Published in final edited form as:

Surgery. 2016 January ; 159(1): 350–356. doi:10.1016/j.surg.2015.05.041.

Prospective evaluation and treatment of familial carcinoid small intestine neuroendocrine tumors (SI-NETs)

Marybeth S. Hughes, MD, FACS^a, Saïd C. Azoury, MD^a, Yasmine Assadipour, MD^a, David M. Straughan, MD^a, Apurva N. Trivedi, MD^b, Ramona M. Lim, MD^b, Grishma Joy, MD^b, Mark T. Voellinger, MD^b, Derek M. Tang, MD^b, Aradhana M. Venkatesan, MD^c, Clara C. Chen, MD^c, Adeline Louie, MD^c, Martha M. Quezado, MD^d, Joanne Forbes, MS, CRNP^b, and Stephen A. Wank, MD^b

^aThoracic and Gastrointestinal Oncology Branch, Bethesda, MD

^bNational Cancer Institute, Digestive Diseases Branch, Bethesda, MD

^cNational Institute of Diabetes, Kidney and Digestive Diseases, Radiology and Imaging Sciences, Bethesda, MD

^dLaboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD

Abstract

Background—The aim of this study was to prospectively screen patients with a positive family history of carcinoid small intestine neuroendocrine tumors (SI-NETs) to elucidate the benefits of early detection and operative intervention.

Methods—A single-center, prospective trial was conducted from 2008 to 2014 that evaluated patients with 2 or more blood relatives with carcinoid SI-NETs. All eligible patients were screened with urine/serum biochemistries and various imaging modalities. Operative intervention was elected in patients found to have at least 1 positive diagnostic study.

Results—Twenty-nine patients from 13 families had occult carcinoid SI-NETs (15 female, 14 male). Twenty-four of the 29 patients (83%) had multifocal disease found in either the distal jejunum or ileum. On average, 75.9 cm (range, 13–195) of bowel was resected in 1 segment. Three patients were found to have stage IV disease at operation. All stage I–IIIB patients who had R0 resections have remained disease-free, with a median follow-up of 35 months.

Conclusion—Familial carcinoid SI-NETs often are asymptomatic and can be diagnosed with aggressive screening. With early detection, there may be a window of opportunity for operative resection to change the natural history of this disease and even prove to be curative.

DURING THE PAST SEVERAL DECADES, there has been an increase in the diagnosed incidence of carcinoid tumors.^{1–3} These tumors arise from neuroendocrine cells in the gastrointestinal tract and other organs (eg, bronchopulmonary system).⁴ More than half (50–

Reprint requests: Marybeth S. Hughes, MD, FACS, Surgical Oncology Research Fellowship Program Director, Thoracic and GI Oncology Branch, Center for Cancer Research National Cancer Institute, National Institutes of Health, 10 Center Drive, MSC1201, RM 4W-5940, Bethesda, MD 20892-1201. hughesm@mail.nih.gov.

Presented at the conference of the American Association of Endocrine Surgeons, May 17–19, 2015, Nashville, TN.

71.4%) of these tumors are found within the gastrointestinal tract, where they are located predominately in the small bowel (24–44%).^{1,2,5,6} Carcinoid tumors are the most common of the small intestine neuroendocrine tumors (SI-NETS).⁵ Analysis of trends during the last decade indicates that the average incidence of small bowel carcinoid is 1 case per 100,000 per year.² Within the small bowel, the majority are discovered in the ileum, followed by the jejunum and duodenum in decreasing incidence.¹

Despite improved diagnostic capabilities, early detection remains challenging, because carcinoid tumors most often are indolent and asymptomatic at early stages and go undiagnosed for years.⁴ These tumors are often discovered incidentally during an operation for a separate pathology/insult or at autopsy.⁵ Primary carcinoid SI-NETS are submucosal in location and often less than a centimeter in size, hence they frequently are diagnosed only after metastasis and lymph node involvement.^{2,5} Compared with other gastrointestinal sites, small bowel carcinoids have a greater rate of metastasis and a poorer prognosis.^{2,7} Production of biologically active molecules leads to carcinoid syndrome in fewer than 20% of patients.² Characteristic symptoms of carcinoid syndrome include bronchoconstriction, diarrhea, and flushing; these clinical manifestations typically signify liver metastasis.⁸

