symptoms.

The selection of patients for treatment, as well as the choice of treatment, has been made more difficult by a lack of accurate prognostic factors. The rarity of NETs has made prognostic studies challenging to perform. Carcinoid tumors, the most commonly occurring NET, have an estimated incidence of only 1–2 per 100,000 population, and pancreatic endocrine tumors are estimated to occur at less than 1 per million (9). In patients with bronchial carcinoid tumors, poorly differentiated or “atypical” histology has been found to be an adverse prognostic factor (10). With the possible exception of elevated serum chromogranin A (CgA) levels (11–16), reliable serologic prognostic markers applicable to all metastatic NETs have been elusive (11, 17–20).

We therefore undertook a retrospective study of potential prognostic factors in 137 patients with confirmed metastatic NETs. Correlations among patient characteristics, tumor site, and serologic markers and survival were investigated using both univariate and multivariate analyses.

## PATIENTS AND METHODS

### Patients

We reviewed the medical records of 137 patients referred to Dana Farber Cancer Institute between January 1997 and June 2003. All patients had histopathologically verified NETs, confirmed independently by analysis of archived pathology slides. Three patients with poorly differentiated neuroendocrine carcinomas were excluded from the analysis due to their known poor prognosis, as were patients with small cell carcinomas. All patients were confirmed to have evidence of metastatic disease either histologically or radiographically.

Information was recorded regarding primary tumor type (carcinoid, pancreatic endocrine tumor), site of primary tumor, presence of symptoms, CgA, liver function tests, and general patient demographics (age, gender). Patients reporting reliable symptoms of flushing and/or diarrhea were classified as having characteristics of the carcinoid syndrome. Survival data were extracted from the medical record; for patients lost to follow-up or followed elsewhere, survival data were checked against the National Social Security Death Index. Follow-up times ranged from 1 to 78 months.

Nearly all patients underwent systemic therapy for metastatic NETs. Only five underwent either noncurative resection and/or tumor ablation with radiofrequency energy or cryoablation. Fourteen patients were treated with at least one cycle of chemoembolization in addition to systemic therapy. Of the 137 patients with metastatic disease, 115 had metastases to the liver.

### Statistical Analysis

Univariate analyses were conducted using two-sided *t*-tests for continuous variables and Pearson  $\chi^2$  tests for categorical

variables to determine whether the characteristics of patients who died were statistically different from those of patients who did not die, with respect to the patient's age at time of diagnosis, gender, type of tumor, primary tumor site, laboratory tests including CgA, alkaline phosphatase, total bilirubin, aspartate aminotransferase (AST), and presence of carcinoid syndrome. The majority of patients received systemic therapy only, whereas only approximately 10% underwent one or more cycles of chemoembolization, and very few (<5%) underwent surgical resection or ablative therapy. Therefore no attempt was made to correlate type of treatment with survival, given the small number of patients receiving locoregional therapy. Fisher's  $\chi^2$  exact test was used when the sample size was small. Patients' survival probabilities were compared and depicted according to various categories of covariates of interest using the Kaplan-Meier method; the survival curves were compared using the log-rank test. Survival time was calculated from the date of cancer diagnosis to the date of death or the defined study end date (June 1, 2003). The date of cancer diagnosis was, in many cases, distant from the date of referral for metastatic disease. Survival was therefore also measured from the time of initial referral and evaluation for known metastases.

A multivariate analysis of survival was performed using the Cox proportional hazards model, which adjusted for age at time of diagnosis, gender, primary tumor site, presence or absence of carcinoid syndrome, alkaline phosphatase level, and CgA level. Total bilirubin and AST, collinear with alkaline phosphatase, were not statistically significant and were removed from the final Cox proportional hazards model.

The Cox proportional hazards regression results are expressed as hazards ratios, corresponding 95% confidence intervals (CI), and *P* values for testing the null hypothesis that the hazard ratio equals 1. A *P* value of 0.05 was used to declare statistical significance. All analyses were performed using SAS software, version 8.2 (SAS Institute).

## RESULTS

### Patient Characteristics

The patient cohort was relatively evenly distributed between men and women, with a mean age of 56 years (Table 1). The tumor type was carcinoid in 70% and pancreatic endocrine tumor in 30%. Of patients with carcinoid tumors, the majority had small intestine (39%) as the primary site. In 16% of cases, the primary site could not be identified. Overall, 46% of patients reported symptoms of the carcinoid syndrome.

