Prognostic Factors and Survival in 324 Patients with Pancreatic Endocrine Tumor Treated at a Single Institution

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Abstract

Purpose: Unequivocal pathologic markers for the prognosis of pancreatic endocrine tumors are often lacking. Suggestions for prognostic guidance include the WHO classification. Recently, a tumor-node-metastasis (TNM) staging system was proposed. We evaluate this system, as well as assess other potential prognostic factors such as tumor Ki67, size, endocrine syndrome, heredity, body mass index (BMI), and plasma chromogranin A, in a large patient material treated at a single institution.

Experimental Design: A total of 324 patients with pancreatic endocrine tumor, consecutively diagnosed and treated at a tertiary referral center, were retrospectively evaluated. Median follow-up was 54 months (range, 1-423 months). Patient and tumor data were extracted from medical records. Univariate and multivariate analyses were done to recognize factors of prognostic value.

Results: The median overall survival was 99 months (95% confidence interval, 81-117). Five- and 10-year survival rates were 64% and 44%, respectively. In univariate analysis, TNM stage, radical surgery, WHO classification, nonfunctioning tumor, Ki67 $\geq$2%, chromogranin A $\geq$3 times the upper normal limit, BMI $<$20 kg/m^2, sporadic tumor, tumor size, and referral from our primary uptake area had a significant prognostic effect. In multivariate analysis, TNM stage, WHO classification, radical surgery, and Ki67 $\geq$2% retained their significance. Having a nonfunctioning tumor was not an independent marker of poor prognosis and neither was heredity.

Conclusions: The recently suggested TNM staging system emerged as a useful clinical tool.

Pancreatic endocrine tumors are rare malignancies, with an estimated incidence of 0.5 per 100,000 (1). They carry a better prognosis than exocrine pancreatic tumors, but are often metastatic at diagnosis. Most pancreatic endocrine tumors are sporadic, but some are part of hereditary cancer syndromes, i.e., multiple endocrine neoplasia type 1 (MEN1) or von Hippel-Lindau disease. Many secrete the protein chromogranin A, and this neuroendocrine marker may be used for diagnosis and follow-up (2). Pancreatic endocrine tumors frequently cause endocrine syndromes by hypersecretion of functional hormones. These so-called functioning tumors are often discovered earlier than their nonfunctioning counterparts, due to symptoms related to the hormone production.

Due to the rarity of neuroendocrine tumors, data regarding survival and prognostic factors exist mainly from smaller series of patients, and studies often include a mix of different tumor entities, such as bronchial carcinoids, midgut carcinoids, as well as pancreatic endocrine tumors. Furthermore, some published studies have included only patients who have undergone surgery, creating a selection bias (3, 4). A median survival of 38 to 104 months (3, 5–8) and a 5-year survival rate of 40% to 60% (6, 9–12) have been reported. Morphologic signs of malignancy, such as nuclear atypia, perineural growth, and pleomorphism are often lacking even in tumors with metastases, making it difficult to predict prognosis. Factors suggested to be of prognostic value include the presence of liver metastases, primary tumor surgery, heredity, presence of endocrine symptoms, tumor cell necrosis, mitotic count, and proliferative index (Ki67; refs. 3, 4, 13). A WHO classification system (14) is often used to divide tumors into three groups: well-differentiated neuroendocrine tumors, well-differentiated neuroendocrine carcinomas, and poorly differentiated neuroendocrine carcinomas. Ki67 has been suggested to have prognostic value using a cutoff of 2%, 5%, or 10% (3, 4, 12, 15–17). One study evaluating patients with pancreatic endocrine tumor or carcinoid as one group found chromogranin A elevation to be related to a poor prognosis in univariate, but not multivariate, analysis (18). They did not measure chromogranin A at diagnosis, but during follow-up. A potential association between chromogranin A elevation at diagnosis and prognosis in pancreatic endocrine tumors has not been studied.

