Turk J Gastroenterol 2009; 20 (3): 214-219

A patient with nonfunctional pancreatic neuroendocrine tumor and incidental metachronous colon carcinoma detected by positron emission tomography: Case report

Fonksiyon göstermeyen pankreas nöroendokrin tümörlü ve pozitron emisyon tomografisiyle saptanmış rastlantısal metakron kolon kanserli bir hasta

Binnaz DEMİRKAN[1], İlkay Tuğba ÜNEK[1], Barbro ERIKSSON[2], Mesut AKARSU[3], Hatice DURAK[4], Özgül SAĞOL[5], Funda OBUZ[6], Çilem BİNİCİER[7], Mehmet FÜZÜN[8], Mehmet ALAKAVUKLAR[9]

Departments of Internal Medicine, Divisions of [1]Medical Oncology and [3]Gastroenterology, [4]Nuclear Medicine, [5]Pathology, [6]Radiology, [7]Internal Medicine, and [8]General Surgery, Dokuz Eylül University, School of Medicine, İzmir
Department of [2]Endocrine Oncology, Uppsala University, Uppsala, Sweden
[9]Kent Hospital, İzmir

Pancreatic neuroendocrine tumors constitute about 2% of all gastrointestinal neoplasms. Approximately half of the pancreatic neuroendocrine tumors are nonfunctional. Due to lack of specific symptoms, most patients with nonfunctional pancreatic neuroendocrine tumors present with locally advanced or metastatic disease. Second primary malignancies are seen very rarely in these patients. Colon carcinoma ranks third in frequency among primary sites of cancer in both men and women in western countries. Presence of a metachronous colon adenocarcinoma in a patient with nonfunctional pancreatic neuroendocrine tumor has not been reported before. We present a patient who had an asymptomatic mass in the head of the pancreas, detected by ultrasonography in 1996. The patient did not consent to operation. In 2002, after the diagnosis of an unresectable, nonfunctional pancreatic neuroendocrine tumor, interferon alpha-2b and octreotide were started. A year after biological treatment, he refused further treatment. In 2004, during the evaluation of dissemination of the asymptomatic disease, positron emission tomography revealed a high uptake by the descending colon despite the failure of other imaging methods. After surgery for operable colon carcinoma, the patient received chemotherapy and biological therapy for both tumors. Since 2005, he has been doing well without any further treatment thus far. In conclusion, computerized tomography/magnetic resonance imaging and octreotide scintigraphy may be insufficient to show disseminated disease and asymptomatic second primary malignancies. Therefore, positron emission tomography is a valuable promising option for the evaluation of gastroenteropancreatic neuroendocrine tumors and concomitant or metachronous malignancies. Lifelong follow-up by a multidisciplinary oncology team is needed so that a long-term survival can be achieved with integrated multimodal systemic treatment approaches.

Key words: Pancreatic neuroendocrine tumor, colon cancer, positron emission tomography

Pankreas nöroendokrin tümörleri, tüm gastrointestinal tümörlerin yaklaşık olarak %2'sini oluşturur. Yaklaşık olarak Pankreas nöroendokrin tümörlerin yarısı fonksiyon göstermez. Fonksiyon göstermeyen pankreas nöroendokrin tümörlü olguların pek çoğu spesifik semptomların olmaması nedeniyle lokal ileri evre veya metastatik hastalıkla tanınır. İkinci primer kanserler bu hastalarda çok nadir olarak görülür. Kolon kanseri, Batı ülkelerinde kadınlarda ve erkeklerde primer kanserler içinde sıklık açısından 3. sırada yer alır. Metakron kolon adenokanseri, fonksiyon göstermeyen pankreas nöroendokrin tümörlü bir hastada, daha önce bildirilmemiştir. 1996 yılında ultrasonografiyle pankreas başında kitle saptanmış ancak yakınması olmaması nedeniyle ameliyatı kabul etmemiş bir hastayı sunmaktayız. Hastamıza, 2002 yılında, rezeke edilemeyen, fonksiyon göstermeyen, pankreas nöroendokrin tümörü tanısıyla, interferon alfa-2b ve oktreotid başlandı. 1 yıllık biyolojik tedavinin ardından hasta daha ileri tedaviyi kabul etmedi. 2004 yılında, hastalık yaygınlığının değerlendirilmesi amacıyla yapılan pozitron emisyon tomografisinde, diğer görüntüleme yöntemleriyle görüntülenemeyen, inen kolonda artmış aktivite tutulumu saptandı. Operabl kolon kanseri için yapılan cerrahiden sonra hasta, her iki tümörü nedeniyle kemoterapi ve biyolojik tedavi aldı. 2005 yılından bugüne kadar tedavisiz genel durumu iyi seyretmektedir. Sonuç olarak, bilgisayarlı tomografi/manyetik rezonans görüntüleme ve oktreotid sintigrafisi, yaygın hastalığı ve asemptomatik ikinci primer kanserleri göstermede yetersiz olabilir. Bu nedenle, pozitron emisyon tomografisi, gastroenteropatik nöroendokrin tümörlerin ve eşzamanlı veya metakron kanserlerin değerlendirmesinde, değerli ümit verici bir seçenektir. Entegre multi-model sistemik tedavi yaklaşımlarıyla, uzun süreli sağkalımın elde edilebilmesi için, multi-disipliner onkoloji ekibi tarafından yaşam boyu izleme ihtiyaç vardır.

