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ORIGINAL PAPER

Retrospective analysis of seventy-one patients with neuroendocrine tumor and review of the literature

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Abstract Neuroendocrine tumors (NET) are rare, but their incidence is gradually increasing. In this study, demographical and tumor characteristics, treatment modalities, responses, and survival rates were evaluated in the patients with NET. Seventy-one patients with NET from 3 tertiary care centers evaluated retrospectively. Overall survival (OS), progression-free survival (PFS), and disease-free survival rates were estimated by Kaplan–Meier Method. Male/female ratio was 0.86 (33/38). Median age was 52 years. Rates for family cancer history and goiter/thyroiditis were 22.4 and 17.8%, respectively. The most common primary site was lung (22.5%), in parallel with the literature, and 31% had the large cell neuroendocrine carcinoma histology. The second most common site was stomach. Carcinoid syndrome rate was found to be 30.6%. Half of the patients were in early stage at diagnosis. Surgical resection rate was 64.7, and 45% of the patient received chemotherapy (CT), 22% received radiotherapy. Seventy-six percent of resected patients had local disease. Thirty-two patients received CT for palliation or concurrent with radiotherapy or in adjuvant setting. Platin/etoposide combination was the most commonly used chemotherapy regimen. Chemotherapy response rate was 35.7%. Five patients had received somatostatin analogue. Radiotherapy was used in adjuvant setting in one-third of the patients. Median OS was 66 months, and median PFS was 30 months. Female gender and fifth decade seem to have higher risk. History for family cancer and goiter/thyroiditis was high in the patients with NET, though there is no data about an association between NET and thyroid disorders in the literature.

Keywords Neuroendocrine carcinoma · Carcinoid tumor · Neuroendocrine tumor · Treatment

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Introduction

Carcinoid tumor was reported first time in two autopsy cases with multiple tumors in distal ileum in 1888 by Lubarsch. Later, Oberndorfer used carcinoid term ["karzinoide" ("carcinoma like")] in 1907 [1, 2].

Neuroendocrine tumors (NET) are rare tumors, which are originated from neuroendocrine cells with an incidence of 5.25/100,000 in the United States. Its incidence has been reported to be increased in the last few decades ($P < 0.001$). In this review, the most common sites were lung for Caucasians and rectum for others [1].

Inactivation of the "Multiple endocrine neoplasia type 1" (MEN-1) gene, a tumor suppressor gene located on 11q13 gene locus, is related to the loss of heterozygosity (LOH) 11q13 and supposed to be responsible for NET carcinogenesis [3]. Lung carcinoid tumors are rare in MEN syndromes, but allele deletions on MEN-1 gene locus may be involving in carcinogenesis of lung carcinoid tumors [4]. It is also reported that LOH in chromosome 11 may be

related to sporadic lung carcinoid tumors [4, 5]. The rate of MEN-1 gene mutation is 40% in sporadic pancreatic endocrine tumors [6]. "β-catenin" mutation and p16 metilation are reported to be prominent in gastrointestinal endocrine tumors [7].

Patients and methods

Between 1997 and 2008, seventy-one patients with NET who were diagnosed or treated in three different tertiary care oncology centers were enrolled to the study. The patients are evaluated retrospectively for demographical and tumor characteristics, second primary cancers, family history for cancer, goiter/thyroiditis, treatment modalities with response rates and survival.

Survival rates were calculated by "Kaplan–Meier" Method. Overall survival (OS) was defined as the interval between the beginning of the treatment and date of death or last known alive. Progression-free survival (PFS) was defined as the interval between the beginning of treatment and progression of the disease in patients who had metastatic or locally advanced disease. Disease-free survival (DFS) was defined as the interval between the beginning of the treatment and relapse in patients who underwent surgical resection.

Results

Patient characteristics

Male-to-female ratio was 0.86 (33/38). The patient characteristics are summarized in Table 1. The diagnosis peak was in the fifth decade, and the most common site was lung, in parallel with the literature.

