A Single Institution's Experience with Surgical Cytoreduction of Stage IV, Well-Differentiated, Small Bowel Neuroendocrine Tumors

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BACKGROUND: Well-differentiated neuroendocrine tumors (NETs) of the gastrointestinal tract are rare, slow-growing neoplasms. Clinical outcomes in a group of stage IV, well-differentiated patients with NETs with small bowel primaries undergoing cytoreductive surgery and multidisciplinary management at a single center were evaluated.

STUDY DESIGN: The charts of 189 consecutive patients who underwent surgical cytoreduction for their small bowel NETs were reviewed. Information on the extent of disease, complications, and Kaplan-Meier survival were collected from the patient records.

RESULTS: A total of 189 patients underwent 229 cytoreductive operations. Ten percent of patients required an intraoperative blood transfusion and 3% (6 of 229) had other intraoperative complications. For all 229 procedures performed, mean (±SD) stay in the ICU was 4 ± 3 days and in the hospital was 9 ± 10 days. Before discharge, 51% of patients had no postoperative complications and 39% of patients had only minor complications. In a 30-day follow-up period from discharge, 85% of patients had no additional complications and 13% had only minor complications. The 30-day postoperative death rate was 3% (5 of 189). Mean survival from histologic diagnosis of NET was 236 months. The 5-, 10-, and 20-year Kaplan-Meier survival rates from diagnosis were 87%, 77%, and 41%, respectively.

CONCLUSIONS: Cytoreductive surgery in patients with well-differentiated midgut NETs has low mortality and complication rates and is associated with prolonged survival. We believe that cytoreductive surgery is a key component in the care of patients with NETs. (J Am Coll Surg 2014; 218:837−845. © 2014 by the American College of Surgeons)

Neuroendocrine tumors (NETs) are rare tumors that arise from Kulchitsky cells. The diffuse nature of the endocrine system implies that these tumors can originate in a multitude of sites.[1] Neuroendocrine tumors are classified based on the location of the primary tumor and are historically described as arising in the foregut, midgut, or hindgut. The majority of NETs arise within the gastrointestinal tract, most commonly in the jejunum, ileum, or proximal colon.[1-3]

Survival in patients with NETs is dependent on the location of the primary lesion, the extent of nodal involvement, and the presence of distant metastases.[4] The North American Neuroendocrine Tumor Society recently published median survival length and 5- and 10-year survival rates (65 months, 54%, 30%, respectively) for patients with well-differentiated, jejunal, or ileal carcinoids with distant stage IV disease. These survival rates were derived from the national Surveillance Epidemiology and End Results database and reflect the compiled survival data of all reporting centers.[5]

The indolent growth of these tumors often lulls the treating physician into using passive treatment plans. A recent study by Modlin and colleagues states that since the 1970s, little progress has been made toward improving the prognosis of patients with midgut NETs, and that these tumors are associated with a 5-year survival rate between 43% and 46%.[1] Similar studies by Turaga

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and Kvols,[6] Garcia-Carbonero and colleagues,[7] and Bilimora and colleagues[8] report higher 5-year survival rates for all stages of midgut NETs (60%, 83%, and 64.6%, respectively). However, these studies espouse similar concepts, with the conclusion being that there has been little to no improvement in survival rates for patients with small bowel NETs during the last decade.[6-8]

Complete surgical excision of a patient's primary tumor and metastatic disease is the only potentially curative option. Many small bowel NET patients will undergo multiple operations to achieve the lowest possible disease burden. The advent of techniques such as radiofrequency ablation, microwave ablation, and tumor ablation with the Nanoknife (Angiodynamics) have made cytoreduction easier and more effective. In addition to aggressive surgical cytoreduction, adjuvant therapies, such as bland or chemoembolization, yttrium-90 microsphere embolization, iodine-131-meta-iodobenzylguanidine therapy, biologic response modifier therapy, chemotherapy, and peptide receptor radionucleotide therapy, can be used to cytoreduce tumor burden.[9]

The aim of this study was to investigate the complication and survival rates of patients with well-differentiated jejunal or ileal NETs undergoing surgical cytoreduction and treatment at a multidisciplinary NET clinic.

METHODS

Clinical data on 1,700 patients with NETS seen at our clinic were entered into a computer-based database (E-VELOS database; VELOS Inc). All patients in the series underwent surgical cytoreduction at our institution between May 2006 and March 2012. Data from patient charts before December 2007 were entered retrospectively, and data from December 2007 onward were entered concurrent with clinic visits. Institutional Review Board consent was obtained to create, maintain, and use this database.

The database was searched for patients diagnosed with well-differentiated ileal, jejunal, or small bowel NETs ($n = 602$). Patients with atypical primaries, unknown primaries, multiple primary tumor sites (multiple primaries within the small bowel were allowed), or small bowel tumors thought to have metastasized via direct invasion from another primary site, were excluded. Primary tumors of the ileocecal valve region were allowed if the tumor was located predominately on the ileal side of the valve. Patients that had local or regional disease, patients with other (non-NET) cancers, or patients with highly significant comorbid conditions were also excluded. Patients that did not undergo a NET-related surgery performed by a surgeon in our practice and patients with only basic referral information in their chart were also excluded.

The medical records of 225 patients that satisfied the entry-level criteria were subsequently reviewed. Thirty-six of 225 (16%) patients did not have their surgical information present in our online hospital record system (HPF Webstation; McKesson Inc.) and were therefore excluded. These data were most likely lost during Hurricane Katrina (August 2005) or acquired shortly thereafter. To maximize the homogenous nature of this group, 189 patients were used in the final analysis. Patients with multiple operations at our institution had all of their NET-related operations included in this study, resulting in a total of 229 surgical encounters for the 189 patient cohort (Fig. 1).