Anahtar kelimeler: Pankreas nöroendokrin tümörü, kolon kanseri, pozitron emisyon tomografisi

Address for correspondence: Binnaz DEMİRKAN
Dokuz Eylül Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı Tıbbi Onkoloji Bilim Dalı 35340, İnciralti, İzmir, TÜRKİYE
Phone: + 90 232 412 48 01 • Fax: + 90 232 277 23 03
E-mail: binnaz.demirkan@deu.edu.tr

Manuscript received: 25.12.2008 **Accepted:** 09.04.2009

doi: 10.4318/tjg.2009.0010

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEPNETs), which constitute about 2% of all malignant gastrointestinal neoplasms, are rather rare malignant diseases (1). The estimated incidence for GEPNETs is approximately 1-2/100,000, and these tumors include both carcinoid and islet cell tumors (2). Islet cell tumors are neuroendocrine neoplasms arising from the pancreas or periampullary region. Most islet cell tumors are sporadic (3). Islet cell tumors, also known as pancreatic neuroendocrine tumors (PNETs), are clinically classified as nonfunctional when they are not related to any definite clinical syndrome (4). Approximately half of the PNETs are nonfunctional (3). Owing to the lack of specific symptoms, most patients with nonfunctional PNETs present with locally advanced or metastatic disease. Only about 25% of patients with nonfunctional PNETs are able to undergo a potentially curative resection (3). Studies on a variety of cancers have shown the value and importance of positron emission tomography (PET) in clinical oncology (5). Using the serotonin precursor 5- hydroxytryptophan (5-HTP) labelled with ^{11}C, PET was shown to detect more than 90% of PNETs due to selective uptake in tumor tissue compared to surrounding tissues (4). In comparative studies on patients with carcinoids and endocrine pancreatic tumors, 5-HTP-PET proved better than computerized tomography (CT) and somatostatin receptor scintigraphy (SRS) for tumor visualization, and many small, previously overlooked lesions were diagnosed by 11C-5-HTP-PET (6). Surgical resection of the primary tumor is the initial management of NETs. Medical treatment with agents such as somatostatin analogues and alpha-interferon (IFN-α), either alone or in combination, is used in patients who are not cured by surgery alone. NETs are less sensitive to chemotherapy than other epithelial malignancies (7, 8).

Colon carcinoma ranks third in frequency among primary sites of cancer in both men and women in western countries. In our country, it is the fifth and eighth most common cancer in women and men, respectively (9, 10).

In this report, we present an interesting case with nonfunctional PNET and asymptomatic metachronous colon carcinoma incidentally detected by PET.

There are several reports on the increased risk for a second primary malignancy (SPM) in patients with carcinoid tumors (11-17), but to our knowledge, no case of colon adenocarcinoma with nonfunctional PNET has been reported previously.