Wide resection of the primary carcinoid SI-NETS with regional lymph nodes has been the standard of care for many years.^{5,9} Although most gastrointestinal carcinoids are sporadic, previous retrospective studies indicate that carcinoid SI-NETS may occur at an increased incidence in patients with a positive family history.^{10–12}

Recently, we demonstrated that familial carcinoid is similar to sporadic disease except for the presence of multiple primary tumors and can occur on a hereditary basis with an autosomal-dominant inheritance.¹³ Accordingly, the aim of this study is to prospectively screen asymptomatic relatives of patients with a family history of carcinoid SI-NETS to try to elucidate any benefits of early detection and operative intervention.

METHODS

Approval of the study was granted by the Institutional Review Board of the National Institute of Diabetes, Digestive and Kidney Disease and registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00646022) (NCT00646022). All patients provided informed consent for participation in the study. A single-center, prospective trial was conducted from 2008 to 2014 at the National Institutes of Health Clinical Research Center.

Included in this study were asymptomatic patients >18 years of age with 2 or more blood relatives diagnosed previously with carcinoid SI-NETS. Individuals with a known familial neuroendocrine tumor syndrome, such as multiple endocrine neoplasia type I and II, neurofibromatosis 1, and Von Hippel-Lindau Disease, were excluded from enrollment, as well as women who were pregnant or actively breastfeeding.

Asymptomatic relatives underwent a medical evaluation every 2 years during a 3- to 5-day hospital stay at the National Institutes of Health clinical center. Evaluation included a thorough history and physical examination and biochemical analyses, including a 24-hour urine 5-hydroxyindoleacetic acid, and serum levels of serotonin and chromogranin A. The

presence of occult tumor was assessed by esophagogastroduodenoscopy, colonoscopy with ileoscopy, computed tomography (CT) of the chest, abdomen, and pelvis with intravenous contrast and oral Volumen (E-Z-EM, Inc, Quebec, Canada; for enterography), capsule endoscopy, and 18-fluorodopa (F-DOPA) positron emission tomography (PET)/CT (Figure 1).

Demographics and operative factors including sex, age, body mass index (kg/m^2), American Society of Anesthesiologists class, site of tumor, tumor stage, and operative treatment also were recorded. The date of diagnosis, type of operative intervention, and last follow-up clinical examination were noted. Operative intervention was elected in patients found to have at least 1 positive diagnostic study. Any suspicious abnormalities observed intraoperatively were biopsied and sent for pathologic evaluation and staging purposes. Details specific to each case were documented, including the number of bowel tumors, the size of the largest tumor, and the site (ie, jejunum, ileum, or jejunum–ileum).

Operative technique

A mini-midline celiotomy was performed through a 5-cm incision to gain access into the abdominal cavity. The abdomen was explored fully to assess for carcinomatosis and/or disease not imaged, after which an ultrasonography evaluation of the liver was performed. The small intestine was evaluated from the ligament of Treitz to the ileocecal valve, and a silk suture was placed on the serosa to tag any suspicious lesion palpated (Fig 2, B). Similarly, the colon, appendix, and pelvic organs were evaluated for masses. Any suspicious abnormalities observed intraoperatively were biopsied and sent for pathologic evaluation and staging purposes. After full exploration, a segmental resection of the tumor-bearing segment of the small bowel was performed, ensuring at least a 5-cm negative margin, proximally, and distally. The draining mesentery and associated lymph nodes were removed en bloc. Additionally, care was taken to remove all of the grossly abnormal or enlarged lymph nodes along the SMA. All postoperative complications documented in the surgical and medical records were noted.

Pathology

Hematoxylin and eosin stains and immunohistochemistry (for chromogranin A, Ki-67 [MIB-1], serotonin, and synaptophysin) were performed on all tumor samples. Final pathology reports were reviewed to document the TNM staging, number of positive lymph nodes, tumor grade, and length of small intestine resection.

