# Second primary malignancies in patients with a gastrointestinal neuroendocrine tumour : a case report and review of the literature

M. Ferrante[1,4], I. Van Boxelaer[1,5], M. De Man[1], A.-M. Schelfout[2], Y. Van Molhem[3], K. Hendrickx[1], J. Vandervoort[1], P. Van Der Spek[1], F. Sermon[1], L. Du Ville[1], L. Lepoutre[1.]

(1) Department of Gastroenterology ; (2) Pathology and (3) Abdominal Surgery, Onze-Lieve-Vrouwziekenhuis, Aalst, Belgium ; Departments of (4) Gastroenterology and (5) Internal Medicine, University Hospital Gasthuisberg, Leuven, Belgium.

## Abstract

**A second primary malignancy (SPM) is frequently reported in patients with a gastrointestinal neuroendocrine tumour (NET). The majority of SPM are located in the gastrointestinal tract, but malignancies at other sites are described as well. This phenomenon might just be coincidental due to high incidence rates of asymptomatic NET lesions in patients who are operated or who undergo autopsy for another primary malignancy. However, other theories have been developed since the observed incidence rates seem to be double as high as expected. Some authors suggest a common genetic predisposition, while others report tumourigenic properties of various neuroendocrine peptides, including secretin, gastrin and cholecystokinin. This review is illustrated by a case report of a patient in whom the radiological diagnosis of a diffuse liver metastasized adenocarcinoma of the rectum changed dramatically after positron emission tomography and explorative laparoscopy to a curable adenocarcinoma of the rectum with a simultaneous well-differentiated neuroendocrine carcinoma.** (Acta gastroenterol. belg., **2010**, 73, **397-402**).

## Introduction

Carcinoid tumours are the most common gastrointestinal neuroendocrine tumours (NET) with reported incidence rates around 2.47 and 2.58 per 100,000 Caucasian men and women per year, respectively (1). The age distribution ranges from the second to the ninth decade with a peak incidence occurring between the ages of 50 and 70. The majority of NETs are located in the gastrointestinal tract (most commonly in the ileum) and the bronchopulmonary system (2).

Symptoms of a NET are infrequent, with flushing and diarrhoea occurring in only 5 to 7 percent of patients with a small bowel NET. Therefore, the tumour is mostly diagnosed incidentally at endoscopy, surgery or autopsy (3). Interestingly, NETs seem to have the tendency to occur synchronously with other, second primary malignancies (SPM) (4). Therefore, the occurrence of liver nodules on traditional imaging studies can be misinterpreted as liver metastasis of a SPM leading to a wrong diagnosis and treatment.

This review article includes an illustrative case of a 52-year old patient with a recent diagnosis of a rectal adenocarcinoma. A CT scan showed mesenterial adenopathies as well as multiple liver nodules. Prior to chemotherapy, an intense uptake was described on a positron emission tomography in both the rectum and the local adenopathies, but there was only a faint uptake in the liver and the mesenterium. Based on this finding a laparoscopy was performed, leading to a dramatic change in diagnosis from a liver metastasized adenocarcinoma of the rectum to a liver metastasized well-differentiated neuroendocrine carcinoma with a simultaneous, locally advanced rectal adenocarcinoma.

## Case report

A 52-year old man known with reflux esophagitis presented to our outpatient clinic because of a 2-months history of diarrhoea with occasionally bright-red blood loss per rectum. He had lost 4 kilograms body weight during the last year. Familial cancer history was negative. A blood analysis conducted by his general practitioner revealed an iron deficiency without clear anaemia (iron 46 µg/dL, transferrin saturation 9.5%, ferritin 14 µg/L, haemoglobin 14.1 g/dL). He had an elevated carcinoembryonic antigen level of 13.2 µg/L (normal < 4.3 µg/L). Further blood exam was normal, including normal kidney, liver and thyroid function tests. Physical examination showed no remarkable abnormalities except for a firm nodular rectal mass palpable with the fingertip.

Some days later a colonoscopy revealed a rectal mass about 8 cm from the anal verge which was not possible to pass with the endoscope. Multiple biopsies were taken for histological analysis. Pathological examination showed a rectal adenocarcinoma. Besides the cancer of the rectum, a CT scan showed multiple adenopathies in the adjacent ischiorectal fat as well as in the mesenterium. Furthermore, multiple nodular lesions were found in the liver and the peritoneum suggestive of metastases of the rectal adenocarcinoma (Fig. 1A-B). There were no signs of lung metastases.