Tumor-node-metastasis (TNM) staging systems are commonly used in the assessment of tumors, but such a system has until recently not been available for pancreatic endocrine tumors. In 2006, a TNM staging system was proposed by a large consensus group (19). Very recently, Fischer et al. presented the first clinical evaluation of this system, concluding that the staging system was clinically relevant (20). This study included 118

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Translational Relevance

Patients with pancreatic endocrine tumors have variable prognoses, and a better knowledge of prognostic factors is needed. Pancreatic endocrine tumor is a rare disease, and published evaluations of large patient materials are few. We evaluate the newly proposed TNM staging system, as well as the proliferation marker Ki67, in a large patient material treated at a single institution. Our findings contribute to a better understanding of the factors of prognostic significance in these tumors, something that could prove useful in stratification of these patients in future clinical trials as well as in guiding the treating physician.

patients, but was limited to patients who had undergone surgery, thus comprising a somewhat selective material.

The Endocrine Oncology Unit at Uppsala University Hospital is a high-volume tertiary referral center, treating patients referred from all over Sweden as well as other countries.

In this article, we present survival data from 324 patients with pancreatic endocrine tumor, consecutively referred to our clinic. We evaluate the newly proposed TNM staging system for pancreatic endocrine tumors, and assess the following factors for prognostic value: sex, the presence of a tumor-associated endocrine syndrome, size of primary tumor, sporadic or familial disease, macroscopically radical surgery, tumor proliferation as measured by Ki67, plasma chromogranin A, and patient body mass index (BMI) at diagnosis. We also compare patients from our primary uptake area with patients referred from external centers.

Patients and Methods

Patients. A total of 324 patients with pancreatic endocrine tumor, diagnosed from 1967 to 2005 and consecutively treated at the Endocrine Oncology Unit in Uppsala, were retrospectively evaluated; the first 84 patients were previously reported (8). Data regarding potential prognostic factors and survival were gathered from medical records, and patient characteristics are summarized in Table 1. The median follow-up was 54 ± 75 mo (range, 1-423 mo).

Nonfunctioning tumors were by far the most common (59%), with insulinoma and gastrinoma second and third (17% and 13%, respectively). Sixteen percent of patients had pancreatic endocrine tumor as part of a familial tumor syndrome, almost exclusively MEN1. Thirty-five percent of patients had macroscopically radical surgery. The vast majority of patients (71%) had well-differentiated neuroendocrine carcinoma. Ninety percent of poorly differentiated neuroendocrine carcinomas were resected. For those not resected, pancreatic origin was determined by radiologic examination together with pathologic and immunohistochemical assessment based on biopsy material. No case lacking a pathologic assessment was included. One of the poorly differentiated tumors had the histology of small cell carcinoma. Sixty percent of patients had distant metastases at diagnosis. The median tumor size at diagnosis was 4.0 cm (range, 0.3-17 cm) and the median BMI at diagnosis was 24.0 kg/m^2 (range, 15-43 kg/m^2). More than half of the patients were external referrals.

Ki67. Data regarding the proliferation marker Ki67 were retrieved from existing pathology reports. For the original assessment, paraffin-embedded sections of 4 μm were used for immunohistochemistry. For antigen retrieval, sections were subjected to pretreatment with 45 min pressure boiling in a citrate buffer (pH 6.0). Immunohistochemistry was done using an autostainer (Dako Cytomation). Sections were incubated with anti-Ki67 (Dako Cytomation) diluted in antibody diluent (Dako Cytomation) at room temperature for 60 min. The reaction product was revealed using Dako kit 50087 (Dako Cytomation). Sections were counterstained with Mayer's hematoxylin. Initial experiments were done with omission of the primary antibody. All sections were scored by a pathologist at the Uppsala University Hospital pathology department, according to the percentage of nuclear staining. At least 500 nuclei in the area with the highest density of staining were counted to yield a "hotspot" Ki67 index. Ki67 was dichotomized with a cutoff of 2%. This cutoff was chosen because it is the one most commonly used in the literature on these tumors.