CASE REPORT

In September 1996, a 57-year-old male patient had a transient ischemic attack and during an ultrasonographic examination of the abdomen, a mass in the head of the pancreas measuring 3x4 cm and multiple periaortic and pericaval lymph nodes were detected incidentally. The patient did not consent to the operation due to his being asymptomatic. When the mass eventually enlarged and

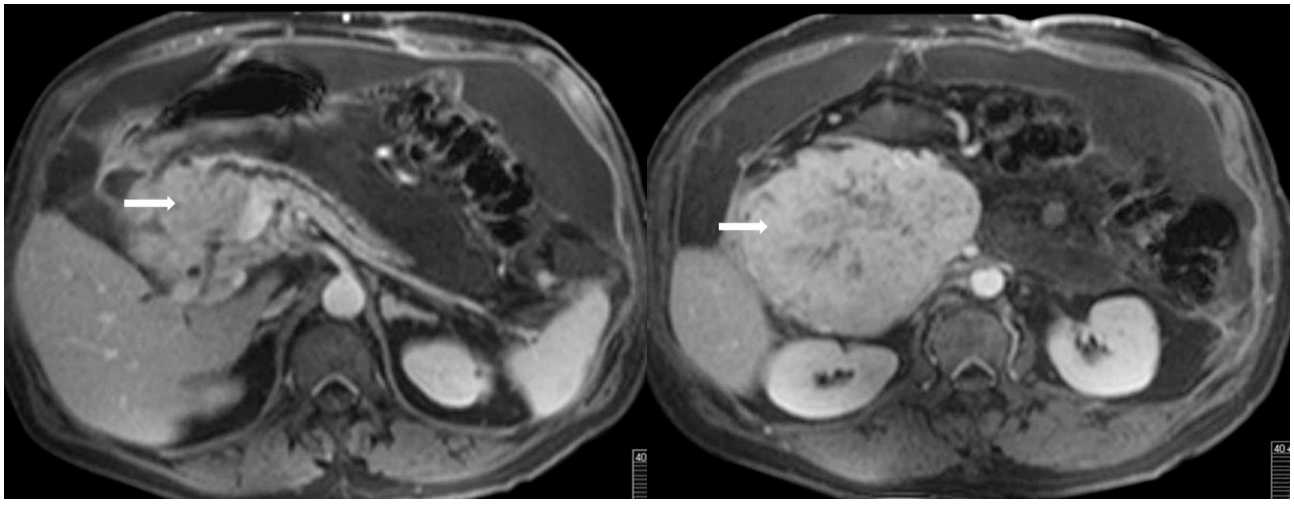

Figure 1 A, B. Contrast-enhanced fat-saturated T1-weighted transverse MR images show a massive, lobulated lesion with regular borders measuring 15x11x10 cm, in the head of pancreas (white arrows). There are no findings of invasion to the surrounding tissues, but it forms a distortion over the vascular structures.

became symptomatic (15x11x10 cm) (Figures 1a, 1b), a laparoscopic biopsy was performed in January 2002. Pathological examination of the specimen revealed well-differentiated neuroendocrine carcinoma. Immunohistochemistry (chromogranin A, synaptophysin and neuron specific enolase-NSE) were positive. The patient had no hormone-related symptoms. Plasma chromogranin A was 29 ng/ml (1.6-5.6 ng/ml), and it was the only elevated tumor marker. The results of the hormonal analysis were as follows: glucagon 128 pg/ml (<140 pg/ml), gastrin 39 ng/L (<60 ng/L), vasoactive intestinal peptide 10 ng/ml (<50 ng/ml), insulin 9.5 µU/ml (5-20 µU/ml), calcitonin 7.6 ng/L (<10 ng/L), and parathyroid hormone 25 pg/ml (10-65 pg/ml). The diagnosis was nonfunctional type PNET. His complete blood count, blood biochemistry, erythrocyte sedimentation rate and thyroid function tests were all within normal range. An exploratory laparotomy revealed a locally advanced, unresectable pancreatic cancer. The patient was admitted to the Hematology-Oncology Department for systemic treatment in May 2002. Chemotherapy with 5-fluorouracil (5FU), folinic acid (FA) and epirubicin was recommended but was refused; therefore, immunotherapy was recommended. A treatment regimen with IFN-α-2b (5 million IU, SC, 3 times a week) and somatostatin analogue-octreotide (Sandostatin®) (0.2 mg, SC, twice a day) was started. During this therapy, he suffered from flu-like syndrome, fever, arthralgia, and arthritis. Two months later, he underwent a follow-up magnetic resonance imaging (MRI) of the abdomen. The treatment response evaluation was stable disease. Meanwhile, because of the side effects, the patient refused IFN and continued with only long-acting release (LAR) octreotide formulation (Sandostatin LAR®). After five months of treatment with Sandostatin LAR® (20 mg), minimal ascites was detected. The dosage of Sandostatin LAR® (30 mg) was increased for the next four months, but thereafter he did not want to go on further treatment and was lost to follow-up for 10 months.