Based on the diagnosis of a metastatic rectal adenocarcinoma, a treatment with 5FU-irinotecan and bevacizumab (Folfiri + Avastin) was proposed during a multidisciplinary oncology meeting. Prior to chemotherapy, a positron emission tomography was performed to eval-

Correspondence to : Marc Ferrante, MD, PhD, Department of Gastroenterology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. E-mail : marc.ferrante@uzleuven.be. Tel. : +32 16 34 42 25. Fax : +32 16 34 44 19.

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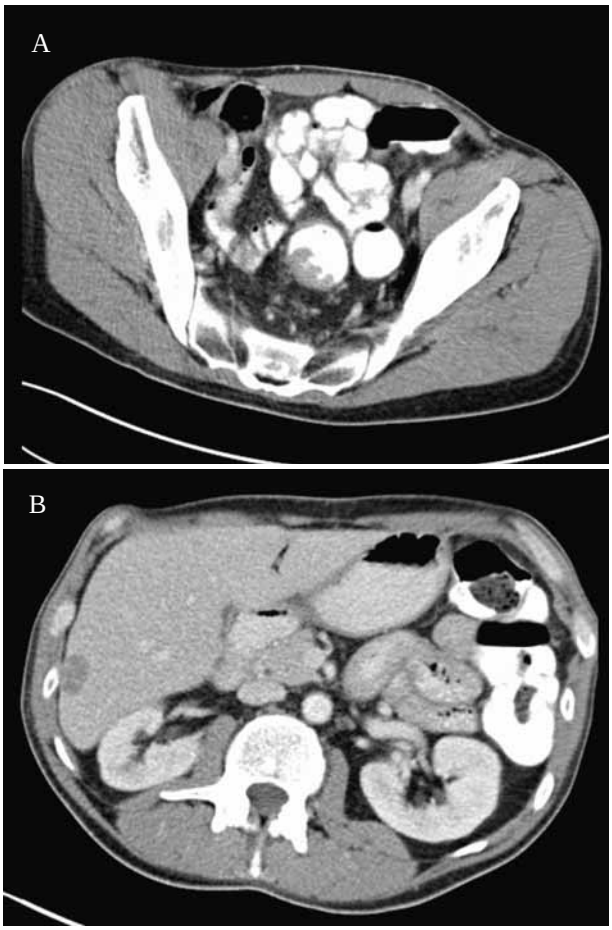


Fig. 1. — CT scan of the abdomen showing a rectal tumour and multiple adenopathies in the adjacent ischiorectal fat (A) as well as multiple lesions in the liver and adenopathies in the mesenterium (B).

uate the possibility of future curative surgery in this young patient. Surprisingly, this exam showed an intense uptake in the rectum and the local adenopathies but only a faint uptake in the liver and the mesenterium (Fig. 2).

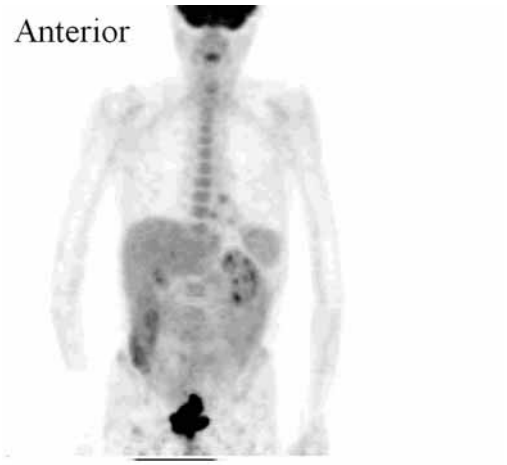


Fig. 2. — Positron emission tomography showing an intense uptake in the rectum and the local adenopathies but only a faint uptake in the liver and the mesenterium.