Table 1 Patient characteristics

Median age (range), year	52 (18–85)
Gender	
Male/female	33/38
Early stage, %	50.7
Advanced disease[a],%	49.3
Primary tumor localizations, %	
Lung	22.5
Gastric	21.1
Pancreatic	12.7
Others[b]	43.7

[a] Locally advanced disease (11.3%), stage IV (38%)

[b] Cancer with primary unknown (17%), small intestine (11.3%), colorectal (5.6%), appendix (2.8%), surrenal (1.4%), timus (1.4%), bladder (1.4%), ovary (1.4%), endometrium (1.4%)

Thyroid disorders and family cancer history

Goiter or thyroiditis history incidence was 17.8, and 22.4% of the patients had family history for cancer. Unfortunately, we could not find information about anti-thyroid antibodies in this retrospective evaluation. A 47-year-old female patient who had NET in cecum had both multinodular goiter and family history for cancer. Her father and aunt had colon cancer.

NET as second primary cancer

None of the patients had synchronous second primary cancer, but three of them had NET as metachronous second primary cancer. A 65-year-old male patient with lung large cell neuroendocrine carcinoma (LCNEC) had been treated for thymoma 8 years ago. Another 61-year-old female patient with gastric NET had breast carcinoma 15 years ago. Finally, a 51-year-old male patient with NET metastasis in liver had renal cell carcinoma 8 years ago. They were all in complete remission for primary cancers.

Carcinoid syndrome

Carcinoid syndrome rate was found to be 30.6%. The most common symptoms were flushing (33.3%) and diarrhea (33.3%).

Surgical procedures

We found that 36 (50.7%) patients had local disease, 27 (38%) had metastatic disease, and 8 (11.3%) had locally advanced disease at diagnosis. Tissue biopsy was the diagnostic method in 85.9% of the patients. Forty-six (64.7%) patients underwent surgical resection. Surgical procedures are summarized in Table 2.

Chemotherapy (CT)

One patient with local gastric NET had been treated by chemotherapy only. Of the 35 patients with resected local disease, 6 had adjuvant CT, 3 had adjuvant chemo-radiotherapy (CRT), one had adjuvant radiotherapy (RT), and another one had somatostatin analogue (SST) in the postoperative period. Most of the patients who received

Table 2 Surgical procedures

Surgery (*n*)	46
Curative surgery	38
Palliative surgery	3
Surgery for metastasis	5

Table 3 Chemotherapy regimens

Chemotherapy (*n*)	32
Adjuvant chemotherapy[a]	8
Adjuvant chemoradiotherapy	3
Chemoradiotherapy[b]	2
Palliative chemotherapy	19
Platin-based chemotherapy (*n*)	28
Platin (P)[c] – Etoposide (E)	19
Cisplatin/5-fluorouracil	3
Cisplatin/gemcitabine	2
Cisplatin/vinorelbine	1
Cisplatin/cyclophosphamide	1
Cisplatin/etoposide/doxorubicin/mitotane	1
Cisplatin/doxorubicin/5-fluorouracil	1
Non-platin chemotherapy (*n*)	4
5-Fluorouracil/leucovorin	2
Cyclophosphamide/doxorubicin/vincristine[d]	2

[a] Timic NET, adjuvant cyclophosphamide/doxorubicin/vincristine with SST analogue (*n*:1)

[b] Lung NET with locally advanced stage

[c] Carboplatin/etoposide (*n*:3)

[d] Chemotherapy with SST analogue (*n*:1)

adjuvant CT had gastric and pancreatic NET (33.3, 33.3%, respectively). Half of the remaining patients had rectal, and the other half had intestinal NET. A patient with locally advanced thymic NET has received adjuvant CT [cyclophosphamide, doxorubicin, vincristine (CAV)] and SST analogue. He was still alive with 4 months of PFS. Two patients had SST analogue without CT.