The patient presented once again for treatment in April 2004 and underwent PET with fluorine-18 fluorodeoxyglucose (^{18}F-FDG) and octreotide scintigraphy to determine the dissemination of the disease. PET revealed a moderate uptake in the pancreatic region but a high uptake on the left side of the abdomen corresponding to the descending colon (Figure 2). Colonoscopy detected an annular vegetative lesion in the descending colon. The biopsy was remarkable for metachronous colon adenocarcinoma. He was asymptomatic for a colon tumor and CT/MRI of his abdomen showed no abnormality other than the pancreatic mass. Octreoscan revealed an intense uptake corresponding to the pancreatic lesion (Figure 3). There was no disseminated disease. In June 2004, left hemicolectomy and colorectostomy operation were performed. The histopathological diagnosis was colon adenocarcinoma, pT4N0. Therefore, he received infusional 5-FU, FA and streptozocin every two weeks for six cycles for both tumors. Due to streptozocin-induced diabetes mellitus, streptozocin was replaced by irinotecan. After six cycles of this chemotherapy regimen and following 12 months of Sandostatin LAR® (30 mg) treatment, the patient has been in good health and active employment with stable disease during the last three-year follow-up period.

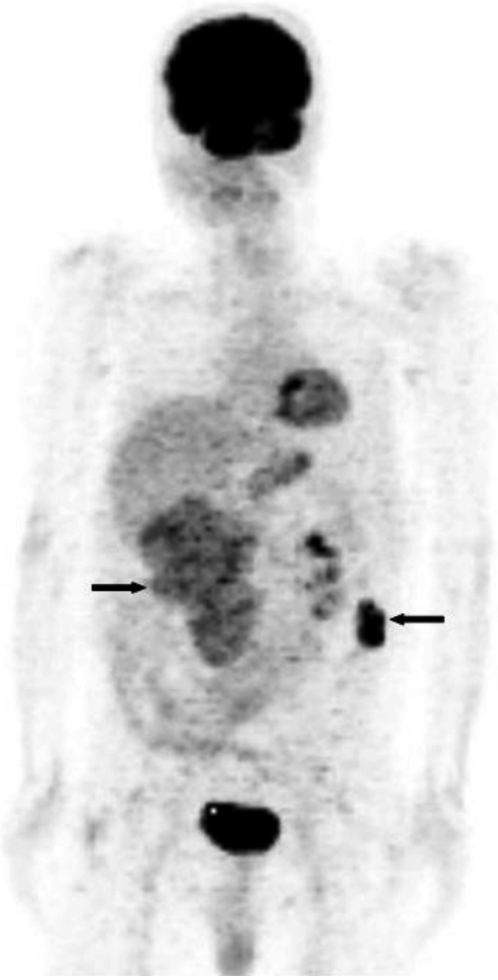

Figure 2. PET imaging shows a moderate uptake in the pancreatic region (upper arrow) but a high uptake on the left side of the abdomen corresponding to the descending colon (lower arrow).

DISCUSSION

Most of the non-carcinoid GEPNETs arise in the pancreas (islet cell tumors). PNETs, less than half of all NETs and only 1-2% of all pancreatic tumors, form an important group with a better prognosis than non-NETs (18). Here, we present a patient with a pancreatic mass of 12 years, diagnosed as nonfunctional PNET, and incidentally diagnosed metachronous colon carcinoma during PET.

Patients with nonfunctional PNETs present a variety of symptoms caused by the pressure effects of the primary tumors or metastases or invasion of surrounding structures. Most of the patients present with abdominal pain. They often have nonspecific symptoms, such as nausea, dyspepsia, steatorrhea, anorexia, and weight loss (3, 4). Histopathologically, nonfunctional PNETs cannot be differentiated from functional tumors by immunocytochemistry. They usually stain positively with chromogranin A and synaptophysin (4). Plasma chromogranin A is elevated in 60%-100% of both functional and nonfunctional PNETs as well as carcinoid tumors (19).