Liver function test results including alkaline phosphatase were available in 113 patients, of whom 46 had alkaline phosphatase levels above the normal range (>127 U/L in our clinical laboratory). No significant variations in total bilirubin or transaminase levels were noted between patients who died and those who did not. CgA levels were recorded in 100 patients; of these patients 78 had elevation of CgA above the normal range (0–39 ng/ml) and 32 had marked elevations in CgA (>500 ng/ml).

TABLE 1. PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS AT TIME OF REFERRAL AND INITIAL WORKUP (N = 137)

Characteristic	N	%	Mean (SD)
Gender			
Male	72	52.6	
Female	65	47.5	
Age at diagnosis	137		56.2 (12.3)
Type of tumor			
Carcinoid	96	70.1	
Pancreatic	41	29.9	
Primary tumor site			
Hindgut*	9	6.6	
Small intestine	54	39.4	
Pancreas	41	29.9	
Pulmonary	11	8.0	
Unknown and other†	22	16.1	
Carcinoid syndrome			
Yes	64	46.7	
No	66	48.2	
Unknown	7	5.1	
Chromogranin A (ng/ml)	100		916.5 (1870.6)
<500 ng/ml	69	50.4	
≥500 ng/ml	32	23.4	
Alkaline phosphatase (U/L)	113		154.8 (136.1)
<127 U/L	67	48.9	
≥127 U/L	46	33.6	
AST (U/L)	113		35.8 (28.9)
<46.5 U/L	94	68.6	
≥46.5 U/L	19	13.9	
Total bilirubin (mg/dl)	113		0.6 (0.4)
<1.35 mg/dl	106	77.4	
≥1.35 mg/dl	7	5.1	

\*Includes patients whose primary tumor site was the large bowel or rectum.

†Includes patients whose primary tumor site was adrenal, stomach, or unknown.

### Univariate Survival Analysis

The median survival from the time of diagnosis for all patients in the cohort was 6.0 years, with a minimum of 48 days and a maximum of 23.4 years. Ninety-two of 137 patients (67%) were alive at the end of the follow-up period. The results of the univariate survival analysis are presented in Table 2. As anticipated, advanced age at the time of diagnosis was associated with shorter survival time ( $P < 0.0003$ ). No significant associations between survival and gender, presence of carcinoid syndrome, tumor site of origin, transaminase levels (AST), bilirubin levels, presence of liver metastases, or presence of bone metastases were noted.

Alkaline phosphatase was analyzed as a dichotomous variable, based on the upper bound of normal for the test in our clinical laboratory (127 U/L). Elevated levels of alkaline phosphatase were significantly related to shorter survival times in the univariate analysis. This relationship held true whether survival was measured from the initial date of diagnosis ( $P < 0.003$ ) or from the actual date of evaluation when laboratory tests were drawn ( $P < 0.005$ ) (Table 2). A Kaplan-Meier survival plot as measured from

the alkaline phosphatase evaluation date is depicted in Figure 1.

Because nearly all (78%) patients in our cohort had CgA levels above the normal range (39 U/L), CgA levels were analyzed as a dichotomous variable, using a cutoff level of 500 ng/ml. CgA levels above 500 ng/ml were associated with decreased survival from the date of evaluation ( $P < 0.030$ ) but not from the time of initial diagnosis (Table 2).

### Multivariate Survival Analysis

A multivariate Cox proportional hazards regression analysis of survival showed that advanced age remained a predictor of shorter survival time (Table 3). Elevated alkaline phosphatase also remained a significant predictor of shorter survival as measured from the date of evaluation, although alkaline phosphatase was not an independent predictor of survival from time of original diagnosis. These relationships were seen when the multivariate regression was performed for the subset of patients with liver metastases (data not shown). Similarly, these relationships were seen when the subset of patients with bone metastases (18/137, or 13% of, patients) was excluded.

In contrast, elevated CgA levels were no longer predictive of survival, as measured from date of evaluation, in the multivariate analysis. The lack of association held true both when CgA was measured as a dichotomous variable, using 500 ng/ml as a cutoff ( $P < 0.276$ ), and when CgA was analyzed as a continuous variable ( $P < 0.0831$ ). We likewise did not detect an association between dichotomized CgA and survival as measured from time of original diagnosis ( $P < 0.339$ ).