Follow-up

Patients had a postoperative clinical assessment and a 3-month postoperative baseline evaluation with urine/serum biochemistries, a CT scan, magnetic resonance imaging of the liver, and 18F-DOPA PET/CT. Patients were then evaluated at 6-month intervals for 2 years and yearly thereafter in the same manner. Disease status duration from the time of operation was defined at the last follow-up visit for the absence, persistence, or recurrence of tumor. Asymptomatic family members who demonstrated no evidence of disease were followed biennially with repeat imaging and laboratory work.

RESULTS

Demographics and operative findings

A total of 129 asymptomatic patients from 13 families were screened, 111 of whom were 40 years of age or older. In total, 36 asymptomatic patients from 13 families with at least 2 pre-existing cases of SI-NETs per family had at least one biochemical or imaging test suggestive of SI-NET and were recommended for operative exploration. Thirty-two consented and underwent a mini-laparotomy, 28 at the National Institutes of Health Clinical Research Center by a single surgeon and 4 at outside institutions by 2 different surgeons. Tumor was detected in 29 asymptomatic relatives, with an average age of (mean $\pm$ SD) 58 ± 9 years. The patients were of equal sex (female, $n = 15$, 51.7%), and majority were American Society of Anesthesiologists class III ($n = 21$, 72%) (Table I). Three patients who were negative for SI-NET at operation were found to have lymphangectasias, lymphangiomas, or lymphoid hyperplasia of Peyer's patches on pathology. Preoperative chromogranin A levels were within the normal range for all patients included in the study and remained normal at follow-up visits after resection. Of the 29 patients with carcinoid SI-NETs, 26 patients had their disease detected on initial screening, and three were detected on subsequent screen 2–4 years later.

Twenty-four of the 29 patients (83%) had multifocal disease found in either the distal jejunum or ileum. In every case, all tumors were resected in a single small bowel segment. The average length of resection was 76 ± 43 cm. The median number of tumors in each resected segment was 4 (range, 1–29), with an average size of 9 ± 6 mm for the largest tumor. The majority of tumors were located in the ileum ($n = 16$, 55%), followed by the jejunum ($n = 7$, 24.1%), and jejunum/ileum ($n = 6$, 20.6%) in decreasing order. Two patients were found to have metastases to the liver (Table II). Median blood loss per case was 50 mL (range, 10–100), and no blood transfusions were required perioperatively.

Pathologic evaluation and follow-up

Surgical specimens were verified histologically to be SI-NETS. All but 1 patient had grade 1 disease; Ki67 index was $<2\%$ and a mitotic count <2 per 2 mm^2 (10 high-power fields, HPF, $40\times$ magnification) for these patients. The one patient with grade 2 disease had a Ki67 of 3% and a mitotic index of 3 per 2 mm^2 .² An average of >15 lymph nodes were resected per case. On pathologic review, 9 patients (31.0%) were stage I, 6 (20.6%) were stage IIA, 1 (3.4%) was stage IIB, 10 (34.5%) were stage IIIB, and 3 (10.3%) were stage IV (Table II).

Median duration of follow-up for the cohort was 35 months. All stage I-IIIB patients ($n = 25$) who had complete resections (confirmed by postoperative imaging that was negative) have remained disease-free. One patient had multiple small bowel lesions noted on preoperative workup and what appeared to be mesenteric lymph node involvement on imaging (Stage IIIB); intraoperatively this patient had nodal disease and 8 small bowel tumors. A thorough operative evaluation and adequate resection was performed; however, on postoperative imaging, this patient was found to have an ^{18}F -DOPA PET/CT positive deep mesenteric lymph node. She has been followed for 64 months since her operation, and her disease has been stable, with no evidence of additional or metastatic disease. Two patients

with stage IV disease have developed hepatic progression on follow-up imaging. A third patient with stage IIIB pathology had preoperative imaging suggesting stage IV disease in the retroperitoneum, mesentery, periaortic, and supraclavicular regions but no evidence of hepatic disease. Intraoperatively, an extensive regional and site-specific lymphadenectomy was performed, including the removal of a supraclavicular node that was negative for tumor; on last follow-up (35 months postoperatively), this patient had progressive lesions identified on imaging in the mesentery, periaortic, and supraclavicular regions, but no disease in the liver. The aforementioned patients with recurrent/persistent disease have been treated with a long-acting somatostatin postoperatively.