The CT regimens are summarized in Table 3. The CT rate in all of the patients was 45% ($n = 32$). One of them had adjuvant CT with SST analogue, and another with local disease had only CT, as it was mentioned before. Chemotherapy was given as adjuvant CT, adjuvant CRT, concomitant CRT for locally advanced disease, and palliative CT for 7, 3, 2, and 18 patients, respectively. One of the patients who received adjuvant CT or CRT relapsed with a DFS of 11 months, whereas others did not. Partial remission was achieved only with platin and etoposide regimen. Response rate with CT was 35.7%, and there was no complete remission. Both patients who received concomitant CRT had stable disease. The most commonly used CT regimen consisted of platin and etoposide. The rate of platin-based CT regimens was 87.5% for all of the patients who received CT. The rates for non-platin regimens were estimated as 50% for 5-fluorouracil (FUFA), 25% for CAV, and 25% for CAV with SST analogue. Carboplatin has been given to 15.7% of the patients receiving platin and etoposide. Cisplatin and etoposide were preferred in 83.3% of the patients who treated by only adjuvant CT. The others received FU/FA in this group.

Somatostatin (SST) analogues

Five patients had received SST analogues. Three of them had SST analogue after operation, and one of them had SST analogue with CT. Other two patients had only SST analogue. Three of these patients had carcinoid syndrome.

Radiotherapy (RT)

Radiotherapy is used for 22.2% of all the patients. One-third of these patients received adjuvant RT. Some of the patients (8.3%) received RT for both primary site at diagnosis and relapsed site after relapse. In RT group, 41.7% of the patients had local disease, 33.3% had locally advanced disease, and 25% had metastatic disease. Two-third of the patients who received RT for metastatic disease received palliative RT at diagnosis, and one-third received palliative RT after disease progression.

Sixteen patients (22.5%) had lung NET, and 5 (31.2%) of them had lung LCNEC. Six patients had local disease, 5 had locally advanced disease, and 5 had metastatic disease. Rate of RT was 46.6% in lung LCNEC. It was determined that 14.2% of them had RT at both diagnosis and relapse, and 14.2% had RT only at relapse. A patient with lung LCNEC had been applied adjuvant RT and 4 cycles of CT (cisplatin, vinorelbine), and he is still alive with 4 years of DFS. Partial remission has been achieved in three patients with cisplatin and etoposide. One of these patients died because of disease progression after 10 months, and other two patients are followed-up without disease progression. Another patient with lung LCNEC had been applied concomitant CRT (RT with gemcitabine and cisplatin) for locally advanced disease. He had stable disease with 6 months of PFS.

Survival

Median OS was 66 months for all of the patients (Fig. 1). Median PFS was 30 months in patients with advanced disease. However, median DFS could not have been reached for others who had been treated for early-stage disease at diagnosis (Figs. 2, 3).

Discussion

Carcinoid tumors are diagnosed in 1/300 of appendectomies and 1/2,500 of proctoscopies [8]. It is known that NET has a slowly growing pattern. It has been reported that lung is the most common site for NET, and gastric NET has been increased threefold while appendical NET has been decreased more than 16-fold in recent years [8]. Lung was also the most common site in our patients, as it was

