

## Neuroendocrine tumors of unknown primary site: gold dust or misdiagnosed neoplasms?

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### ABSTRACT

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**Aims and background.** Neuroendocrine tumors of an unknown primary site are rarer than other neuroendocrine tumors (0.6-2% of all neuroendocrine tumors) and have a poor prognosis. The aim of the study was to review the cases of unknown primary site neuroendocrine tumors encountered at the Istituto Nazionale Tumori di Milan between 1984 and 2008 in order to verify their incidence and evaluate their characteristics and prognosis.

**Methods and study design.** During the study period, 750 neuroendocrine tumor patients attended our Institute, 82 of whom (10.9%) were diagnosed as having neuroendocrine tumors of an unknown primary site. The data from their medical records were analyzed descriptively, and survival probabilities were calculated using the Kaplan-Meier method and the logrank test, considering patient, tumor and treatment-related characteristics.

**Results.** The 82 patients with neuroendocrine tumors of an unknown primary site (34 males) had a median age of 60 years; 57 (69.5%) had histologically well-differentiated tumors, 3 (3.7%) poorly differentiated tumors, and 22 (26.8%) had tumors that could not be classified. Of the 52 patients (62.2%) who underwent Octreoscan<sup>®</sup> (Bykgulden Italia SpA), 40 (78.4%) showed a pathological uptake and 11 (21.6%) were negative. Thirty-one patients (37.8%) underwent metastatic site surgery, which was radical in 11 cases (35.4%). Forty-eight patients (58.5%) received somatostatin analogues, and 41 (50.0%) underwent chemotherapy. At the end of the study period, 59 patients (72.0%) had died, 31 (53.0%) because of disease progression, and 23 (28.0%) were still alive.

**Conclusions.** Neuroendocrine tumors of an unknown primary site are difficult to identify but their incidence is higher than previously reported, and the prognosis remains unfavorable.

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### Introduction

Tumors of an unknown primary site (UPS) are heterogeneous and represent a challenging problem for oncologists because of their poor prognosis and the lack of information available to establish appropriate treatment. Various incidence rates have been published<sup>1</sup>: in a series of 1285 patients from south-east Netherlands, UPS tumors accounted for 4% of all cancers, and median survival was 11 weeks<sup>2</sup>. Neuroendocrine tumors (NET) are rare and account for no more than 0.5% of all malignancies, and, among NET, those with a UPS are even rarer (0.6-2% of all NET).

The incidence of UPS NET has recently been critically reviewed on the basis of advances in diagnostic techniques. A survey of the SEER registry data showed that the 35,825 NET recorded over the last 29 years in the United States included 4,752 NET of UPS (13%)<sup>3</sup>. Metastatic UPS NET can be divided into three subsets: low-grade NET,

**Key words:** neuroendocrine tumors, Octreoscan, rare tumors, unknown primary site.

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Received October 20, 2010;

accepted May 12, 2011.

which usually involve the liver and show symptoms associated with the secretion of vasoactive peptides; small-cell NET, whose histological features and clinical behavior are similar to those of small-cell lung cancer; and poorly differentiated NET<sup>4</sup>.

Compared with other tumors, NET have different embryological, biological and histopathological characteristics, which has led to problems in their classification. However, a classification based on their aggressiveness or differentiation (poorly differentiated and well-differentiated NET) has proved to be highly appropriate for identifying the best therapeutic approach<sup>5,6</sup>. When feasible, surgery is the most valuable therapeutic option, but hormone therapy is considered the treatment of choice for well-differentiated NET, and chemotherapy is recommended for progressive disease and poorly differentiated tumours<sup>7,8</sup>.

The prognosis of UPS NET is generally poor and deserves further investigation. It has been found that the 10-year survival rate of patients with UPS NET is less than that of patients with carcinoids of known origin (22% vs 62%, 50% and 48% for foregut, midgut and hindgut carcinoids) but similar to that of patients with midgut carcinoids and distant metastases (22% vs 28%)<sup>9</sup>.

In the light of the above findings, the aim of the present study was to review all of cases of UPS NET observed in our Institute in order to verify their incidence, characteristics and prognosis.

## Patients and methods

### Study design

This single-center, retrospective, observational study included the patients with UPS NET observed at the Medical Oncology Unit 2 of the National Cancer Institute of Milan (Italy) between 1984 and 2008. A case report form was used to collect: demographic data; baseline clinical and instrumental diagnostic data, including general symptoms, carcinoid symptoms, histopathology, disease site(s), the markers chromogranin A, neurone-specific enolase and 5-hydroxyindolacetic acid, and staging (computed tomography scan, Octreoscan<sup>®</sup> and endoscopy); clinical data concerning disease progression; information regarding treatments (surgery, chemotherapy, somatostatin analogues, hormone therapy, metabolic radiotherapy, trans-arterial chemoembolisation, radiofrequency treatment, and transplantation); follow-up data on relapses and survival.