There were no mortalities observed or reported within the study period. There were no surgical site occurrences postoperatively nor any infectious, renal, cardiovascular or hemorrhagic complications. One patient experienced prolonged ileus and delayed return of bowel function, which necessitated nasogastric tube insertion on postoperative day 7. This patient had return of bowel function within 48 hours of tube insertion and was discharged on postoperative day 11 in good condition. Four patients (14%) developed *Clostridium difficile* colitis that resolved after a standard antibiotic course. These patients received the same type and 24-hour course of perioperative prophylactic antibiotics as those who did have this infection. Furthermore, the hospital course of these 4 patients did not overlap and hence we do not believe that this was a result of infectious spread between the patients, and the exact reason for these occurrences is unknown.

DISCUSSION

The screening performed in this study was able to identify carcinoid SI-NETs in 29 asymptomatic relatives from 13 families with a history of carcinoid SI-NET. Of these patients, 16 (55%) had local Stage I or II disease, 10 (34%) had regional stage IIIB disease, but 3 (10%) had distal metastatic Stage IV disease. All patients with locoregional disease have remained disease-free since resection with a median follow-up of 35 months. Our outcomes are in stark contrast to the typical presentation of carcinoid SI-NETs, in which only 29% of SI-NETS in the jejunum or ileum presented with localized disease, 41% had regional disease, and 30% had distant metastases.³ Survival of SI-NETS decreases drastically as the disease spreads, with 100%, 91%, and 50–78% 5-year survival for local, locoregional, and metastatic disease, respectively.^{3,14} Therefore, screening demonstrated a clinically relevant survival benefit by increasing the number of patients who can be diagnosed and treated at an early stage of disease. Survival also decreases with poorly differentiated histology, regardless of stage.³ All but 1 patient with familial carcinoid SI-NETs in our study had grade 1, well-differentiated tumors and would, therefore, benefit most from diagnosis of early stage disease.

In our early experience, the most valuable imaging studies were 18F-DOPA PET/CT and capsule endoscopy followed by CT. There was not a single test that was positive in all patients. During the course of this investigation, imaging studies evolved in equipment and technique; hence, further investigation is necessary to accumulate sufficient data to evaluate the same imaging modalities to determine their relative sensitivity and specificity before we can recommend a single or ordered group of diagnostic imaging tests.

Patients with metastatic disease have limited options. Although the advent of octreotide has helped improve management of symptoms and decreased the morbidity related to the carcinoid syndrome, there are no conclusive data that somatostatin analogs provide for a duration of disease stabilization, and organ failure is the major cause of mortality. Chemotherapy and radiotherapy have minimal efficacy at the cost of decreased quality of life.¹⁵ Operative resection is the primary treatment modality for carcinoid SI-NETs and has proven beneficial in the setting of both locoregional disease and metastatic spread, both for symptom relief and prolonged overall survival.^{5,16–19}

Strong evidence suggests a genetic cause for many carcinoid SI-NETs.^{10–12,20} There is a high incidence of carcinoid SI-NETs in first-degree relatives of patients with carcinoid SI-NETs. Up to a 30-fold increased risk of concordant carcinoid histology is seen among siblings, and 10-fold increase among parent/child pairs is also observed.¹¹ Using the Swedish Family-Cancer Database, Hiripi et al¹⁰ observed a significantly increased relative risk (RR 4.33) of gastrointestinal carcinoid tumors among individuals with a positive parental history of the disease. Recently, we reported our experience with familial carcinoid SI-NETS, which has demonstrated an autosomal-dominant inheritance pattern, a propensity for multiple synchronous primary tumors, and a well-differentiated histology.¹³