Our patient had no hormone-related symptoms. When the mass enlarged, he presented with symptoms of tumor bulk. Results of hormone analyses were consistent with nonfunctional PNET, and plasma chromogranin A was the only elevated tumor marker. The patient could not be operated because of locally advanced-unresectable pancreatic cancer.

Somatostatin receptor scintigraphy, based on the presence of somatostatin receptors (SSTR 1-5) in 80-90% of NETs, is a routine investigation tool today in all newly diagnosed patients with GEPNETs (20). In this case, SRS was the method used for assessment of the tumor dissemination. SRS revealed an intense uptake in the pancreas, but there were no metastatic lesions.

For oncological imaging, ^{18}F-FDG has evolved as a powerful functional imaging modality in a variety of cancers. Unfortunately, FDG-PET has not been advantageous for imaging GEPNETs, and only tumors with high proliferative activity and low differentiation have shown an increased FDG uptake. Therefore, PET using 5-HTP labelled with ^{11}C was developed for the imaging of NETs (6). In a recent study, ^{11}C-HTP-PET revealed 84% of primary tumors compared to 58% by SRS and 42% for CT (21). Since 5-HTP-PET is not available in our country, our patient was reassessed with FDG-PET. There was a moderate uptake in the pancreatic region, but surprisingly, the area corresponding to the descending colon showed high uptake. The colonoscopic biopsy revealed the colon adenocarcinoma.

Carcinoid tumors are frequently associated with synchronous or metachronous SPM, mainly of the gastrointestinal (GI) and genitourinary (GU) tracts (11-17), but presence of a SPM in patients with sporadic islet cell tumors is very rare. Sigmoid tumor in a patient with insulinoma (22) and Wilms' tumor in a patient with nonfunctional islet cell tumor (23) were reported. Prommegger et al. (11) reviewed 14 patients with NET and SPM, and among those patients, a NET of pancreatic localization was detected in only one patient whose SPM was gastric adenocarcinoma.

This is the first case report of asymptomatic incidental colon adenocarcinoma in a patient with sporadic nonfunctional islet cell tumor.

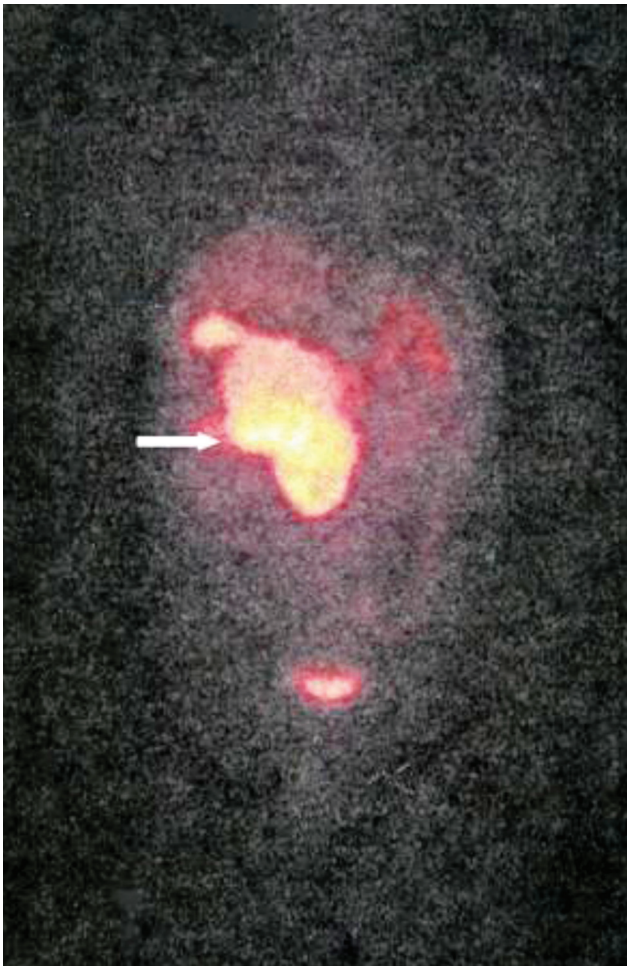

Figure 3. Somatostatin receptor scintigraphy shows an intense uptake corresponding to the pancreatic lesion (white arrow). There are no uptakes in the liver or the descending colon.