Analysis of plasma chromogranin A. Data regarding plasma chromogranin A were retrieved from patient charts, and reported as times upper normal limit at the time of diagnosis. Blood from fasting subjects had been drawn into chilled tubes containing sodium heparin and 400 units/mL kallikrein inhibitory aprotinin, and centrifuged at 4°C, before measurement by RIA, as previously described (21, 22).

BMI. BMI was calculated as kg/m^2 at the time of diagnosis, and data were gathered from medical records.

WHO classification. Tumors were classified into three groups (well-differentiated neuroendocrine tumor, well-differentiated neuroendocrine carcinoma, and poorly differentiated neuroendocrine carcinoma) according to the WHO classification, based on number of

Table 1. Patient characteristics

	No. (%)
Sex	
Female	147 (45)
Male	177 (55)
Tumor type	
Nonfunctioning	190 (59)
Insulinoma	54 (17)
Gastrinoma	43 (13)
Glucagonoma	19 (6)
VIPoma	15 (5)
Cushing	3 (1)
Hereditary status	
Sporadic	274 (84)
MEN1	43 (15)
vHL	4 (1)
Surgery of primary tumor	114 (35)
WHO classification (n = 241)	
I	47 (20)
II	173 (71)
III	21 (9)
Stage (n = 302)	
I	33 (11)
IIa	24 (8)
IIb	14 (5)
IIIa	9 (3)
IIIb	42 (14)
IV	180 (60)
Referred from	
Primary uptake area	135 (42)
External referral	188 (58)
Median size of primary tumor (cm)	4.0 (range, 0.3-17)
Median age at diagnosis, y	53 (range, 12-86)
Median chromogranin A at diagnosis (n = 139)	3.7 × UNL (range, 0.4-1,280)
Median BMI at diagnosis, kg/m^2 (n = 155)	24.0 (range, 15-42)

Abbreviations: VIP, vasoactive intestinal peptide; vHL, von Hippel Lindau disease; UNL, upper normal limit.

mitoses, percentage of Ki67-positive cells, and the presence of vascular, perineural, or gross invasion. Tumors with a mitotic rate ≥10 per 10 high power fields were considered poorly differentiated, in accordance with the WHO guidelines (23). A reevaluation of all cases was done based on pathology, surgery, and radiology reports. In ambiguous cases new pathology assessments were done.

TNM staging. TNM staging was done according to the recently suggested definitions (19). Stage I is defined as only a primary tumor, confined to the pancreas and <2 cm. Stage IIa means the primary tumor is confined to the pancreas and is 2 to 4 cm; IIb primary tumor is >4 cm or invading the duodenum or bile duct. Stage IIIa is defined as a tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis, superior mesenteric artery). The presence of lymph node metastases defines stage IIIb, and distant metastases stage IV. Staging reflected tumor burden at diagnosis, and was based on data retrieved from medical records. A reevaluation of all cases was done based on pathology, surgery, and radiology reports. In ambiguous cases new pathology assessments or radiologic reevaluations were done.

Statistical analysis. Kaplan-Meier methodology was used to estimate survival, which was calculated as the time from diagnosis to the last date of follow-up or death from any cause. The log-rank test was used to test differences in survival. Multiple Cox regression models were used to explore the independent effects of several prognostic factors. A separate multivariate analysis was done to evaluate Ki67, which was not included in the main multivariate analysis because of too few observations (n = 115). This analysis included Ki67, sex, surgery, the presence of an endocrine syndrome, primary/external referral, hereditary status, and tumor size. All multivariate analyses were controlled for patient age. The proportional hazards assumption was assessed with a graphic approach. Univariate and multivariate analyses were also done in a subgroup of patients, excluding patients with poorly differentiated carcinomas. A P value of <0.05 was considered significant. Statistical analyses were done with the SPSS statistical package (version 14.0).

Ethical approval. This study was approved by the local ethics committee.