In this experience, more than 80% of patients with familial carcinoid SI-NET had multiple synchronous tumors, many of which were <5 mm in size on pathologic evaluation. Although laparoscopy may provide a better view of the peritoneal surfaces, we performed preferentially an open, mini-midline laparotomy, given the submucosal location and small size of these tumors. We believed that such an approach would provide adequate access for manual palpation of the bowel to help ensure negative resection margins. In each case of our study, all synchronous small bowel tumors were within close proximity to one another, and a single segmental small bowel resection was possible. Because more than one-third of the patients evaluated had stage IIIB or greater disease, the open approach allowed for a thorough ultrasonographic evaluation of the liver, the most frequent distant site of midgut carcinoid metastasis.^{21,22} Wedge resection of liver lesions should be performed with the goal of negative margins.²³ Furthermore, efforts should be made to remove all obvious mesenteric disease, because tumor-induced fibrosis can lead to intestinal obstruction and compression of the mesenteric vessels.²³ Although laparoscopic and other minimally invasive techniques of resection for SI-NETs have been described and demonstrated to be safe, long-term outcomes compared with open techniques are unknown.^{24,25} Additional studies are necessary to determine whether either these approaches is safer or more effective than the other. If proven to be equally effective and as safe as the open approach, laparoscopic resection may have a role for early stage disease.

Our study shows that screening of asymptomatic relatives of families with 2 or more blood relatives with carcinoid SI-NETs can lead to detection of early stage disease. Furthermore, a comprehensive family history should be obtained in all patients, particularly those presenting with multiple tumors. Although the study is limited by the duration of the follow-up period for this slow-growing tumor, our early experience is promising and suggests that asymptomatic members of families affected by carcinoid SI-NETs should be screened so

that operative intervention can offer an opportunity to change the natural history of the disease and even prove to be curative.

DISCUSSION

Dr Martha A. Zeiger (Baltimore, MD) I have no disclosures. I have 2 questions for you. First, how did you get 129 patients who are relatives to undergo all of this screening? It just seems like a formidable task, and what was the denominator of all the relatives of those 13 families that should have been screened? Second, I may have missed it, but I don't think I did. What was the test that was most sensitive and specific, keeping in mind that the National Institutes of Health will do all tests on every patient, but we in the real world want to know what tests we should be using?

Dr Saïd C. Azoury To answer your second question first, the imaging studies are actually part of an ongoing study that we are performing currently. In our early experience, albeit we have small numbers and our experience is still early, our 18F-DOPA PET/CT scan and capsule endoscopy were the most valuable diagnostic studies of this study. However, that, as I mentioned, is part of an ongoing investigation, and we hope to have those results here in the near future. In terms of how we were able to recruit so many members both of the relatives and the members that were part of this study, we are fortunate to be at a place like the National Institutes of Health, which has so many valuable resources. As part of this protocol, I'm very thankful to these patients. We really were able to attract about, as I mentioned, 13 families, of which 29 of those patients were included in this study. Of the actual relatives that were screened, actually, those came from greater than 30 families. Again, I think it's partly just having these resources so accessible at the National Institutes of Health and having so many patients that we owe a lot to for studies like this.

Dr Martha Zeiger Do you happen to know the denominator of the relatives you tried to screen? You said 129 relatives. Do you know how many you attempted to bring in for screening?

Dr Saïd C. Azoury I do not, no.

Dr James R. Howe (Iowa City, IA) I was just curious whether those individuals had other tumors or other disease-specific associations. You mentioned it was autosomal-dominant. I just wanted to hear a little more about that. You had also hinted that a paper recently came out where you might have done exome sequencing and found a mutation in one family. Was that mutation found in the other families?

Dr Saïd C. Azoury With regard to these patients, as part of our exclusion criteria, we excluded patients with a known familial neuroendocrine syndrome, such as neurofibromatosis and Von Hippel-Lindau. These patients were themselves asymptomatic, without any other separate tumor pathologies. Again, these were the main tumors that were found in these patients. With regard to the mutation I mentioned it was autosomal-dominant with incomplete penetrance, and that mutation was only found in one family and was not found in the other families.