The initial management of NETs comprises surgical resection of the primary tumor. Medical treatment with agents such as somatostatin analogues and IFN-α, either alone or in combination, is used in patients who are not cured by surgery alone. Somatostatin and its long-acting analogues (octreotide acetate) are effective in symptom control in functionally active GEPNETs. They also have antiproliferative properties. Stabilization of tumor growth occurs in 35-50% of patients with NETs. Anti-angiogenic and immunomodulatory effects have also been described. Thus far, somatostatin analogues have been used as antineoplastic agents in the treatment of functional and nonfunctional NETs (24, 25). Antitumor effects of IFN-α include anti-proliferation, apoptosis, differentiation, and anti-angiogenesis. IFN-α-2b is used in the treatment of patients with NETs, and stabilization of tumor growth occurs in 10-15% of the patients (24, 26). The antiproliferative effect of the somatostatin analogues, IFN-α or a combination of the two is similar for functional and nonfunctional NETs (27). The combination treatment with octreotide acetate plus IFN-α is superior to treatments with either compound (28). Based on these data, our patient was treated with IFN-α and Sandostatin®. The disease was stabilized but, because of the side effects of IFN, treatment was continued with Sandostatin® alone. Minimal progressive disease developed initially, with disease stabilization after the increased dosage of Sandostatin LAR®.

NETs are less sensitive to chemotherapy than other epithelial malignancies. In general, islet cell tumors and anaplastic (poorly differentiated) NETs have a higher sensitivity than carcinoid tumors (7, 8). A chemotherapy regimen consisting of doxorubicin, streptozocin and 5FU has great and significant activity in patients with locally advanced and metastatic pancreatic endocrine carcinomas (29, 30). A combination of streptozocin with the De Gramont infusional 5FU regimen is also efficacious with low toxicity profile for the treatment of unresectable NETs (31). After the diagnosis of operable colon cancer, our patient had surgery. He was then treated with streptozocin plus the De Gramont infusional 5FU regimen every two weeks for six cycles and stable disease was achieved. However, due to secondary primary colon cancer and streptozocin-induced diabetes mellitus in our patient, the chemotherapy regimen was changed to the De Gramont infusional 5FU and irinotecan. There is no universally accepted, standard treatment for advanced PNETs. Somatostatin analogues and IFN-α are rarely associated with tumor regression. While islet cell carcinomas are more likely to respond to streptozocin-based chemotherapy, second-line therapy options are limited. Recently, there has been an interest in developing molecularly targeted therapy for this group of diseases. Encouraging results were observed in studies with vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) inhibitors (32).

In conclusion, second primary malignancies are very rare in patients with sporadic islet cell tumor. Lifelong follow-up of cancer patients is necessary. Clinicians should be alert and these patients must be carefully and extensively evaluated for SPM during the follow-up period. CT/MRI and octreotide scintigraphy may be insufficient to visualize these tumors or a disseminated disease. Thus, PET is a new option for the evaluation of GEPNETs and SPM. Via advances in molecular oncology and new targeted therapies, long-term survival can be achieved with integrated multimodal systemic treatment approaches.

REFERENCES

1. Öberg K. Neuroendocrine gastrointestinal tumors- a condensed overview of diagnosis and treatment. Ann Oncology 1999; 10(Suppl 2): 3-8.
2. Öberg K. The use of chemotherapy in the management of neuroendocrine tumors. Endocrinol Metab Clin North Am 1993; 22: 941-52.
3. Nakakura EK, Bergsland EK. Islet cell carcinoma: neuroendocrine tumors of the pancreas and periampullary region. Hematol Oncol Clin N Am 2007; 21: 457-73.
4. Öberg K, Eriksson B. Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterology 2005; 19: 753-81.
5. Strauss LG, Conti PS. The application of PET in clinical oncology. J Nucl Med 1991; 32: 623-48.
6. Eriksson B, Bergström M, Sundin A, et al. The role of PET in localization of neuroendocrine and adrenocortical tumors. Ann N Y Acad Sci 2002; 970: 159-69.
7. Kaltsas G, Mukherjee JJ, Plowman PN, Grossman AB. The role of chemotherapy in the nonsurgical management of malignant neuroendocrine tumours. Clin Endocrinol 2001; 55: 575-87.
8. Arnold R, Rinke A, Schmidt Ch, Hofbauer L. Chemotherapy. Best Pract Res Clin Gastroenterol 2005; 19: 649-56.
9. Cancer Incidence in Five Continents Vol. VIII. IARC Scientific Publication No. 155. http://www.iarc.fr/en/Publications/PDFs-on line/Cancer-Epidemiology