Because of the conflicting results, the patient underwent an explorative laparoscopy. During this procedure the surgeon described the rectal mass as well as some ascites, peritoneal implants, suspect mesenterial adenopathies and subcapsular liver nodules. The surgeon took samples of all described abnormalities. Pathological examination of the rectal lesion confirmed the diagnosis of a CK7-/CK20+, chromogranin negative adenocarcinoma (Fig. 3A-D). However, the cytological examination of the ascitic fluid as well as the histological examination of the peritoneal implants, the mesenterial adenopathies and the liver nodules showed a CK7-/CK20-, chromogranin positive neuroendocrine tumour (Fig. 4A-D). The Ki-67 proliferation index of 4% and the mitotic index of 2 per 10 high power fields were diagnostic for a well-differentiated neuroendocrine carcinoma.

Based on the histological report, therapy for the rectal adenocarcinoma changed from a metastatic to a curative setting and the patient underwent flash radiotherapy (5 Gray during 5 consecutive days). An octreotide scan showed two hypercaptation foci in the umbilical region as well as multiple foci in the liver, confirming the diagnosis of a second metastatic NET of unknown, but probably gastrointestinal, primary origin (Fig. 5). The serum chromogranin level was 384 µg/L (normal 40-170 µg/L) in this patient under proton pomp inhibition therapy. A 24-hour urine collection for 5-hydroxyindolacetic acid (5-HIAA) was not performed.

Two weeks after the last radiotherapy, the patient underwent a low-anterior rectosigmoidal resection with total mesorectal excision and construction of a coloanal pouch. Final histological exam of the rectal mass showed a locally advanced, moderately differentiated adenocarcinoma with one positive lymph node (1 out of 26, pT3N1). Some weeks after surgery an adjuvant 5FU chemotherapy (simplified De Gramont scheme, 12 cycles, every 2 weeks) was started and this in combination with a monthly injection of 30 mg sandostatin LAR. A CT scan after the first 6 cycles of chemotherapy showed similar lesions in the mesenterium and the liver without arguments for local recurrence at the coloanal pouch. The CEA level normalized to 1.6 µg/L and the chromogranin level decreased to 180 µg/L.

## Discussion

Carcinoids were first described in 1888 by the German Otto Lubarsch. The term *karzinoide*, or cancer-like, highlights the mostly benign course of these tumours despite the possibility of liver metastases. NETs are a heterogeneous group of tumours that arise form enterochromaffin cells located throughout the lung, ovary and the gastrointestinal tract. Traditionally, NETs have been classified based upon their origin from the embryonic division of the alimentary tract, foregut (including lungs, bronchi and stomach), midgut (including small intestine, appendix and proximal colon), or