Dr Marybeth Hughes (Bethesda, MD) Some of the autosomal-dominant with incomplete penetrance is still being worked out. It's interesting that the way the families distribute, but greater than 50% of the families end up being affected but not everybody in the families are affected. The N for the number of patients that were screened completely for Dr Zeiger is in the 500 range.

Dr Steven K. Libutti (New York, NY) Clearly, a yeoman's effort in terms of screening that number of patients. You've certainly demonstrated that an aggressive screening program will identify these tumors, and then you can make a choice on what you are going to do once you have identified the tumors. One of your conclusions were that you believed this could alter the natural history of the disease. One thing I didn't see in your abstract and I didn't get from your talk is, what is the natural history of the disease for these patients? If these patients are not undergoing operation, because the majority of the lesions you removed are low-grade tumors, what percentage of patients will develop metastatic disease if undiagnosed and untreated? The second question is, you removed a lot of tumors from patients. They range in size, and many of them are small. Do you actually believe that in these patients you operated on, you got every tumor out?

Dr Saïd C. Azoury To address your first question, as I mentioned for how we sort of came up with these patients, each one of these patient has to have had 2 relatives with the disease. As part of the initial protocol, we actually compared these asymptomatic patients with their symptomatic relatives. Within a 5-year period, their symptomatic relatives, greater than 50% of those, went on to succumb to their disease. Again, our results are early and ongoing, but that at least sheds some light that we are screening these patients and detecting disease at an earlier stage. If they were to go on and potentially become symptomatic and present at a later stage of disease, that they would potentially become like their relatives and unfortunately succumb to their disease, as I mentioned.

Dr Steven K. Libutti My second question was that these patients each have a number of these tumors. They are numerous and they're throughout the small bowel, as you've pointed out, and they can be very small, so my question was, how confident are you that in a patient you have operated on, you have actually removed all of the tumors, so you have removed their at-risk sites for disease?

Dr Saïd C. Azoury That's a valid point. We cannot say for sure, although, as I mentioned, with our screening and with our follow-up, we continue to perform certain diagnostic studies on these patients. I can say that of the ones that we included and of the ones that were completely resected, at least on those diagnostic imaging studies, no new disease was found for those patients.

References

1. Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. *Ann Surg.* 2004; 240:117–22. [PubMed: 15213627]
2. Mocellin S, Nitti D. Gastrointestinal carcinoid: epidemiological and survival evidence from a large population-based study (n = 25 531). *Ann Oncol.* 2013; 24:3040–4. [PubMed: 24050954]

3. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, 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. [PubMed: 18565894]
4. Caplin ME, Buscombe JR, Hilson AJ, Jones AL, Watkinson AF, Burroughs AK. Carcinoid tumour. *Lancet*. 1998; 352:799–805. [PubMed: 9737302]
5. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. *Gastroenterology*. 2005; 128:1717–51. [PubMed: 15887161]
6. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*. 2003; 97:934–59. [PubMed: 12569593]
7. Onaitis MW, Kirshbom PM, Hayward TZ, Quayle FJ, Feldman JM, Seigler HF, et al. Gastrointestinal carcinoids: characterization by site of origin and hormone production. *Ann Surg*. 2000; 232:549–56. [PubMed: 10998653]
8. Dierdorf SF. Carcinoid tumor and carcinoid syndrome. *Curr Opin Anaesthesiol*. 2003; 16:343–7. [PubMed: 17021482]
9. Strodel WE, Talpos G, Eckhauser F, Thompson N. Surgical therapy for small-bowel carcinoid tumors. *Arch Surg*. 1983; 118:391–7. [PubMed: 6830429]
10. Hiripi E, Bermejo JL, Sundquist J, Hemminki K. Familial gastrointestinal carcinoid tumours and associated cancers. *Ann Oncol*. 2009; 20:950–4. [PubMed: 19150948]
11. Kharazmi E, Pukkala E, Sundquist K, Hemminki K. Familial risk of small intestinal carcinoid and adenocarcinoma. *Clin Gastroenterol Hepatol*. 2013; 11:944–9. [PubMed: 23500615]
12. Hemminki K, Li X. Familial carcinoid tumors and subsequent cancers: a nation-wide epidemiologic study from Sweden. *Int J Cancer*. 2001; 94:444–8. [PubMed: 11745428]
13. Sei Y, Zhao X, Forbes J, Szymczak S, Li Q, Trivedi A, et al. A hereditary form of small intestinal carcinoid associated with a germline mutation in inositol polyphosphate multikinase. *Gastroenterology*. 2015; 149:67–78. [PubMed: 25865046]
14. Strosberg JR, Weber JM, Feldman M, Coppola D, Meredith K, Kvols LK. Prognostic validity of the American Joint Committee on Cancer staging classification for midgut neuroendocrine tumors. *J Clin Oncol*. 2013; 31:420–5. [PubMed: 23248248]
15. Paulson AS, Bergsland EK. Systemic therapy for advanced carcinoid tumors: where do we go from here? *J Natl Comp Canc Netw*. 2012; 10:785–93.
16. Shebani KO, Souba WW, Finkelstein DM, Stark PC, Elgadi KM, Tanabe KK, et al. Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. *Ann Surg*. 1999; 229:815–21. discussion 22–3. [PubMed: 10363895]
17. Akerstrom G, Hellman P, Hessman O, Osmak L. Management of midgut carcinoids. *J Surg Oncol*. 2005; 89:161–9. [PubMed: 15719373]
18. Hellman P, Lundstrom T, Ohrvall U, Eriksson B, Skogseid B, Oberg K, et al. Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. *World J Surg*. 2002; 26:991–7. [PubMed: 12016480]
19. Koopmans KP, de Vries EG, Kema IP, Elsinga PH, Neels OC, Sluiter WJ, et al. Staging of carcinoid tumours with 18F-DOPA PET: a prospective, diagnostic accuracy study. *Lancet Oncol*. 2006; 7:728–34. [PubMed: 16945767]
20. Hassan MM, Phan A, Li D, Dagohoy CG, Leary C, Yao JC. Risk factors associated with neuroendocrine tumors: A U. S.-based case-control study. *Int J Cancer*. 2008; 123:867–73. [PubMed: 18491401]
21. Hoeffel C, Job L, Ladam-Marcus V, Vitry F, Cadiot G, Marcus C. Detection of hepatic metastases from carcinoid tumor: prospective evaluation of contrast-enhanced ultrasonography. *Dig Dis Sci*. 2009; 54:2040–6. [PubMed: 19034651]
22. Zacherl J, Scheuba C, Imhof M, Zacherl M, Langle F, Pokieser P, et al. Current value of intraoperative sonography during surgery for hepatic neoplasms. *World J Surg*. 2002; 26:550–4. [PubMed: 12098044]
23. Åkerström G, Hellman P, Hessman O. Midgut carcinoid tumours: surgical treatment and prognosis. *Best Pract Res Clin Gastroenterol*. 2005; 19:717–28. [PubMed: 16253896]
24. Reissman P, Shmailov S, Grozinsky-Glasberg S, Gross DJ. Laparoscopic resection of primary midgut carcinoid tumors. *Surg Endosc*. 2013; 27:3678–82. [PubMed: 23572224]

25. Suzuki S, Ishii N, Uemura M, Deshpande GA, Matsuda M, Iizuka Y, et al. Endoscopic submucosal dissection (ESD) for gastrointestinal carcinoid tumors. *Surg Endosc*. 2012; 26:759–63. [PubMed: 21993939]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig 1. Diagnostic imaging of small intestinal (SI) carcinoid tumors from asymptomatic patients with familial carcinoid tumor. (A) and (B) Several enhancing primary SI tumors (*white arrows* indicate the same tumor) noted in the arterial phase of CT enterography. (C) and (D) Several SI carcinoids detected on 18F-DOPA PET/CT (*white* and *black arrows* are the same tumor; the 2 symmetric posterior enhancing areas represent ureteral excretion). (E) and (F) Representative images of SI submucosal carcinoid tumors (*black arrows*) detected with wireless capsule endoscopy.

