Usefulness of Chromogranin A, Neuron-specific Enolase and 5-Hydroxyindolacetic Acid Measurements in Patients with Malignant Carcinoids*

ANNA ZAIRA MANFÈ1, LORENZO NORBERTO1, MARCO MARCHESINI2 and FRANCO LUMACHI1

1Department of Surgical and Gastroenterological Science, School of Medicine and 2School of Pharmacy, University of Padua, Padova, Italy

Abstract. Background: Neuroendocrine tumors (NETs) of the gastro-entero-pancreatic (GEP) system are a heterogeneous group of cancers more common in the small intestine. In patients with malignant NETs, especially carcinoids, a number of prognostic parameters have been considered, such as age, clinical symptoms related to the neoplasm, TNM staging and histological grade, as well as urinary 5-hydroxyindolacetic acid (5-HIAA), chromogranin A (CgA) and neuron-specific enolase (NSE) serum levels.

Patients and Methods: The data from a series of 14 patients (median age 56 years, range 33-72 years) with gastric (N=8), ileal (N=1), colorectal (N=4) or appendiceal (N=1) malignant carcinoids were retrospectively reviewed. Results: The specificity of CgA, NSE, and 5-HIAA was 86%, 86% and 93%, while the sensitivity was 64%, 36%, and 36%, respectively. There was no relationship between survival and or urinary 5-HIAA (R=0.12, p=0.45), CgA (R=0.22, p=0.21) nor serum NSE (R=0.12, p=0.76) levels. Conclusion: The sensitivity of tumor markers is generally low in patients with malignant carcinoids, and both 5-HIAA and CgA levels are independent of survival.

Neuroendocrine tumors (NETs) of the gastro-entero-pancreatic (GEP) system, which comprise nonfunctioning neuroendocrine pancreatic tumors, pancreatic islets tumors and carcinoids, are a heterogeneous group of carcinomas more common in the small intestine (1). NETs have extremely varying clinical presentations. In the USA, a global clinical incidence between 2.5-5 cases/100,000 per year has been estimated, with a prevalence of 35/100,000 for GEP NETs (2, 3).

Gastric carcinoids, accounting for 4-5% of all carcinoids, originate from enterochromaffin-like (ECL) cells, and it has long been observed that ECL cells are the source of several hormonal substances, including histamine, serotonin, and chromogranin A (CgA), a glycoprotein protein consisting of 439 amino acids, all of which are contained in secretion granules of the cells (2, 4).

Each NET, depending on its anatomical site, arises from a different neuroendocrine cell, exhibiting different functionality and biological behavior (5). Thus, prediction of the outcome of a single malignant NET is difficult, although the US National Cancer Institute predicted approximately 8,000 deaths attributable to malignant NET for 2011 (6). Because of widespread and long-term use of proton pump inhibitors, and subsequent chronic hypergastrinemia, an increased risk of gastric carcinoids has been reported (7, 8).

Appendiceal endocrine tumors, found incidentally in about 0.1% of appendicectomies, are often very small, and are usually benign (9, 10). Rectal carcinoids are infrequent, and discovered on coloscopy in fewer than 0.1% of patients (11, 12). Data from various sources suggest that both the incidence and the prevalence of GEP NETs is increasing (13). Several studies have tried to identify prognostic factors, especially in malignant small intestine NETs and metastatic carcinoids (14, 15).

In patients with malignant carcinoids, a number of prognostic parameters have been considered, such as age, clinical symptoms related to the neoplasm, TNM staging and histological grade, as well as urinary 5-hydroxyindolacetic acid (5-HIAA), CgA, and serum neuron-specific enolase (NSE) levels. 5-HIAA is a metabolite of serotonin, and thus it is a specific marker of carcinoids producing serotonin (9, 10). The sensitivity of each tumor marker (TM) largely depends on the histological grade (well-differentiated vs.

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Correspondence to: Professor Franco Lumachi, University of Padua, School of Medicine, Department of Surgical and Gastroenterological Sciences, Via Giustiniani 2, 35128 Padova, Italy. Tel: +39 0498211812, Fax: +3 0498214394, e-mail: flumachi@unipd.it

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poorly differentiated carcinoids), disease extent (i.e. lymph node metastasis) and the presence of a functioning tumor (11, 16).