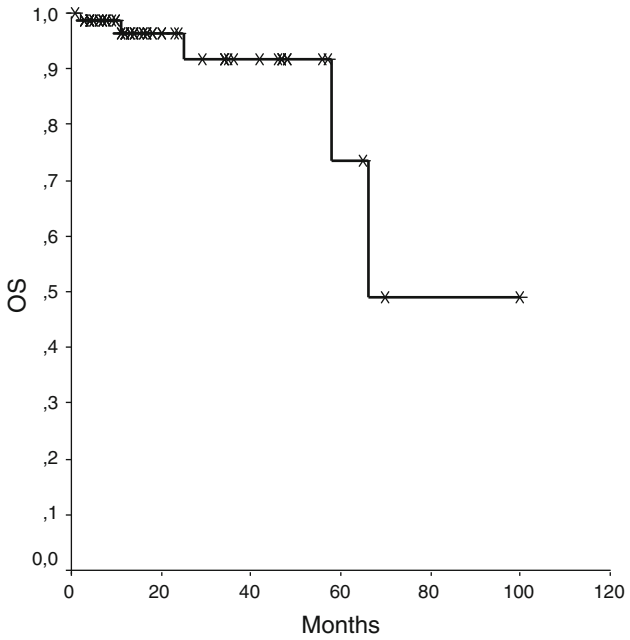

Fig. 1 Overall survival (OS) curve for all patients

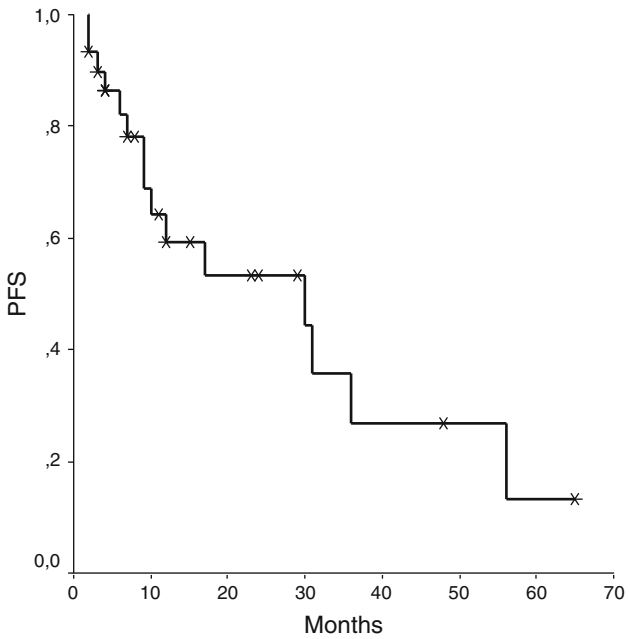

Fig. 2 Progression-free survival (PFS) curve in patients with advanced disease

discussed before. More than half of our patients had metastatic disease at diagnosis. We considered that it might have been associated with long asymptomatic period because of slowly growing pattern.

It was conspicuous that three patients had NET while they were in complete remission for their first primary

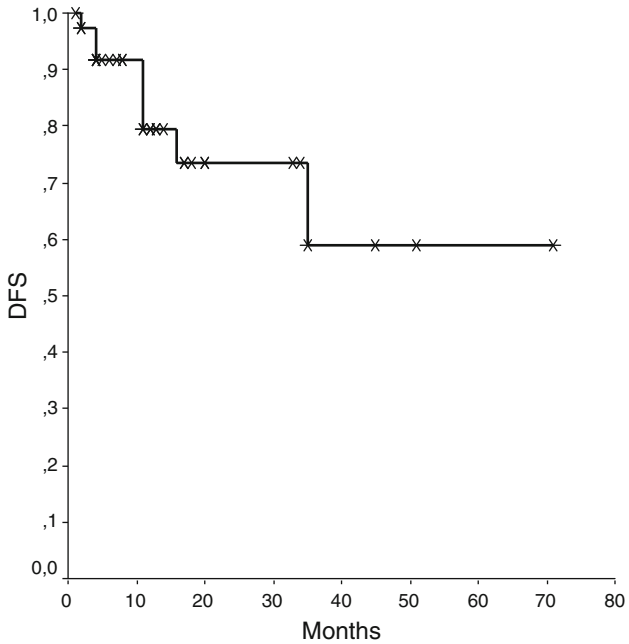

Fig. 3 Disease-free survival (DFS) curve (in patients with resected tumor)

cancers. One of them had thymoma 6 years before the diagnosis of NET. It is well known that thymoma is a tumor that has neuroendocrine differentiation. The patients with cancer should be followed-up more closely for synchronous or metachronous second primary cancers. If first primary is a tumor with neuroendocrine differentiation, NET might arise as a second primary cancer, like other cancer types, even after many years. There is no data about relationship between NET and thyroid disorders. However, 17.8% of our patients had synchronous goiter/thyroiditis. Cancer risk is higher in some autoimmune diseases, such as lymphoma in Hashimoto thyroiditis and Sjogren's syndrome. It is not known whether autoimmune mechanisms also contribute to NET or not. It would have been better if thyroid autoantibodies had been evaluated. We believe that it should be investigated with further trials whether there is an association between NET and thyroid diseases, especially autoimmune disorders. Soga et al. [9] reported carcinoid syndrome rate as 7.7% after 49-year follow-up of 11,842 patients, and they emphasized that the rate was higher (28.8%) in 1960's than last years. The rate was almost higher (30.6%) in our patients.