Results

Survival. The median overall survival was 99 months (95% confidence interval, 81-117 months). The 5- and 10-year survival rates were 64% and 44%, respectively.

Univariate analysis. In univariate analysis, several variables had a significant negative effect on survival (Table 2). A shorter survival was seen in patients with tumors with TNM classification stages IIIa [hazard ratio (HR), 4.6; P = 0.002], IIIb (HR, 2.6; P = 0.011), and IV (HR, 6.5; P < 0.001), i.e., patients with tumor invasion of large vessels, lymph node metastases, or distant metastases (Fig. 1), compared with patients on stage I. The absence of macroscopically radical surgery was a highly significant predictor of poor prognosis, with a HR of 4.8 (P < 0.001). Tumor Ki67 ≥2% was an even stronger predictor (HR, 6.0; P < 0.001; Fig. 2). WHO classification as well-differentiated or poorly differentiated neuroendocrine carcinoma predicted shorter survival (HR, 4.4 and 14.9, respectively; P < 0.001; Fig. 3). Patients with nonfunctioning tumors had a shorter survival compared with patients with functioning tumors (HR, 1.6; P = 0.004). Having a sporadic tumor, as opposed to a hereditary syndrome, also meant a poorer prognosis (HR, 2.7; P < 0.001). A plasma chromogranin A elevated three times the upper normal limit or more at diagnosis was a significant predictor of shorter survival (HR, 2.6; P < 0.001). Patients who were underweight at diagnosis (BMI <20 kg/m^2) had a poorer prognosis (HR, 2.5; P = 0.006; Fig. 4). A negative prognostic effect of a primary tumor ≥3 cm was seen, and patients from the primary uptake area had a shorter survival compared with patients referred from external centers (HR, 1.4; P = 0.032).

Univariate analyses excluding patients with poorly differentiated carcinoma produced very similar results. The same factors

Table 2. Prognostic factors

		Univariate analysis		Multiple models			
		All available cases		n = 191		n = 93	
Variable	n	HR (95% CI)	Sig.	HR (95% CI)	Sig.	HR (95% CI)	Sig.
Male sex	324	1.0 (0.7-1.3)	P = 0.909	1.0 (0.6-1.5)	P = 0.864	0.9 (0.4-2.0)	P = 0.858
No macroscopically radical surgery	305	4.8 (3.3-7.0)	P < 0.001	2.5 (1.2-4.9)	P = 0.010	8.4 (0.9-75)	P = 0.057
WHO classification	240						
Well-differentiated carcinoma		4.4 (2.4-8.0)	P < 0.001	1.2 (0.4-3.5)	P = 0.700		
Poorly differentiated carcinoma		14.9 (7.1-31.4)	P < 0.001	9.9 (2.9-34)	P < 0.001		
Nonfunctioning tumor	324	1.6 (1.2-2.2)	P = 0.004	1.0 (0.6-1.6)	P = 0.937	1.0 (0.3-3.3)	P = 0.992
Ki67 >2%	115	6.0 (2.7-13.6)	P < 0.001			5.2 (1.8-15)	P = 0.002
CgA ≥ 3 × UNL	137	2.5 (1.5-4.2)	P = 0.001				
BMI (kg/m^2)	155						
20-24.9		1.4 (0.9-2.2)	P = 0.202				
<20		2.5 (1.3-4.7)	P = 0.007				
Primary referral	323	1.4 (1.0-1.9)	P = 0.023	1.9 (1.2-3.0)	P = 0.007	1.7 (0.8-3.6)	P = 0.200
Sporadic tumor	320	2.7 (1.7-4.3)	P < 0.001	1.0 (0.4-2.4)	P = 0.953	1.2 (0.1-21)	P = 0.917
Stage	302						
IIa		0.6 (0.2-1.8)	P = 0.338	0.5 (0.1-2.8)	P = 0.444		
IIb		1.8 (0.7-4.8)	P = 0.250	2.3 (0.5-11)	P = 0.270		
IIIa		4.6 (1.8-12.0)	P = 0.002	3.5 (0.7-19)	P = 0.142		
IIIb		2.6 (1.2-5.5)	P = 0.011	2.2 (0.5-9.2)	P = 0.290		
IV		6.5 (3.5-12.0)	P < 0.001	5.9 (1.3-26)	P = 0.020		
Size (cm)	260						
3-3.9		3.1 (1.7-5.7)	P < 0.001	1.0 (0.4-2.7)	P = 0.941	0.2 (0.0-1.3)	P = 0.087
4-4.9		2.2 (1.2-4.2)	P = 0.014	0.9 (0.3-2.3)	P = 0.832	0.3 (0.1-0.4)	P = 0.121
5-9.9		3.6 (2.3-5.8)	P < 0.001	1.6 (0.7-3.7)	P = 0.233	0.6 (0.1-2.8)	P = 0.647
≥10		3.8 (1.9-7.6)	P < 0.001	2.6 (1.0-7.1)	P = 0.063	0.6 (0.1-3.1)	P = 0.575