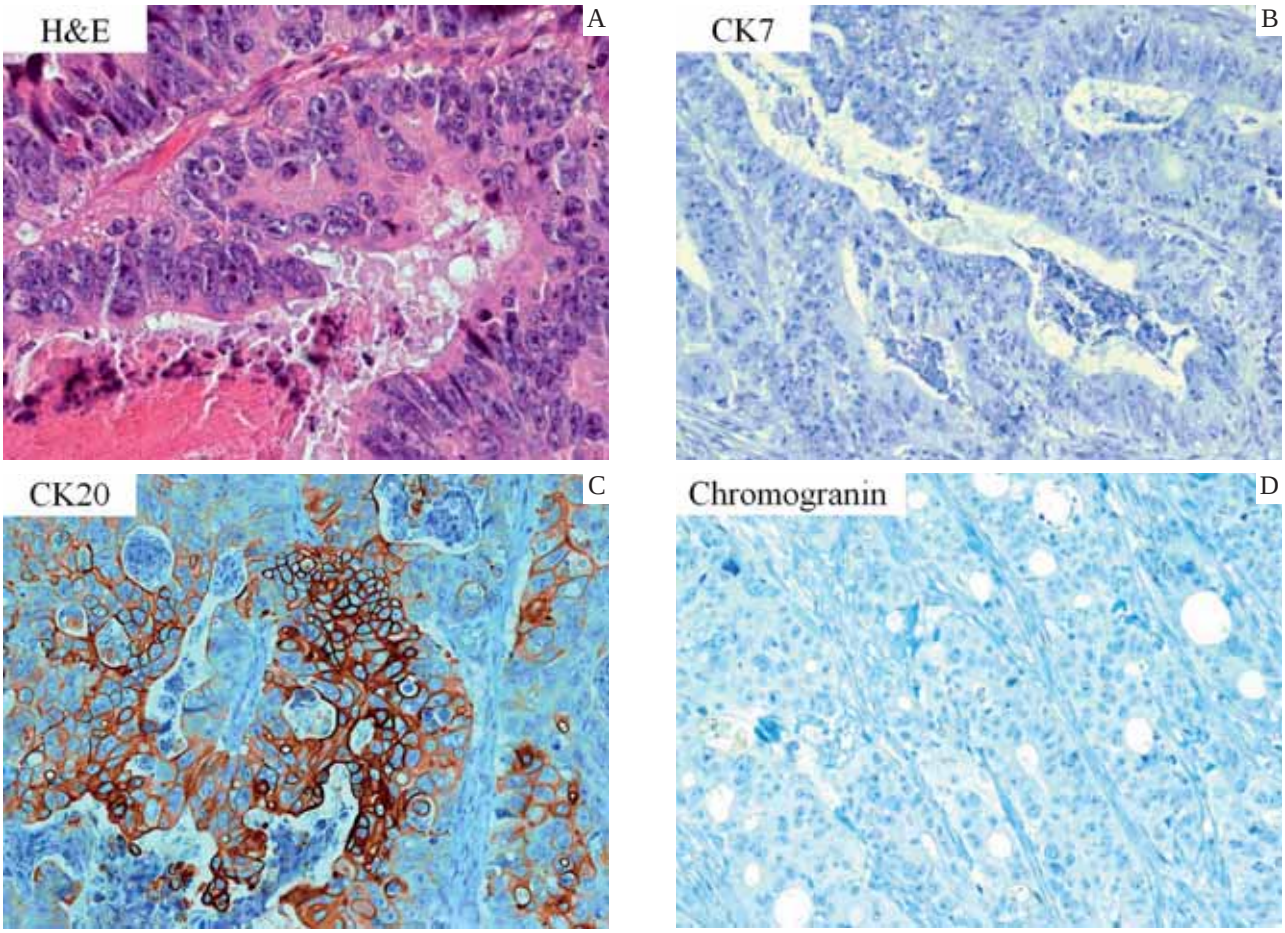


Fig. 3. — Invasive adenocarcinoma of the rectum with proliferation of epithelial cells, gland formation, cellular atypia, pleomorphism, a high mitotic rate and areas of necrosis (Fig. 3A, H&E, ×40). The tumour cells do not stain for cytokeratin 7 or chromogranin, but they do stain for cytokeratin 20. (Fig. 3B-D, staining for CK7, CK20 and chromogranin respectively, ×20).

hindgut (including distal colon, rectum and genitourinary tract) (5). In addition, NETs have been categorized based upon histological characteristics as "typical" well differentiated tumours containing small regular cells with rounded nuclei, or "atypical" anaplastic tumours (6). More recently, the World Health Organization proposed a new classification into well-differentiated neuroendocrine tumours (carcinoid, benign), well-differentiated neuroendocrine carcinomas (low grade malignant) and poorly differentiated neuroendocrine carcinomas (high grade malignant). This classification with prognostic relevance is based on the presence of metastases, the Ki-67 proliferation index and the number of cells in mitosis per 10 high power fields (mitotic index) (7).

Distinction between benign and malignant NETs is based upon presence or absence of metastases rather than histology alone. The rate of metastasis to regional lymph nodes or distant sites is as high as 60%, depending on the site of origin (1,2). Appendical NETs have the lowest rate of metastasis because they are still small when they become clinically apparent. In contrast, metastasis rates are higher for jejunoileal and rectal NETs that do not present clinically until they are large enough to cause obstruction, bleeding, infarction or intussusception.

Initial clinical features might be nonspecific, but several patients present with a carcinoid syndrome, including flushing, watery diarrhoea, abdominal pain or wheezing depending on the location and the extent of the tumour (1,2). These symptoms can be attributed to a high serotonin (5-IHAA) production and release into the systemic circulation from the primary NET, but more frequently, from the liver metastases. Nevertheless, up to 53% of NETs are found incidentally at endoscopy, surgery or autopsy, as illustrated in our case (3).

Synchronous NETs with non-carcinoid neoplasms in the gastrointestinal tract were first noted by Pearson and Fitzgerald in 1949 (8), with an incidence rate of SPM in 23% of patients with a NET at autopsy. In the literature (3,9-25), the rate of SPM in patients with a NET ranges from 7 to 47%, with an average of 14% (Table I). The available reports include single centre cohorts as well as nationwide registries. As shown in Table I, 1400 patients with an SPM are reported in a total of 9,684 patients with a NET (14%). Depending on the type of the study (single centre Vs. nationwide registry, surgical cases Vs.