Differentiation degree has importance in NET prognosis [10]. Median survival rate is better in well-differentiated local disease [1]. Primary tumor size and invasion depth correlated with locoregional dissemination and distant metastasis in a retrospective analysis of 1,102 intestinal carcinoid tumors [11]. In this study, 5-year OS rate was significantly higher in non-metastatic patients (90% vs. 68%).

Lung NET is classified as typical carcinoid tumor (low grade), atypical carcinoid tumor (moderately grade), LCNEC (high grade), and small cell carcinoma according to WHO classification [12]. Asamura et al. [13] reported that high grade was an independent prognostic factor, and 44% of 318 patients with lung NET were LCNEC in a retrospective trial. In our study, most of lung NETs was LCNEC. It was reported that neither lymph node status nor pathological characteristics with molecular changes had affected survival, with a 1-year OS rate of 27%, in a retrospective study including 18 operated lung LCNEC patients [14].

Surgery is the main therapy for local disease. A multidisciplinary approach including surgery, CT, RT, chemoembolization, and SST analogues should be considered, and the treatment should be individualized for the patients with NET.

Expression of somatostatin receptors in majority of NETs leads use of SST analogues in treatment. SST analogues are effective via somatostatin receptors (SR), especially SR-2 and SR-5. They not only inhibit tumor growth but also contribute to symptomatic control, especially in patients with carcinoid syndrome. Radionuclide therapy may be applied in selected patients, according to octreotide scintigraphy. SST analogues that are labeled with radioactive agents, like I^{121}, I^{131}, lutetium^{177}, and DOTA, are used for both diagnosis and treatment [15].

Interferon might up-regulate SRs. Response rates with interferon are around 10–20% [16, 17]. None of our patients had been applied interferon as first-line therapy, and 2 patients had interferon as second-line therapy after failure with cisplatin/5FU and cisplatin/doxorubicin/5FU in our study.

Response rates with CT are 20–67% in the literature [18, 19]. Our response rate with CT was 35.7% that is similar to the literature. Cisplatin and etoposide regimen seems to be more effective than others are. In our study, the most frequent treatment modality was surgery, followed by CT. Platin-based CT was most common in our patients with predominance of cisplatin and etoposide. It was conspicuous that the rate of SST analogue use was lower than CT in our patients. Including patients in early 2000s and even before 2000 might have contributed to the lower rate of SST analogue use in this study.

There are phase II trials about novel therapeutics, such as taxane, temozolamide, thalidomide, and targetted therapies, like bevacizumab, sunitinib, and everolimus [20–24]. However, these agents seem to be more toxic, especially in terms of hematologic toxicities, besides their higher costs. It has been demonstrated that both chromogranin A secretion and proliferation of tumor cells are inhibited via activation of "Notch-1" pathway by histone deacetylase inhibitors, such as valproic acid and suberoyl bishydraxamic acid, and also by lithium via inhibition of glycogen synthase kinase-3 beta in carcinoid cell lines [25]. However, we need further trials about these agents.

We consider that pharmacogenetic trials might contribute to the best-tailored therapy with better clinical outcome and lower toxicity. Pharmacogenetic analysis will also lead a cost-effective treatment by avoiding unnecessary treatment modalities.

In conclusion, female gender and the fifth decade seem to have higher risk. We consider that there may be a relationship between thyroid disorders, maybe autoimmune diseases, and NET because of co-incidence of goiter/thyroiditis with a rate of 17.8%. However, association should be evaluated in further trials including analysis of thyroid autoantibodies. A multidisciplinary approach should be considered, and therapy should be individualized. SST analogues and radionuclide therapy should be applied to the patients who have positive uptake in octreotide scintigraphy, and SST analogues can be given to the patients with carcinoid syndrome for symptomatic relief. Operable patients should be operated, and selected patients might have adjuvant CT and/or RT. We need further trials to evaluate the efficacy of adjuvant therapy, especially RT. Platin-based CT seems to be effective. Cost effectivity and higher toxicity rates should be kept in mind while considering novel therapeutics.