All of the original histological diagnoses of NET were verified by our Pathology Unit. The slides were graded according to the WHO classification and, if the original diagnosis had been made before 2000, the grading was converted to the new classification. The plasma levels of chromogranin A and neurone-specific enolase and the urinary levels of 5-hydroxyindolacetic acid recorded in

the medical records were measured using the standard analytical procedures of the time.

Attempts to locate the primary site had been made using chest and abdominal computed tomography scans, endoscopy (and echo-endoscopy, if necessary), Octreoscan<sup>®</sup> or positive emission tomography (PET) in poorly differentiated neoplasms and, in some cases, laparoscopy or laparotomy. Octreoscan<sup>®</sup> was used for all of the patients examined in and after 1995, when the method became routinely used in our clinical practice.

The patients initially diagnosed as having UPS NET in whom the primary site was subsequently discovered were not included in the analysis.

Informed consent for the study was obtained from the patients still alive at the time it was carried out.

### Statistical analyses

This was a retrospective observational study, so, as no hypothesis was being tested, the clinical and laboratory data collected from the hospital records were only descriptively analyzed over time. The results are given as mean values  $\pm$  standard deviation, or median values and ranges, including the 95% confidence interval when pertinent. Kaplan-Meier plots were used to evaluate survival from the time of diagnosis to death, and the Mantel-Cox logrank test was used to compare the survival curves of the subgroups of patients with hepatic lesions alone and those with  $\geq 2$  metastatic sites. All of the analyses were made using SAS software, version 8.0.

## Results

Between 1984 and 2008, 750 NET patients were seen at our Institute; retrospective analysis showed that 82 (10.9%) had UPS NET, of whom only 14 were diagnosed during the first decade (1984-93).

The histological diagnosis of UPS NET was confirmed in 57 patients (69.5%) who had well-differentiated tumors and 3 (3.7%) with poorly differentiated tumors. The histological material relating to the remaining 22 patients (26.8%) was insufficient to allow any definite conclusion.

Table 1 shows the characteristics of the patients and tumors. The patients' median age was 60 years (range, 30-76), and there was a prevalence of females; 39 patients (47.5%) had liver metastases alone, and 52.5% had  $\geq 2$  metastatic sites. Carcinoid syndrome was ascertained in 14 patients (17.1%). No marker analysis was available for 36 patients (43.9%); plasma chromogranin A levels were increased in 26/46 (56.4%), and urinary 5-hydroxyindolacetic acid and plasma neurone-specific enolase levels were increased in 10/46 (21.7%). Fifty-one patients (62.2%) underwent Octreoscan<sup>®</sup>, 40 (78.4%) of whom showed a pathological uptake and 11 (21.6%) were negative.

Thirty-one patients (7.8%) underwent metastatic site surgery, which was radical in 11/31 cases (35.4%); 48 pa-

**Table 1 - Patient and tumor characteristics**

	No. patients (%)
No. patients	82
Gender	
Male	34 (42.0)
Female	48 (58.0)
Median age, yr (range)	60 (30-76)
Metastatic sites	
Liver only	39 (47.5)
≥2 metastatic sites	43 (52.5)
Carcinoid syndrome	
Yes	14 (17.1)
No	68 (82.9)
Tumor markers positivity	
Not available	36 (43.9)
Chromogranin A	26 (56.6)
Neurone-specific enolase	10 (21.7)
5-Hydroxyindolacetic acid	10 (21.7)

tients (58.5%) received somatostatin analogues, and 41 (50.0%) underwent chemotherapy; 3 (3.6%) were treated with a combination of somatostatin analogues and interferon. Ten patients (12.2%) did not receive any treatment.

At the end of the study period, 59 patients (72.0%) had died, 31 (53.0%) because of disease progression. Of the 23 (28.0%) who were still alive, 3 (13.1%) were disease free, 15 (65.2%) had progressive disease, and 5 (21.7%) were lost to follow-up. Figure 1 shows that the median overall survival of the cohort as a whole was 48 months (range, 1-202). Figure 2 shows median overall survival in the patients with hepatic lesions alone (72 months, range, 6-202) and those with ≥2 metastatic sites (40 months, range, 1-118).

In order to evaluate whether these data were consistent with those relating to patients with other gastroenteropancreatic NET showing liver involvement alone, we compared 125 patients with gastroenteropancreatic NET and only hepatic lesions (taken from our database) and 39 of the patients with liver metastases included in this study

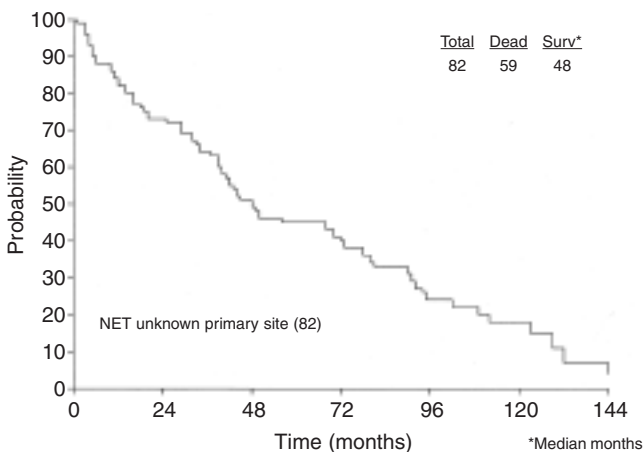


Figure 1 - Overall survival: median survival after 48 months (n = 82). NET, neuroendocrine tumors.