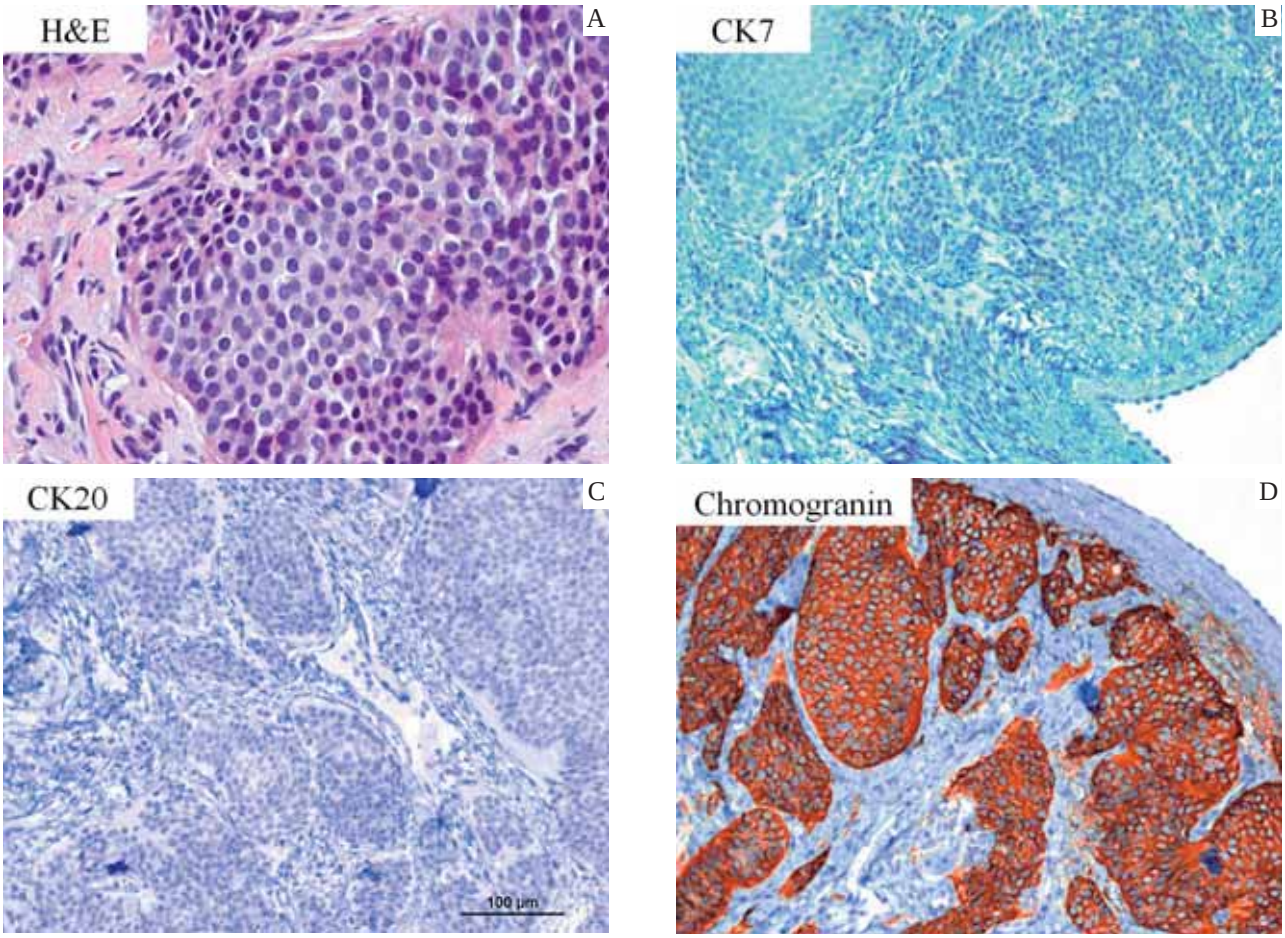


Fig. 4. — Neuroendocrine tumour with proliferation of well circumscribed monomorph cells with round monomorph nuclei and eosinophil cytoplasm (Figure 4A, H&E, ×40). The tumour cells do not stain for cytokeratin 7 or cytokeratin 20, but they do stain for chromogranin (Figures 4B-D, staining for CK7, CK20 and chromogranin respectively, ×20).