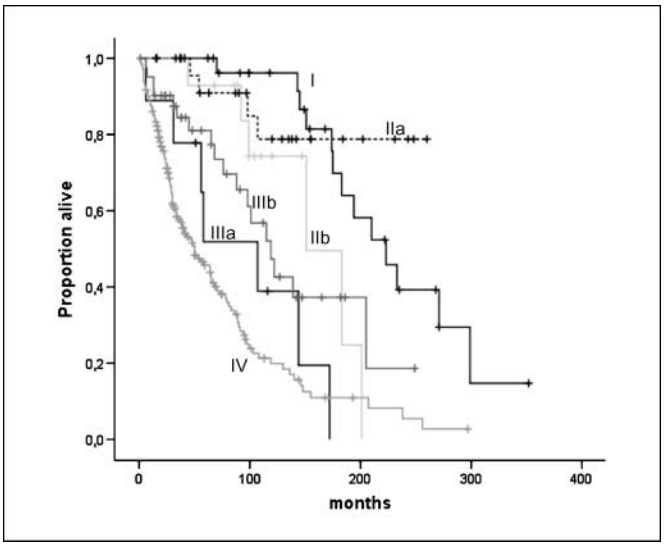

Fig. 1. Overall survival (mo), comparison of TNM stages.

were significant, and there were no significant changes in hazard ratios.

Multivariate analysis. Two multiple Cox proportional hazard models were used to evaluate prognostic factors. The first included sex, primary tumor surgery, WHO classification, functioning or nonfunctioning tumor, primary or external referral, sporadic or hereditary tumor, TNM stage, and primary tumor size. Ki67, chromogranin A, and BMI were excluded because there were far fewer observations (115, 139, and 155, respectively). Results were controlled for age and year of diagnosis. In this analysis, four variables retained their significant prognostic effect (Table 2). TNM stage IV (i.e., distant metastases) was a strong predictor (HR, 5.9; $P = 0.020$). Stage IIIa was associated with a higher HR than stage IIIb, although this was not significant. WHO classification as poorly differentiated neuroendocrine carcinoma was the strongest predictive variable (HR, 9.9; $P < 0.001$), whereas classification as well-differentiated neuroendocrine carcinoma was no longer a significant prognostic factor. The absence of macroscopically radical surgery remained a significant negative prognostic factor in this multiple model (HR, 2.5; $P = 0.010$). Referral from the primary uptake area as opposed to external centers remained a significant negative prognostic variable (HR, 1.9; $P = 0.007$). Having a nonfunctioning or a sporadic tumor was not a negative prognostic factor, and neither was having a larger tumor.

A multivariate analysis including the above-mentioned variables excluding all patients with poorly differentiated carcinoma yielded similar results. Some small changes were seen; having a tumor stage IV just barely lost its significance ($P = 0.052$), and having a tumor >5 cm emerged as a significant prognostic marker.