10. Kadınlarda ve Erkeklerde En Çok Görülen Kanser Türü, 1999. http://www.saglik.gov.tr
11. Prommegger R, Ensinger C, Steiner P, et al. Neuroendocrine tumors and second primary malignancy- a relationship with clinical impact? Anticancer Res 2004; 24: 1049-51.
12. Lotlikar U, Fogler R, Novetsky AD, Yoon NY. Concurrent colonic carcinoma and small-bowel carcinoid tumor. Case reports and review of the literature. Dis Colon Rectum 1982; 25: 375-82.
13. Rivadeneira DE, Tuckson WB, Naab T. Increased incidence of second primary malignancy in patients with carcinoid tumors: case report and literature review. J Natl Med Assoc 1996; 88: 310-2.
14. Tse V, Lochhead A, Adams W, Tindal D. Concurrent colonic adenocarcinoma and two ileal carcinoids in a 72-year-old male. Aust N Z J Surg 1997; 67: 739-41.
15. Chemli S, Dhouib RS, Mrad K, et al. Synchronous association of ileal carcinoid and colorectal carcinoma. A case report. Tunis Med 2007; 85: 607-9.
16. Tichansky DS, Cagir B, Borrazzo E, et al. Risk of second cancers in patients with colorectal carcinoids. Dis Colon Rectum 2002; 45: 91-7.
17. Gerstle JT, Kauffman GL, Koltun WA. The incidence, management, and outcome of patients with gastrointestinal carcinoids and second primary malignancies. J Am Coll Surg 1995; 180: 427-32.
18. Barakat MT, Meeran K, Bloom SR. Neuroendocrine tumours. Endocr Relat Cancer 2004; 11: 1-18.
19. Jensen RT. Pancreatic endocrine tumors: recent advances. Ann Oncology 1999; 10 (Suppl): 170-6.
20. Ricke J, Klose KJ, Mignon M, et al. Standardisation of imaging in neuroendocrine tumours: result of a European delphi process. Eur J Radiol 2001; 37: 8-17.
21. Orlefors H, Sundin A, Garske U, et al. Whole-body 11C-HTP-PET as a general imaging technique for detection of neuroendocrine tumors - a comparison with somatostatin receptor scintigraphy and computer tomography. J Clin Endocrinol Metab 2005; 90: 3392-400.
22. Nowicki K, Adamczyk B, Stachowiak M. A case of patient with insulinoma of the pancreas and inflammatory tumor of the sigmoid colon - one-step operation treatment. Przegl Lek 2004; 61: 1452-4.
23. Aszodi A, Leeming RA, Lash RH, et al. Giant nonfunctioning islet cell tumor requiring pancreaticoduodenectomy and complete liver revascularization. J Surg Oncol 1993; 53: 273-6.
24. Plöckinger U, Rindi G, Arnold R, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. Neuroendocrinology 2004; 80: 394-424.
25. Arnold R, Simon B, Wied M. Treatment of neuroendocrine GEP tumours with somatostatin analogues. Digestion 2000; 62(Suppl 1): 84-91.
26. Öberg K. Interferon in the management of neuroendocrine GEP-tumors. Digestion 2000; 62(Suppl 1): 92-7.
27. Faiss S, Pape UF, Bohmig M, et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors—the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol 2003; 21: 2689-96.
28. Fjallskog ML, Sundin A, Westlin JE, et al. Treatment of malignant endocrine pancreatic tumors with a combination of α-interferon and somatostatin analogs. Med Oncol 2002; 19: 35-42.
29. Rivera E, Ajani JA. Doxorubicin, streptozocin, and 5-fluorouracil chemotherapy for patients with metastatic islet-cell carcinoma. Am J Clin Oncol 1998; 21: 36-8.
30. Kouvaraki M, Ajani J, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004; 22: 4762-71.
31. Gonzalez MA, Biswas S, Clifton L, Corrie PG. Treatment of neuroendocrine tumours with infusional 5-fluorouracil, folinic acid and streptozocin. Br J Cancer 2003; 89: 455-6.
32. Yao JC. Molecular targeted therapy for carcinoid and islet-cell carcinoma. Best Pract Res Clin Endocrinol Metab 2007; 21: 163-72.