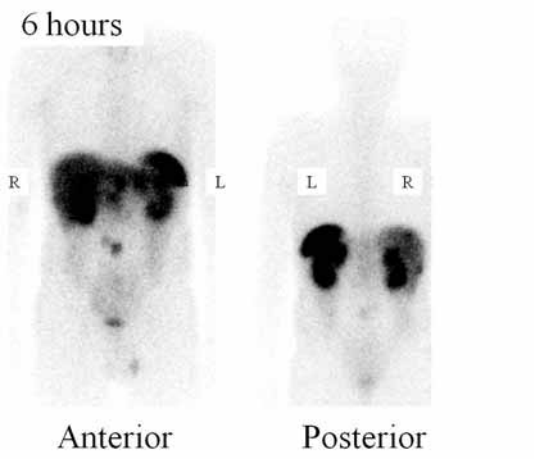


Fig. 5. — Octreotide scan showing two hypercaptation foci in the umbilical region as well as multiple foci in the liver about 6 hours after contrast injection.

autopsy cases) incidence rates vary from 7 to 47% Most commonly the SPM is diagnosed synchronously with the NET, with frequencies ranging from 60 to 91%, with an average of 68% (Table I).

The highest rate of SPM is seen in patients with a NET of the small bowel (30%), followed by the appendix (15%), the colorectum (13%) and the stomach (10%). The majority of SPM present concurrently with the NET (62%), while the remaining SPM develop either before or several years after the NET. The most common site of SPM is the gastrointestinal tract, which is involved in approximately 47% of the cases, followed by the genitourinary tract (20%) and the pulmonary tract (12%). Several patients develop more than one SPM. Colonic adenocarcinomata are consistently reported as most common SPM. The SPM is usually the more aggressive malignancy. Consequently, most patients with both a NET and a SPM die from the SPM (20). Differentiation between metastases from either the NET or the SPM may be difficult. As in our patient, functional PET imaging can be helpful in these cases (26).

The average incidence rate of 14% SPM in patients with a NET is significantly higher than the expected incidence based on gender- and age adjusted cancer rates in nationwide registries, such as the National Cancer Institute Surveillance, Epidemiology, and End Result (SEER) (24). The aetiology of this higher risk of SPM in patients with a gastrointestinal NET remains

Table I. — **Reported rates of second primary malignancies in gastrointestinal NETs**