Previous studies have reported that CgA levels may be predictive of survival in patients whose tumors are of midgut origin (19). When our analysis was limited to the subset with tumors of midgut origin, the results mirrored the cohort as a whole, in that elevated CgA correlated with shorter survival from time of evaluation in univariate analysis but not multivariate analysis (data not shown). Likewise, gender, site of tumor origin, transaminase levels, bilirubin levels, and presence of carcinoid syndrome did not affect survival for patients with midgut carcinoid tumors.

### DISCUSSION

NETs are characterized by a relatively indolent growth pattern, and patients may live for several years even with metastatic disease. The median survival time from time of diagnosis in our cohort was 6.0 years, a figure that compares favorably to historical data (21). We also, however, noted a broad range of survival times among our patients; whereas the shortest survival time was 48 days

TABLE 2. UNIVARIATE RESULTS OF COX PROPORTIONAL HAZARDS MODEL FOR DEATH (DEPENDENT VARIABLE—PROBABILITY OF DEATH; SURVIVAL TIME VARIABLE—DAYS FROM DIAGNOSIS TO DEATH†)

<i>Characteristic</i>	<i>Hazards ratio</i>	<i>(95% CI)</i>	<i>P value</i>
Chromogranin A $\geq$ 500 ng/ml			
Survival from diagnosis	1.119	(0.590, 2.119)	0.729
Survival from chromogranin A test date‡	2.159	(1.069, 4.362)	0.030*
Alkaline phosphatase $\geq$ 127 U/L			
Survival from diagnosis	2.434	(1.339, 4.424)	0.003*
Survival from liver function test date‡	2.402	(1.299, 4.444)	0.005*
AST $\geq$ 46.5 U/L			
Survival from diagnosis	1.857	(0.891, 3.868)	0.098
Survival from liver function test date‡	1.356	(0.649, 2.833)	0.417
Total Bilirubin $\geq$ 1.35 mg/dl			
Survival from diagnosis	0.683	(0.165, 2.828)	0.599
Survival from liver function test date‡	0.720	(0.173, 3.008)	0.653
Gender			
Female	1.118	(0.618, 2.022)	0.710
Male	Reference		
Age at diagnosis (years)	1.049	(1.022, 1.077)	0.000*
Tumor origin			
Hindgut§	1.984	(0.694, 5.672)	0.197
Small bowel	0.664	(0.346, 1.276)	0.215
Pancreatic	1.042	(0.543, 1.998)	0.902
Pulmonary	Reference		
Unknown and other¶	1.696	(0.853, 3.375)	0.129
Carcinoid syndrome			
Yes	0.929	(0.513, 1.683)	0.806
No/unknown	Reference		
Liver metastases			
Yes	0.590	(0.298, 1.166)	0.129
No	Reference		

\*Denotes statistical significance at the 5% level.

†Survival times are measured from day of diagnosis to death unless indicated otherwise.

‡Survival measured from the date of evaluation and laboratory testing.

§ Includes patients whose primary tumor site was the large bowel or rectum.