A second multivariate analysis was done to assess the prognostic value of Ki67 ($n = 93$; Table 2), which was not included in the first multivariate analysis because of too few observations. This analysis included Ki67, sex, surgery, the presence of an endocrine syndrome, primary/external referral, hereditary status, and tumor size. In this analysis, only Ki67 $\geq$2% was a significant negative prognostic variable (HR, 5.2; $P = 0.002$). However, surgery had a higher HR (8.4) and was close to significant ($P = 0.057$). The material did not permit a multivariate analysis including Ki67 after poorly differentiated tumors had been excluded.

Discussion

We report survival data and prognostic factors from 324 patients with pancreatic endocrine tumor treated at a single center. Considering the unusual nature of this disease, this constitutes a rather large patient material. This was a retrospective evaluation, with the limitations that it implies. Further, the study spans a long time period, something that can cause problems due to changes in definitions, diagnosis, and treatment. However, this is a rare tumor entity, with an indolent course. Thus, a long follow-up is necessary. Median overall survival in our material was 99 months. This is similar to the figure reported from a smaller series of patients from our department in 1989 (104 months).

A TNM classification has been suggested for pancreatic endocrine tumors, and has recently been evaluated, independently from our study, in a surgical patient material by Fischer et al. (20). In the present study, in univariate analysis, we found tumors stage IIIa, IIIb, and IV to be significant negative prognostic factors. Stage IV was highly significant also in multiple analysis, and there was a tendency toward stages IIb, IIIa, and IIIb having a negative effect on prognosis although this was not statistically significant. We conclude that the proposed staging system seems to be relevant. There was a tendency toward stage IIIa, meaning a poorer prognosis compared with IIIb. Perhaps an adjustment of the definitions of TNM staging for these tumors will be considered when more clinical evidence is available. Already after this first evaluation one might suspect that invasion of large vessels (IIIa) is a more ominous sign than mere lymph node metastases (IIIb). The prognostic significance of stage IV (distant metastases) seems unambiguous. Evaluation in a larger patient material is needed to further elucidate the prognostic effect of stages II and III.

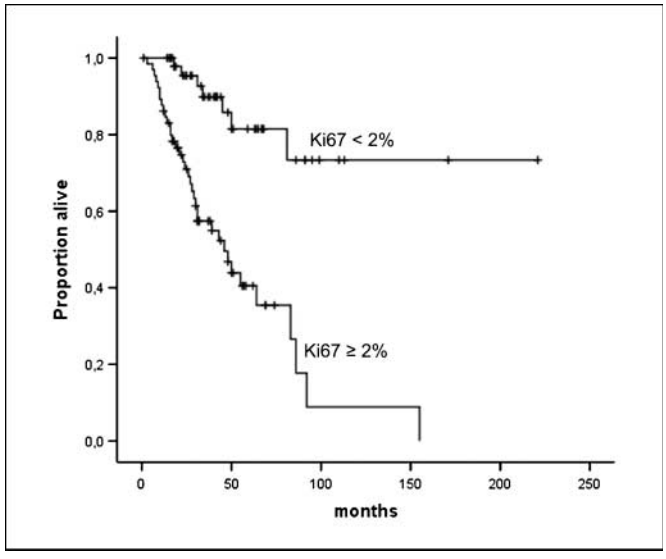

Fig. 2. Overall survival. Patients with tumors with Ki67 >2% have a significantly shorter survival.