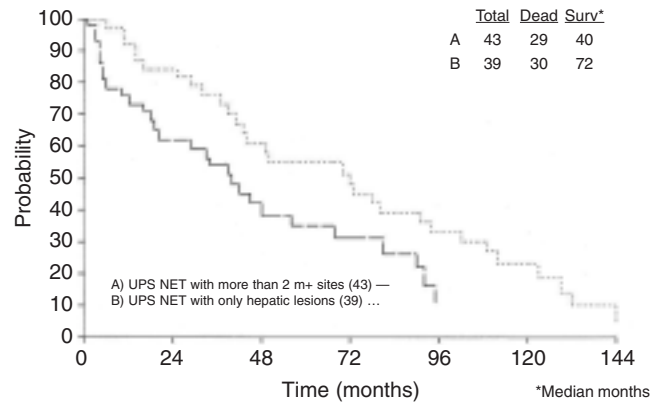


Figure 2 - Overall survival: patients with ≥2 metastatic sites (A, solid line) had a median survival of 40 months (n = 43); patients with liver involvement alone (B, broken line) had a median survival of 72 months (n = 39). UPS, unknown primary site; NET, neuroendocrine tumors.

(Figure 3). Median survival was 111 months (range, 2-274) in the former and 72 months (range, 6-202) in the latter.

**Discussion**

The information obtained in this observational study provides new evidence concerning the importance of seeking the origin of UPS NET and shows that they are less rare than originally thought<sup>1</sup>. The support given by the recent development of more reliable investigational tools makes it possible to identify UPS NET patients more precisely and has thus greatly increased the possibility of treating them appropriately on the basis of the extent and biological behavior of the tumor.

Our findings indicate that the incidence of UPS NET is underestimated. Of the 750 NET examined at our Institute over a period of 24 years, 10.9% were UPS NET,

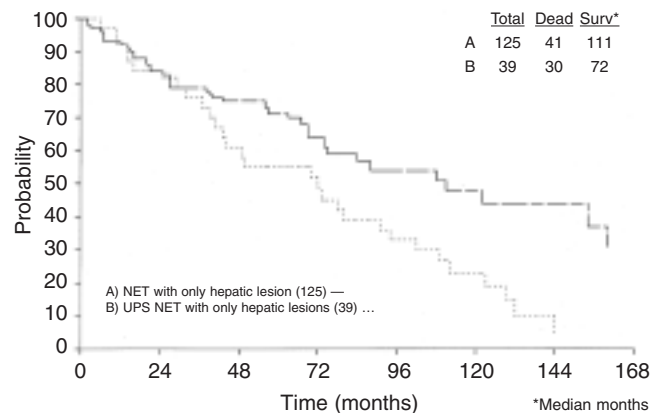


Figure 3 - Overall survival in patients with hepatic lesions and gastroenteropancreatic NET (A, solid line) or UPS NET (B, broken line). Group A (n = 125), median survival 111 months; Group B (n = 39), median survival 72 months. UPS, unknown primary site; NET, neuroendocrine tumors.

which is in line with the 13% found in the SEER registry of 35,825 cases observed over a period of 29 years<sup>3</sup>.

In terms of the diagnosis of patients with UPS NET, Octreoscan® did not seem to be fully reliable, because it generally failed to identify the primary tumor and only localized metastases.

The survival data are very interesting. Median survival in the cohort of UPS NET patients as a whole was 48 months and, after a follow-up of 144 months, 28% of the patients were still alive and 13% were disease free. The very long median survival of our patients is almost certainly due to the often indolent nature of NET and the prevalence of well-differentiated tumors.

Our findings also provide information concerning the prognosis of UPS NET patients by type and site of metastases. Comparison of the survival curve of the patients with liver lesions alone and that of those with  $\geq 2$  metastatic sites suggests that the former definitely have a better prognosis, as their median survival was respectively 72 and 40 months.

Finally, comparison of patients with liver metastases alone and a UPS and patients with liver metastases alone and a known primary site showed that the latter survive substantially longer. One of the reasons for this may be that the doubts and uncertainties relating to UPS patients leads oncologists to adopt a more conservative approach, and this may have a negative impact on survival. However, we are aware that this is largely speculation and that other factors affect outcome in patients with a known primary tumor site.

The findings of this retrospective analysis suggest that it is not sufficient to distinguish UPS NET, but it is necessary to make every effort to find their origin because this can improve patient prognosis.

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