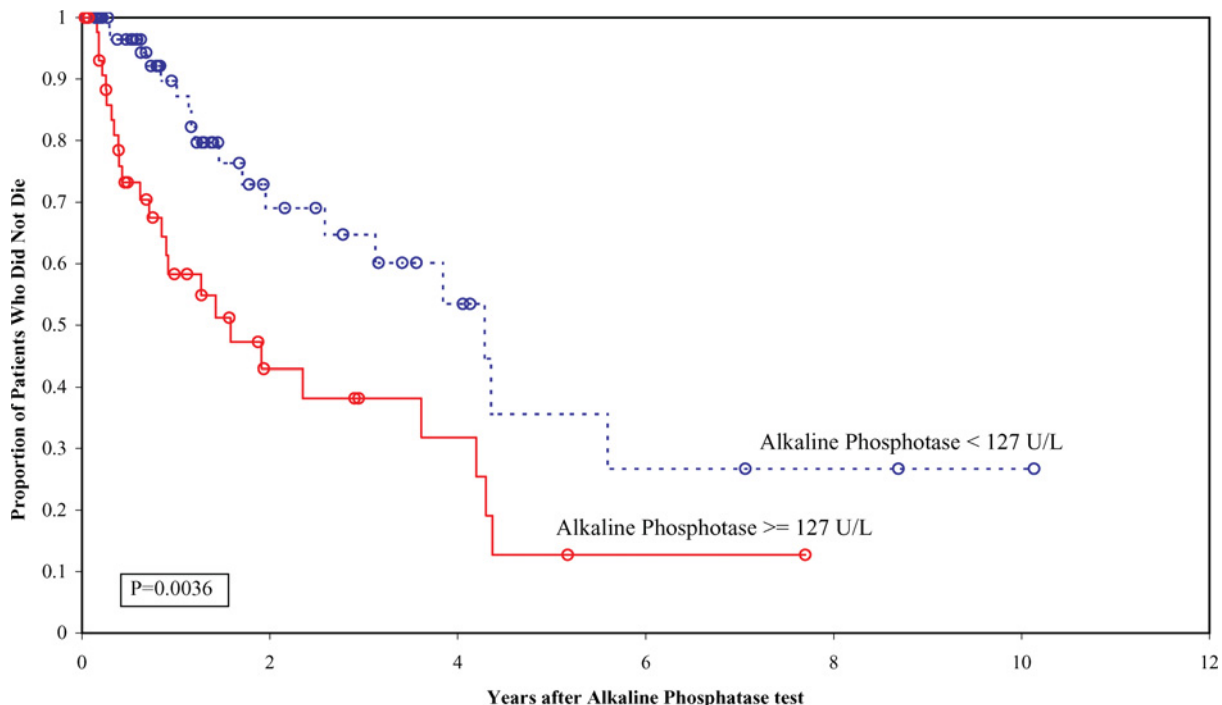
¶ Includes patients whose primary tumor site was the adrenal, stomach, or unknown.

from diagnosis, most patients (67%) in the cohort were alive at the end of the follow-up period, with the upper range of survival of 23.4 years from the time of initial diagnosis. To date, few prognostic factors for patients with metastatic NETs have been identified, in large part due to the rare nature of these tumors (1, 17).

The liver is one of the most common sites of metastases for NETs. Indeed, among patients who present with NETs, the presence of liver metastases is a primary determinant of decreased survival; patients with NETs metastatic to the liver are reported to have a 10-year survival of 26–30%, compared with the 83–93% 15-year survival of NET patients without metastases (1, 22). Even with liver metastases, patients may have largely preserved liver function, as demonstrated by the fact that the median AST and bilirubin levels in our patient cohort were both within the normal range. In contrast, however, the median alkaline phosphatase level was mildly elevated. Using a standard of normal defined as  $<127$  U/L in our assay, patients with alkaline phosphatase  $>127$  U/L had a significantly shorter survival times. Elevated alkaline phosphatase levels were

independently predictive of survival as measured from the time of evaluation and assay but not from the time of original diagnosis.

The cohort demonstrates a wide range of times between original cancer diagnosis and referral to our center, at which time laboratory values were documented. Whereas some presented with metastatic disease at diagnosis, one patient had a 23-year span between initial diagnosis and the date of evaluation, presumably due to delayed development of metastases. The median duration between original diagnosis and referral for metastatic disease is approximately 5 months. Although the date of diagnosis represents the date when the primary tumor was recognized and treated, the precise date of diagnosis of metastatic disease developed is more difficult to quantify. The date of referral to our center for evaluation of metastatic disease may therefore serve as a surrogate for the approximate date at which metastatic disease was recognized. Any factor which correlates to survival from the time of initial evaluation and laboratory analysis may therefore more accurately predict survival of patients with metastases.



**Fig 1.** Effect of alkaline phosphatase level on survival. Kaplan-Meier plot of survival after diagnosis versus alkaline phosphatase level at referral; survival is measured from alkaline phosphatase evaluation date. Survival is significantly decreased for patients with elevated alkaline phosphatase (>127 U/L). The *P* value testing the hypothesis of equal survival rates between the two groups was calculated using the log-rank test.