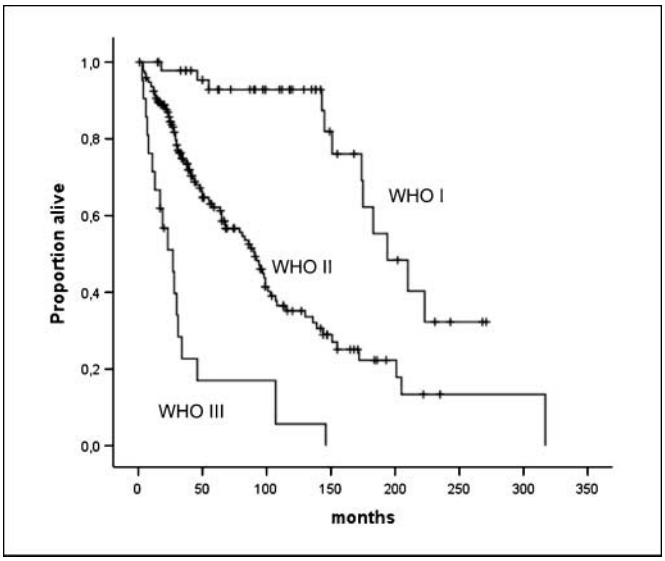

Fig. 3. Overall survival (mo). Comparison based on WHO classification. WHO I, well-differentiated neuroendocrine tumor; WHO II, well-differentiated neuroendocine carcinoma; WHO III, poorly differentiated neuroendocrine carcinoma.

The WHO classification divides pancreatic endocrine tumors into three groups. In univariate analysis both well-differentiated and poorly differentiated carcinoma meant a poorer prognosis compared with well-differentiated neuroendocrine tumors. In multiple analysis only patients with poorly differentiated carcinomas did significantly worse. In fact, this prognostic factor had the highest HR of all evaluated variables. Patients with well-differentiated tumors as expected fared much better than the two other groups. There was, however, a decline in survival with time, indicating that these tumors cannot automatically be regarded as entirely benign.

Both the WHO classification and the TNM staging system seem to be of prognostic value.

Both systems have advantages and disadvantages. The WHO classification is well understood and liked by clinicians. However, it relies heavily on detailed and time-consuming pathologic examination, which can be regarded as a downside. TNM classifications are used for most types of cancers, and it is thus reasonable that there should be one for pancreatic endocrine tumors as well. A negative aspect of this way of classifying tumors is that it might reflect the timing of the diagnosis rather than the tumor's inherent malignant potential.

Reported frequencies from other institutions of nonfunctioning tumors have increased from 15% to 24% in the 1980s (8, 9) to over 60% in recent reports (3, 6), and a similar increase could be observed at our clinic. In fact, after the year 2000, the frequency was 74%. This increase is, we believe, partly due to a more correct and consistent interpretation of the terms "functioning" and "nonfunctioning." Tumors not causing any endocrine syndrome, today correctly defined as nonfunctioning, were previously sometimes wrongly classified as functioning merely on the basis of immunoreactivity for, or raised plasma levels of, a certain hormone. It also reflects the fact that many patients with nondifferentiated endocrine carcinomas, previously misdiagnosed as exocrine, are today receiving a correct diagnosis. Some of these are highly malignant, and with this increase in more malignant, nondifferentiated endocrine carcinomas being treated at our clinic, it would be reasonable to expect that survival would have diminished compared with the previous study from 1989. However, this is not the case. This might be a reflection of improved intervention and treatment, but controlled trials that could answer this question are lacking.

The prognostic significance of the presence of hormonal symptoms has been debated. Clinically, it has been widely accepted that nonfunctioning tumors are more aggressive than their functioning counterparts. In univariate analysis, we did indeed find a significantly shorter survival for patients with nonfunctioning tumors. However, this difference completely disappeared in multiple analysis. Prediction of the malignant potential of a pancreatic endocrine tumor thus should not be influenced by the functional status per se, but rather be guided by other prognostic factors.

Patients with pancreatic endocrine tumors as part of the MEN1 syndrome often do better than patients with sporadic tumors. This fact is sometimes used as an argument for less aggressive treatment of these tumors (24). However, one study showed a significantly shortened life expectancy in MEN1 patients compared with age-matched healthy controls (25). Pancreatic endocrine tumor is a common cause of death for MEN1 patients, and another study showed a median age of death from pancreatic malignancy of only 46 years (26). We did not find hereditary disease to be an independent positive prognostic factor. The longer survival from diagnosis of pancreatic endocrine tumors in MEN1 patients seems related to other factors than hereditary status, such as timely diagnosis due to screening. This implies that MEN1-related tumors should be managed similarly to sporadic tumors, and should not be considered less malignant simply on the basis of heredity.

