Neuroendocrine Tumors and Second Primary Malignancy-A Relationship with Clinical Impact?

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Abstract. Background: Neuroendocrine tumors (NET) are frequently associated with synchronous or metachronous secondary primary malignancies (SPM). The aim of this study was to report on 14 patients with NET and SPM from a series of 96 patients with NET. Patients and Methods: Fourteen patients with NET and synchronous or metachronous SPM were reviewed for primary site and characteristics of NET and associated SPMs as well as the outcome of these combined malignancies. Results: From 1987 to 2002, 14 (14.6%) out of 96 patients with NET were identified with SPM. The median age of the patients at diagnosis of NET was 69 years (range: 56–86 yrs.) There were nine female and five male patients. The localization of NET was: four in appendix, three ileum, two duodenum, one stomach, one jejunum, one pancreatic tail, one rectum and one lung. Five patients had synchronous SPM (two colon cancers with one double colon cancer, one gastric cancer, one bladder cancer, one ovarian cancer) and nine metachronous SPM (two basal cell carcinomas, one colon cancer, two breast cancer, one gastric MALT-lymphoma, one ductal pancreatic adenocarcinoma, one bladder cancer, one hepatocellular carcinoma), three months to five years after diagnosis of NET. Five patients died of metastatic tumor (three SPM: 1,7,10 yrs; two NET: 1,9 yrs), two patients died of other causes (1,7 yrs), three patients are alive with metastatic tumor (two NET: 5,6 yrs; one SPM: 10 yrs) while four patients are tumor-free (6ms,2,9,10 yrs). Conclusion: NET is associated to a high degree with gastrointestinal and genitourinary SPM. In 5/14 (36%) patients SPM was diagnosed synchronously, while in 8/14 (57%) patients SPM was diagnosed metachronously. In 8/14 patients (57%) primary symptoms were caused by SPM. As a consequence, every NET should be regarded as an index tumor and risk-adapted follow-up with thorough investigation, mainly of the GI and genitourinary tracts, is to be recommended.

As the lung develops from the foregut bud, neuroendocrine tumors (NET), commonly termed carcinoid tumors, may develop in the entire gastrointestinal tract as well as in the lung. The first carcinoid tumors (NET) were described by Lubarsch (1), who thought these tumors were carcinomas, while Oberndorfer (2) coined the term carcinoid because of the cancer-like but slow-growing biological behavior of these tumors. NET prognosis is mainly dependent on tumor localization and size at diagnosis.

NET association with other malignancies is an increasingly appreciated phenomenon (3-9). Rates of associated secondary primary malignancies (SPM) are reported to range up to 55% (3). These SPM are mainly localized in the gastrointestinal and genitourinary tract (3), but may occur in almost every tissue (3). Even in children suffering from NET, these SPM occur (10) although another series with 36 appendiceal carcinoid tumours in children showed no SPM during the observation period (11). In a metaanalysis the frequency of SPM after NET averaged 17% (3), which is more than double the rate of expected SPM after non-neuroendocrine malignancy (12). The aim of our retrospective analysis was to describe the characteristics of 14 NET tumors with associated SPMs and the outcome of these combined malignancies.

Patients and Methods

Between 1987 and 2002, 14 patients (nine women, five men) out of 96 NET (14.6%) were diagnosed with NET and SPM at Innsbruck University Hospital, Austria. The charts of these patients were retrospectively reviewed for age, gender, localization and staging of NET and SPM. NET and SPM were regarded as synchronous when they were diagnosed at the same time and as metachronous when they appeared after a certain time interval. Information on patients who had already died was obtained from general practitioners, whereas all patients alive were called for a check-up. In none of the patients was MEN I syndrome diagnosed. For localization of NET and type of SPM see Table I.
Results

In 8/14 (57%) patients’ symptoms of SPM led to diagnosis. The median age at diagnosis was 69 years (range 56-86 yrs). In six patients the primary symptom was caused by NET; 5/13 (38.5%) SPM were diagnosed synchronously. In 9/13 (69%) patients NET and SPM were diagnosed within one year. Three patients died of metastatic SPM, two patients died of metastatic NET, while two patients are alive with metastatic NET. Only one patient is alive five years after diagnosis of ileal NET with bone metastases after breast cancer. Two patients died of a cause other than NET or SPM (cardiac failure and non-tumor-associated cachexia). Currently, three patients are tumor-free two, nine and ten years after diagnosis of NET and one, five, six and ten years after SPM, respectively. None of the patients had known metastatic NET and metastatic SPM at the same time. A total of 12/14 (86%) SPM cases were localized in the gastrointestinal (7/14, 50%) or genitourinary (5/14, 36%) tracts. In six patients NET surgery was the primary intervention, while four patients were operated on for SPM with NET being incidentally found in the specimen. The two NET of the duodenum were diagnosed and removed endoscopically, while in two patients appendectomy was performed for acute appendicitis and NET was incidentally detected in the specimen. In one patient multicentric type-I gastric carcinoid reactive to elevated gastrin and atrophic gastritis was treated by partial removal of the multicentric carcinoids and subsequent gastrin-inhibiting therapy with somatostatin analogues. There was no obvious relationship of a certain NET tumor feature with localization, tumor stage or outcome of SPM. For follow-up data see Table II.