The aim of this study was to look for a relationship between TMs 5-HIAA, CgA and NSE and survival in patients with gastrointestinal carcinoids.

Patients and Methods

The data from a series of 14 patients (8 men, 6 women, median age 56 years, range 33-72 years) with histologically confirmed gastric (N=8), ileal (N=1), colorectal (N=4) and appendiceal (N=1) malignant carcinoids were retrospectively reviewed. All the patients had undergone surgery and three had liver metastases at the time of diagnosis. Written informed consent was obtained from all the participants still alive at the time of the data review. CgA was measured by immunochemiluminometric assay using an amino and carboxyl directed antibody, and NSE by enzyme-linked immunosorbent assay (17, 18). The measurement of 5-HIAA in urine was obtained by high-performance liquid chromatography (19). Sensitivity was defined as true-positives/(true-positives + false-negatives) and specificity as true-negatives/(true-negatives + false negatives). The Pearson’s correlation coefficient (R) was also calculated, and a two-sided error level of p<0.01 was considered statistically significant.

Results

The specificity of the TMs was 86%, 86%, and 93%, while the sensitivity was 64%, 36% and 36% for CgA, NSE and 5-HIAA, at a cut-off of 5 UI/l, 12 μg/ml and 50 μmol/24 h, respectively. In patients with liver metastases, all the TMs were above the cut-off, the urinary 5-HIAA ratio was >5 times and the CgA ratio was >10 times the upper limit of normal. The overall survival was 35.5±41.4 months (median 18, range 4-132 months), while the 5-year survival was 28.6%. There was no relationship between survival and either urinary 5-HIAA (R=0.12, p=0.45) and CgA (R=0.22, p=0.21), or serum NSE (R=0.12, p=0.76) levels (Figure 1).

Discussion

Unfortunately, the neuroendocrine system of the GEP has at least 16 different types of endocrine cells that produce more than 50 amines or peptides, being the widest NET system of the whole body (5, 9). NET of the small intestine have an incidence of 0.1-0.5 cases/100,000 per year, and are usually (>85%) asymptomatic (2). Serum CgA measurement seems to be a useful TM for the diagnosis and follow-up of patients with malignant carcinoids, and might have some diagnostic utility in patients with negative somatostatin receptor scintigraphy (20, 21), while NSE is usually considered a generic TM, with lower diagnostic accuracy than CgA and 5-HIAA (12, 22).

In some studies, both 5-HIAA and CgA measurements are considered the minimally required biochemical tests in all patients with NETs, and the reported sensitivity in patients with endocrine tumors of the midgut was 87% and 73% for CgA and 5-HIAA, respectively (23). However, our data confirm a sensitivity ranging from 36% to 64% for TMs, and no relationship between survival and serum CgA.

Recently, with the aim of better assessing the prognosis and risk of progression of patients with small intestine NETs, a nomogram from 15 variables, including age, symptoms, 5-HIAA, CgA, TNM staging, liver function tests, etc, has recently been developed (24). The mean survival of patients with a NET nomoscore <75, 75-95, and >95 was 15.5±4.3, 9.7±2.5, and 6.4±1.1 months, respectively.

In several studies, CgA is considered the most important circulating TM for diagnosis and follow-up of NETs, while 5-HIAA is the specific marker for carcinoids producing serotonin (9, 11, 22). Unfortunately, the classical carcinoid syndrome is relatively uncommon, although the protean and intermittent symptoms of NETs are critical for timely diagnosis (25). Surgery is the only possible curative approach and so represents the traditional first-line therapy; some authors found a correlation between CgA and prognosis (13, 26).

In conclusion, the sensitivity of 5-HIAA, CgA and NSE is generally low in patients with malignant carcinoids and the urinary or serum levels of these TMs are independent of survival. Further studies will be needed to confirm the usefulness of TMs in predicting survival of patients with malignant carcinoids.

Figure 1. Relationship between survival, chromogranin A (CgA) and neuron-specific enolase (NSE) serum levels.
References


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