We found Ki67 $\geq$2% to be a significant negative prognostic factor in both univariate and multivariate analysis. These results support previous reports suggesting this cutoff to be of clinical value. The material did not permit inclusion of WHO classification and stage in our multiple model evaluating Ki67, due to high correlation between these variables. Because

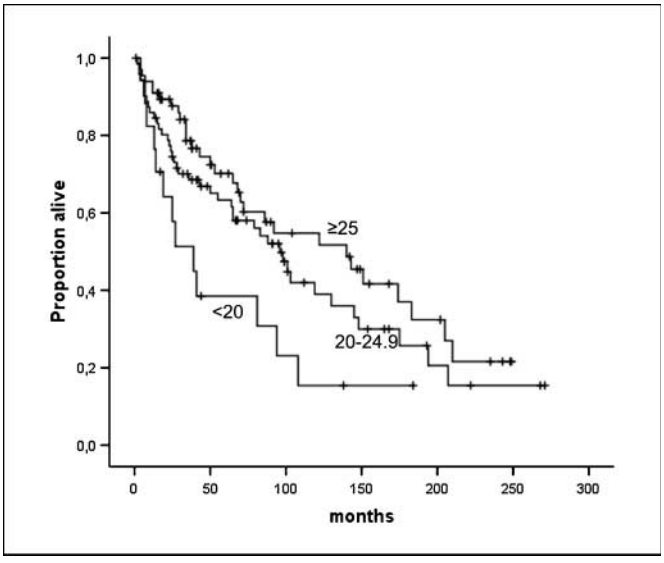

Fig. 4. Overall survival (mo) stratified according to BMI.

Ki67 assessment was not widely done at our clinic before 1998, the present statistical analysis includes mostly patients with a more recent diagnosis. In this cohort, there were slightly more men, slightly more patients with poorly differentiated neuroendocrine carcinomas, and more patients presenting with a stage III or higher tumor compared with the entire patient material. The number of patients with nonfunctioning tumors in this group was 80%. This probably reflects the fact that a higher number of poorly differentiated, nonfunctioning tumors with a high tumor stage are diagnosed today.

It is hardly surprising that patients who have undergone macroscopically radical surgery have a better prognosis than patients who have not. This is of course due to the beneficial effects of surgery, but it also represents the fact that the patients who undergo primary surgery are those with a limited tumor burden. However, the negative prognostic effect of the absence of macroscopically radical surgery remained after correction for tumor stage.

A chromogranin A elevation three times the upper normal limit or more was a negative prognostic factor, as was being underweight. Cancer cachexia is generally a bad sign. A prognostic relevance of BMI in patients with pancreatic endocrine tumor has, however, not previously been reported. Patients from our primary uptake area unexpectedly had a significantly shorter survival compared with externally referred patients, both in univariate analysis and when controlled for stage, WHO classification, age, and tumor size for example. When controlled for tumor Ki67, the HR was 1.7, although this was no longer significant. This might be due to a selection bias based on factors not included in our analysis. Alternatively, experienced oncologists hesitate to refer patients they intuitively feel have a bad prognosis. We believe that this difference in survival represents a selection bias; patients with an apparent poor prognosis are to a lesser degree referred to a tertiary referral center, because of the increase in cost and effort for the patient and the referring clinic.

We conclude that, in a large series of patients treated at a single institution, surgery, WHO classification, TNM stage, and Ki67 $\geq$2% were prognostic variables. Interestingly, the functioning status of the tumor and hereditary syndrome were not. Furthermore, the recently proposed TNM staging system emerged as a useful clinical tool.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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