| | Number of patients with SPM, stratified by location of primary NET (%) | | | | | | Timing of SPM | | Site of SPM (%)[2] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CENTRE | Total | Stomach | Duodenum | Small intestine | Appendix | Colon Rectum | Sync (%) | Meta (%) | Gastro-intestinal | Genito-urinary | Pulmonary | Other |
| Mayo [9] | 61/209 (29) | - - | - - | 61/209 (29) | - - | - - | - - | -- | 33/70 (48) | 8/70 (11) | 8/70 (11) | 21/70 (30) |
| Mayo [10] | 19/144 (13) | - - | - - | - - | 19/144 (13) | - - | - - | - - | 6/22 (27) | 10/22 (46) | 0/22 (0) | 6/22 (27) |
| Michigan [11] | 23/72 (32) | 0/1 (0) | 1/2 (50) | 11/28 (39) | 6/16 (37) | 5/25 (20) | - - | - - | 10/23 (43) | 5/23 (22) | 3/23 (13) | 5/23 (22) |
| New Orleans [12][3] | 35/135 (26) | 2/10 (20) | 3/12 (25) | 14/37 (38) | 4/29 (14) | 12/47 (26) | - - | - - | - - | - - | - - | - - |
| Bethesda [13][1,4] | 207/2837 (7) | 2/61 (3) | - - | 66/612 (11) | 77/1160 (7) | 50/595 (8) | 128/207 (62) | 79/207 (38) | 89/207 (43) | - - | - - | - - |
| Cornell, NY [14] | 39/107 (36) | - - | - - | - - | - - | - | 93/107 (87) | 14/107 (13 | - - | - - | - - | - - |
| Rochester, NY [15][1] | 17/96 (18) | 1/2 (50) | 1/2 (50) | 9/34 (26) | 5/45 (11) | 1/11 (9) | 14/23 (61) | 9/23 (39) | 9/23 (39) | 7/23 (30) | 2223 (9) | 5/23 (22) |
| Chicago [16] | 22/101 (22) | - - | - - | - - | - - | - - | - - | - - | 10/22 (45) | 6/22 (27) | 3/22 (14) | 3/22 (14) |
| Lund, Sweden [17] | 23/156 (15) | - - | - - | - - | - - | - - | - - | - - | 10/23 (43) | 2/23 (9) | 2/23 (9) | 9/23 (39) |
| Oregon [l8] | 14/30 (47) | - - | - - | - - | - - | - - | - - | - - | - - | - - | - - | - - |
| New Orleans [19][3] | 28/112 (25) | - - | - - | - - | - - | - - | 19/29 (66) | 10/29 (34) | 16/29 (55) | 4/29 (14) | 2/29 (7) | 7/29 (24) |
| Missouri [3][1] | 10/55 (18) | 0/1 (0) | 1/3 (33) | 5/22 (23) | 2/17 (12) | 2/8 (25) | - - | - - | 3/12 (25) | 4/12 (33) | 2/12 (17) | 3/12 (25) |
| Pennsylvania [20] | 32/69 (46) | - - | - - | - - | - - | - - | 32/35 (91) | 3/35 (9) | 15/35 (43) | 9/35 (26) | 3/35 (8) | 8/35 (23) |
| New Heaven [21-23][1,4] | 1080/8305 (13) | 21/265 (8) | - - | - - | 235/1570 (15) | - - | - - | - - | - - | - - | - - | - - |
| Philadelphia [24][1,4] | 1080/8305 (13) | - - | - - | - - | - - | 271/2086 (13) | 179/299 (60) | 120/299 (40) | 149/299 (50) | 59/299 (20) | 42/299 (14) | 49/299 (16) |
| Taipei [25][1] | 32/228 (14) | 2/7 (29) | - - | 4/11 (36) | 1/1 (100) | 18/141 (13) | - - | - - | 18/34 (53) | 5/34 (15) | 4/34 (12) | 7/34 (20) |
| TOTALS | 1400/9684 (14) | 28/276 (10) | 3/7 (43) | 90/304 (30) | 268/1793 (15) | 297/2271 (13) | 337/493 (68) | 156/493 (32) | 279/592 (47) | 119/592 (20) | 71/592 (12) | 123/592 (21) |

1 : Including non GI NETs or metastatic NETs without clear primary.
2 : Some patients developed more than one SPM.
3 and 4 : Overlap between study populations, only the latest data were taken into account for the total cohort.
Sync : synchronous ; Meta : metachronous.

unclear, but might be due to a common predisposing carcinogen or genetic alteration. This hypothesis is supported by several case series and case reports of a so called mixed adeno-carcinoid tumour, a gastrointestinal tumour with features of both an adenocarcinoma and a NET (27-29). However, the high percentage of SPM in the genitourinary and pulmonary tract in patients with a gastrointestinal NET, refutes the hypothesis of a single premalignant stem cell which differentiates into several tumour types.

Another theory suggests that the development of SPM might be the result of the secretion of multiple biologically active compounds by neuroendocrine cells (30). Growth factors such as platelet-derived growth factor, epidermal growth factor, transforming growth factor, fibroblast growth factor and insulin-like growth factor have all been demonstrated in gastrointestinal NETs and might play a role in the genesis of SPM in these patients (31). Furthermore, peptides such as secretin, gastrin, cholecystokinin, VIP, bombesin and neurotensin might have growth factor properties and receptors for these peptides have been described on the surface of non-carcinoid tumour cells (30).

Finally, the high incidence rate of SPM might just be explained by the frequent incidental finding of an asymptomatic NET in patients with a non-carcinoid tumour (20). As in our patient, this is the case in the vast majority of the patients. Nevertheless, although a direct link between the NET and an SPM is not proven, it seems appropriate to search for a synchrone as well as a metachrone SPM in patient with a diagnosis of a NET. Ideally such an evaluation should include an endoscopic evaluation of the gastrointestinal tract.

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