In this cohort with metastatic NETs, liver metastases were the most commonly seen site of metastasis (115 or 137 patients). Liver metastases were not an independent predictor of survival in comparison to other metastatic sites. The observed relationships between alkaline phosphatase levels and survival held true when analysis was limited to the subset of patients with liver metastases. No attempt was made to correlate alkaline phosphatase levels with a volumetric analysis of metastatic burden in this study; in fact, precise volumetric information was unavailable. Whether alkaline phosphatase levels correlate with disease burden and extent of metastases or are a function of disease aggressiveness is therefore not clear. Of the 22 patients without evidence of liver metastases, 2 had elevated alkaline phosphatase levels. Bone metastases were noted in 18 patients (13% of this cohort with metastatic NETs). The presence of bone metastases did not correlate with survival on univariate analysis in this cohort, and the observed relationship between survival and alkaline phosphatase was maintained when patients with bone metastases were removed from multivariate analysis. The decrease in survival observed with elevated alkaline phosphatase levels therefore does not seem to be a function of bone metastases.

While elevated alkaline phosphatase is independently predictive of decreased survival in patients with liver

metastases from non-NETs, it has not previously been shown to be predictive in NETs (23, 24). Previous studies evaluating alkaline phosphatase in patients with NETs, however, were small, with fewer than 20 patients, and were therefore likely underpowered to detect survival differences. The current study is significantly larger than previously reported cohorts and suggests that elevated levels of alkaline phosphatase represent a potentially useful prognostic marker in patients with metastatic NETs.

CgA is a 49-kD protein that is contained in the neurosecretory vesicles of NET cells and has been identified in the plasma of patients with endocrine neoplasms. Compared with other markers for NETs such as neuron-specific enolase (NSE) and 5-hydroxyindolacetic acid (5-HIAA), CgA is felt to be the most sensitive (13–16).

In our analysis, the absolute level of CgA appeared to be a less robust prognostic marker than alkaline phosphatase. When survival was analyzed from time of diagnosis, we found no association between survival and CgA level in either univariate or multivariate analysis. When survival was analyzed from the time of the assay date, however, elevated CgA levels were predictive of shorter survival in the univariate but not the multivariate analysis. To ensure we were not missing a potential association, we also analyzed associations using CgA as a continuous variable as well as at various cutoff points (other than 500 ng/ml),

TABLE 3. MULTIVARIATE RESULTS OF COX PROPORTIONAL HAZARDS MODEL FOR DEATH (DEPENDENT VARIABLE—PROBABILITY OF DEATH; SURVIVAL TIME VARIABLE—DAYS FROM DIAGNOSIS TO DEATH<sup>†</sup>)

Characteristic	Hazards ratio	95% CI	P value
Chromogranin A (ng/ml)			
Survival from diagnosis			
<500 ng/ml	Reference		
≥500 ng/ml	1.486	(0.659, 3.350)	0.339
Survival from CgA test date <sup>‡</sup>			
<500 ng/ml	Reference		
≥500 ng/ml	1.536	(0.710, 3.325)	0.276
Alkaline phosphatase (U/L)			
Survival from diagnosis			
<127 U/L	Reference		
≥127 U/L	1.633	(0.844, 3.162)	0.146
Survival from liver function test date <sup>‡</sup>			
<127 U/L	Reference		
≥127 U/L	3.126	(1.571, 6.223)	0.001*
Gender			
Female	1.991	(0.999, 3.971)	0.050
Male	Reference		
Age at diagnosis (years)	1.077	(1.038, 1.117)	<0.0001*
Tumor origin			
Hindgut <sup>§</sup>	1.979	(0.390, 10.05)	0.410
Small intestine	0.206	(0.042, 1.010)	0.052
Pancreatic	1.314	(0.325, 5.315)	0.702
Pulmonary	Reference		
Unknown and other <sup>¶</sup>	0.617	(0.127, 2.999)	0.550
Carcinoid syndrome			
Yes	1.995	(0.704, 5.653)	0.194
No/unknown	Reference		

\*Denotes statistical significance at the 5% level.

<sup>†</sup>Survival times are measured from day of diagnosis to death unless indicated otherwise.

<sup>‡</sup>Survival measured from the date of evaluation and laboratory testing.

<sup>§</sup>Includes patients whose primary tumor site was the large bowel or rectum.