Discussion

Neuroendocrine tumors, generally named carcinoid tumors, may be localized throughout the gastrointestinal tract or lung. They develop from neuroendocrine cells scattered in these tissues. The different biological behavior is dependent on localization within the gastrointestinal tract. The most important parameter besides localization for predicting metastatic potential of NET is the tumor diameter at time of diagnosis. Most NET develop in the appendix and have the best prognosis. They have low metastatic potential and become symptomatic at an early stage by concomitant appendicitis. Most NET show an indolent course and are detected incidentally during endoscopy. In contrast, small bowel or classical carcinoids have a poorer prognosis, are metastatic at an early stage and are usually multicentric tumors. The multicentricity of small bowel NET may be explained by the fact that these NETs produce a number of growth factors (9).

Pearson and Fitzgerald in 1944 reported, for the first time, a high incidence of carcinoid tumors with SPM in an autopsy series (5). Meanwhile, further reports demonstrated NET-associated SPM in up to 55% (3-10) of cases. In a metaanalysis, NET-associated SPM averaged 17% in 5280 patients. This rate is more than double the rate of SPM after non-neuroendocrine primary malignancies (12). Tichansky (7) found a rate of 46% for SPM after colorectal NET. These patients were compared to patients in the National Cancer Institute’s Surveillance, Epidemiology and End Result (SEER) registry (1973-1999), which means that patients in the control group were patients suffering from other primary malignancies. In other studies the outcome was mostly influenced by SPM, which showed faster progression than NET (3). In our patients the outcome seemed not to be determined by SPM, because two patients died of metastatic NET and two patients are alive with metastatic NET, while three patients died of metastatic SPM and one patient is alive with metastatic SPM. Most NETs were appendiceal carcinoids. In accordance with the literature, most of the associated SPMs were seen to be colon cancers.
produced and released by NET, stimulates brain tumors (15,16). Bombesin, a neuropeptide frequently in large amounts in the tissues of lung, ovarian, thyroid and (6,14). Recently, receptors for CCK and gastrin were detected can stimulate gastric mucosal and pancreatic cell growth factor properties. Gastrin and cholecystokinin (CCK) characterized. Many of these neuropeptides have specific 1902, when the first neuropeptide secretin was discovered, SPMs overexpress receptors for these compounds (13). Since the existence of a cofactor prompting gastric carcinoid tumors has not yet been described. Evidence for a heritable cause of NET is only available for MEN I-syndrome, in which carcinoid tumors occur with concomitant adenomas of the pituitary, pancreas and parathyroid glands. These MEN I-associated multieentric gastric type II carcinoid tumors can also be explained by stimulation of gastric ECL cells by elevated gastrin, which is released by MEN I-associated gastrinomas.

NETs produce and secrete various neuropeptides, while SPMs overexpress receptors for these compounds (13). Since 1902, when the first neuropeptide secretin was discovered, about 60 brain gut- peptides (neuropeptides) have been characterized. Many of these neuropeptides have specific growth factor properties. Gastrin and cholecystokinin (CCK) can stimulate gastric mucosal and pancreatic cell growth (6,14). Recently, receptors for CCK and gastrin were detected in large amounts in the tissues of lung, ovarian, thyroid and brain tumors (15,16). Bombesin, a neuropeptide frequently produced and released by NET, stimulates *in vitro* growth of human breast cancer cells (17) and is a potent autocrine growth factor in small cell lung cancers (18). On the other hand, a number of non-neuropeptide growth factors such as PDGF, FGF and TGF are produced by NET (19).

Although NET-associated SPMs are present in up to 55% of patients (3), not all patients with NET develop SPM. In MEN I syndrome, where gastrin released by gastrinomas stimulates gastric ECL cells, associated carcinoid tumors of the stomach occur in only 13 % of patients. Therefore, the existence of a cofactor prompting gastric carcinoid tumors must be assumed. As a consequence, apart from risk-adapted follow-up, every patient diagnosed with NET should undergo thorough investigation of the entire gastrointestinal and genitourinary tracts for concomitant SPM. We recommend that a whole body CT scan and endoscopic investigation of the gastrointestinal tract should be performed. In a situation where the patient is operated on for adenocarcinoma and NET is incidentally found in the specimen, no further treatment is necessary. It may be speculated that inhibition of the release of growth-stimulating neuropeptides and blocking receptors for these compounds on SPM may pose new treatment options.

**References**


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