References

1. Yao JC, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35, 825 cases in the United States. J Clin Oncol. 2008;26:3063–72.
2. Matthew HK, Mayer RJ. Carcinoid tumors. N Engl J Med. 1999; 340:858–68.
3. Larsson C, Skogseid B, Oberg K, Nakamura Y, Nordenskjold M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. Nature. 1988;332:85–7.
4. Debelenko LV, et al. Identification of MEN-1 gene mutations in sporadic carcinoid tumors of the lung. Hum Mol Genet. 1997;6: 2285–90.
5. Jakobovitz O, et al. Carcinoid tumors frequently display genetic abnormalities involving chromosome 11. J Clin Endocrinol Metab. 1996;81:3164–7.
6. Klöppel G, Peren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. Ann N Y Acad Sci. 2004;1014:13–27.
7. Peren A, Komminoth P, Heitz PU. Molecular Genetics of Gastroenteropancreatic endocrine tumors. Ann N Y Acad Sci. 2004; 1014:199–208.
8. Doherty GM. Carcinoid tumors and the carcinoid syndrome. In: De Vita Jr VT, Hellman TS, Rosenberg SA, editors. Cancer principles and practice of oncology. 8th ed. Philedelphia: Lippincott Williams & Wilkins; 2008. p. 1721–4.
9. Soga J. Carcinoids, their variant endocrinomas. An analysis of 11842 reported cases. J Exp Clin Cancer Res. 2003;22:517–30.
10. Solcia E, et al. Clinicopathological profile as a basis for classification of the endocrine tumors of the gastroenteropancreatic tract. Ann Oncol. 1999;10(suppl 2):S9–15.

11. Soga J. Carcinoids of the small intestine: a statistical evaluation of 1,102 cases collected from the literature. J Exp Clin Cancer Res. 1997;16:353–63.
12. Rekhtman N. Neuroendocrine tumors of the lung: an update. Arch Pathol Lab Med. 2010;134:1628–38.
13. Asamura H, et al. Neuroendocrine neoplasms of the lung: a prognostic spectrum. J Clin Oncol. 2006;24:70–6.
14. Mazières J, et al. Large cell neuroendocrine carcinoma of the lung: pathological study and clinical outcome of 18 resected cases. Lung Cancer. 2002;37:287–92.
15. de Araújo EB, et al. A comparative study of 131I and 177Lu labeled somatostatin analogues for therapy of neuroendocrine tumours. Appl Radiat Isot. 2009;67:227–33. [Epub 2008 Oct 5].
16. Oberg K. Interferon in the management of neuroendocrine GEP-tumors: a review. Digestion. 2000;62:92–7.
17. Moertel CG, Rubin J, Kvols LK. Therapy of metastatic carcinoid tumor and the malignant carcinoid syndrome with recombinant leukocyte A interferon. J Clin Oncol. 1989;7:865–8.
18. Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cis-platin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer. 1991;68:227–32.
19. Engstrom PF, Lavin PT, Moertel CG, Folsch E, Douglass HO Jr. Streptozocin plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. J Clin Oncol. 1984;2:1255–9.
20. Hainsworth JD, Spigel DR, Litchy S, Greco FA. Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine carcinoma: a Minnie Pearl Cancer Research Network Study. J Clin Oncol. 2006;24:3548–54.
21. Kulke MH, et al. Phase II study of temozolamide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol. 2006;24:401–6.
22. Yao JC, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. J Clin Oncol. 2008;26:1316–23.
23. Kulke MH, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol. 2008;26:3403–10.
24. Yao JC, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low-to intermediate-grade neuroendocrine tumors: results of a phase II study. J Clin Oncol. 2008;26:4311–8.
25. Adler JT, Hottinger DG, Kunnimalaiyaan M, Chen H. Combination therapy with histone deacetylase inhibitors and lithium chloride: a novel treatment for carcinoid tumors. Ann Surg Oncol. 2009;16:481–6.