Fig 2. Representative gross pathologic small bowel resection from an asymptomatic patient with familial carcinoid tumor. (A) Resected gross external view of the ileum indicating the wide distribution of multiple tumors denoted by sutures. (B) Gross luminal appearance of 2 representative carcinoid tumors (*black arrows*).

Table 1

Demographics and operative details

N	Age	Sex	ASA class	Tumors, no.	Primary size, mm*	Site	EBL
1	53	F	3	4	16	J-I	100
2	55	M	3	11	5	I	50
3	61	F	2	4	2	J-I	100
4	56	F	3	8	10	J-I	100
5	62	M	3	9	12	I	50
6	71	F	3	1	8	I	25
7	44	F	3	1	2	J	n/a
8	45	F	3	3	8	I	n/a
9	48	M	3	2	1	J	n/a
10	51	M	3	6	21	J-I	100
11	67	F	3	1	5	J	50
12	65	M	3	2	6	J-I	50
13	60	M	3	5	5	I	100
14	57	M	3	7	7	J	n/a
15	56	M	2	3	6	I	50
16	52	F	3	10	25	I	30
17	56	M	3	4	8	I	10
18	74	M	3	9	11	J	30
19	68	M	3	1	8	I	50
20	58	M	2	29	11	J	50
21	62	F	2	9	5	I	10
22	63	F	2	1	4	I	10
23	43	F	3	2	9	J	n/a
24	57	F	3	2	13	I	100
25	53	F	3	6	9	I	n/a
26	57	F	2	1	12	I	20
27	82	M	3	28	11	I	20
28	51	M	2	5	6	J-I	30

N	Age	Sex	ASA class	Tumors, no.	Primary size, mm*	Site	EBL
29	59	F	2	17	20	1	25

* Size of the largest tumor on pathologic specimen.

ASA, American Society of Anesthesiologists class; *EBL*, estimated blood loss; *F*, female; *I*, ileum, *J*, jejunum; *J-I*, involvement of both jejunum and ileum; *M*, male; *n/a*, not available.

Table II

Pathologic evaluation and follow-up

N	Positive lymph nodes, no.	TNM stage	Class	Grade	LOR, cm	NED, mo*
1	7	T1N1M0	IIIB	G1	100	64
2	0	T1N0M0	I	G1	110	43
3	2	T4N1M0	IIIB	G1	100	38
4	3	T4N1M0	IIIB	G1	90	n/a (41)
5	6	T2N1M0	IIIB	G1	77	28
6	0	T1N0M0	I	G1	42	3
7	0	T1N0M0	I	G1	70	15
8	0	T3N0M0	IIIB	G1	130	61
9	0	T1N0M0	I	G1	90	58
10	11	T4N1M1	IV	G1	150	n/a (59)
11	0	T1N0M0	I	G1	20	62
12	0	T1N0M0	I	G1	75	57
13	0	T2N0M0	IIA	G1	45	68
14	1	T4N1M0	IIIB	G1	75	68
15	0	T1N0M0	I	G1	81	46
16	15	T4N1M0	IIIB	G2	70	46
17	0	T1N0M0	I	G1	75	39
18	3	T3N1M1	IV	G1	127	n/a (35)
19	0	T2N0M0	IIA	G1	13	25
20	4	T2N1M0	IIIB	G1	195	28
21	1	T2N1M0	IIIB	G1	42	22
22	0	T2N0M0	IIA	G1	20	19
23	0	T2N0M0	IIA	G1	25	26
24	4	T4N1M1	IV	G1	49.2	n/a (10)
25	0	T2N0M0	IIA	G1	19	6
26	0	T2N0M0	IIA	G1	60	6
27	5	T2N1M0	IIIB	G1	119.6	5
28	0	T1N0M0	I	G1	49.4	4

N	Positive lymph nodes, no.	TNM stage	Class	Grade	LOR, cm	NED, mo [*]
29	14	T3N1M0	IIIB	G1	83	3

* Indicates time interval (in months) from the date of operation until last follow-up, at which point there was no evidence of disease (NED); n/a indicates that the patient had persistent or recurrent/metastatic disease at last follow-up at the National Institutes of Health.

LOR, Length of resection.