<sup>¶</sup>Includes patients whose primary tumor site was the adrenal, stomach, or unknown.

again failing to find a significant association. As previous investigators have suggested a significant relationship between elevated CgA and survival specifically for midgut endocrine tumors (19), a subset analysis was performed in which survival from CgA test date was analyzed only for the small intestinal tumors. These data mirrored the cohort as a whole, with significant relationships seen in univariate but not multivariate analysis.

Our results differ in some respects from previous reports, in which investigators have suggested a relationship among tumor burden, survival, and plasma CgA levels (11, 18, 19). Plasma CgA levels are also commonly used clinically to monitor response to therapy (25, 26). In one cohort of 351 patients with carcinoid tumors, Janson *et al.* found that elevated CgA levels were predictive of decreased survival in a subset of 71 patients with midgut carcinoids. The study was limited by the fact that, of 256 total patients with midgut tumors in the study, only 71 were included in multivariate analysis due to a lack of complete patient information. Another difference between this previous study and our study is that the cutoff

for plasma CgA was >5000 ng/ml. The use of 5000 ng/ml as a threshold for poor prognosis suggests a difference in assay techniques; whereas the median CgA for midgut tumors was 2325 ng/ml and more than 30 patients had levels >5000 ng/ml in the study by Janson *et al.* (19), the mean CgA level in our study was 907 ng/ml, with only 4 of 104 patients with CgA recorded having levels >5000 ng/ml.

Our inability to confirm a strong association between serum CgA levels and survival, from either time of diagnosis or date of evaluation, suggests that absolute CgA levels should be used with caution as a marker of overall prognosis. We note, however, that our findings do not exclude the possibility, as others have suggested, that changes in CgA over time may have significance as markers of either response to therapy or tumor progression.

While the presence of carcinoid syndrome or other symptoms of hormone excess has been related by some to prognosis in NETs, we did not confirm this observation in our series. In the Swedish cohort of 301 carcinoid patients, presence of carcinoid syndrome, as defined by flush or diarrhea, was detected in 74% of patients and was

associated with decreased prognosis in univariate but not multivariate analysis (19). Some authors have reported a lower 5-year survival for nonfunctioning tumors and have suggested that functioning tumors may in fact lead to earlier diagnosis and longer overall survival times (27). Still other studies have shown no difference in survival between functioning and nonfunctioning NETs (9, 28–30). The latter view is supported by our study, in which there was no correlation between hormonal symptoms and survival.

Site of origin has also been demonstrated to be a predictor of survival in previous studies. Most of these studies have focused primarily on patients with localized disease, with tumors of appendiceal origin generally having a better prognosis and tumors of pancreatic or midgut origin faring worse (31–33). In these studies, the perceived survival differences between NETs arising in different sites may well be related to tumor stage at diagnosis rather than inherent differences in tumor biology. In one study of 336 patients with gastrointestinal carcinoids that included patients with metastatic disease, survival appeared to be longer in patients with metastatic midgut carcinoids compared to patients with metastatic disease from other sites. These findings were not confirmed, however, in a multivariate analysis controlling for other potential prognostic factors (30). Our study, which included metastatic NETs from diverse sites of origin, found no association between site of origin and prognosis on univariate or multivariate analysis.

Gender has been related to survival with NETs, with males having a significantly worse prognosis in some studies (32, 33) but not others (19). The difference between prior findings and ours may be due to slight differences in the groups studied; prior studies were not limited to patients with metastatic disease and women in some cases were found to have a lower incidence of metastases. Survival in these cases was not investigated independent of metastatic disease (32). In our cohort, consisting of patients with metastatic NETs, gender was not significantly related to overall survival. Age, however, was a highly significant predictor of overall survival in this cohort. This likely represents an inverse relation between age and survival rather than any increased aggressiveness of NETs in older patients.

In conclusion, our findings confirm a prolonged median survival time for patients with metastatic NETs. The majority were treated with systemic therapy alone, with a small number (10%) undergoing chemoembolization, and only a few (<5%) undergoing surgical resection or ablative therapy. Gender, the presence of carcinoid syndrome and primary tumor site did not have prognostic significance in this large cohort of patients with metastatic disease. We also found no independent asso-

ciation between absolute serum CgA level and survival. In contrast, elevated alkaline phosphatase, as measured from time of assay, was a robust independent prognostic factor for decreased survival. The measurement of alkaline phosphatase may therefore be a useful clinical tool in making treatment decisions for patients with metastatic NETs.

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