Patient's sex, date of birth, medications, and pre-/postoperative condition were collected from the medical records. Operative reports were reviewed to determine the date(s) of each surgery, the specific operative procedure performed, and relevant preoperative, intraoperative, and postoperative information, including complications. The only procedures of interest were tumor-related cytoreductive operations. Surgical procedures for non-NET−related indications, that were exploratory in nature, or were done to obtain limited biopsy material, were not included. Subsequent washouts or second-look procedures resulting from a patient's primary debulking procedure were also excluded. Pathology reports were reviewed to confirm that all tumors were well-differentiated jejunal or ileal primaries and to obtain the size of the primary tumor, information relating to metastases, and the date of original histologic diagnosis. These data were supplemented by imaging studies. Histologic diagnosis was defined as the date the patient was first determined to have a NET, even if the primary location was unknown.

Postoperative complications were classified according to a grading system established by Dindo and colleagues.[10] This system grades postoperative complications based on their severity as a grade I, II, III (IIIa and IIIb), IV (IVa and IVb), or V. We added the suffix "d" to denote a complication that persisted at the time of discharge. Dindo and colleagues' classification scheme of surgical complications is as follows. A grade I complication includes any deviation from the normal postoperative course, but without the need for pharmacological treatment (except as noted) or other intervention. Pharmacologic treatments that are allowed in the grade I classification include antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. Grade I classification also includes wounds opened at the bedside. Grade II classification denotes complications requiring

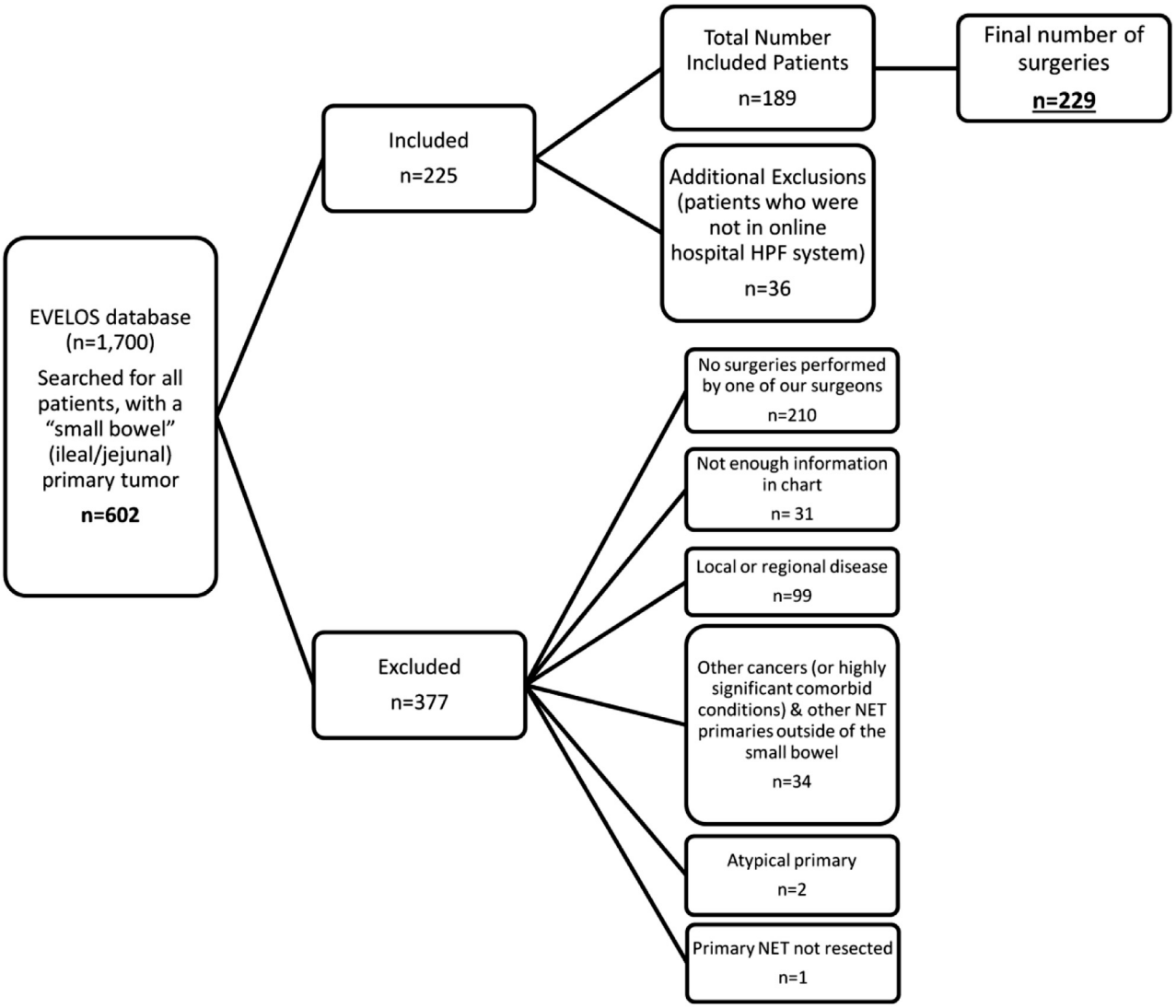

Figure 1. Schematic outlining patient selection for the study.

pharmacologic treatment with drugs other than those allowed in grade I, including blood transfusions. Grade IIIa classification indicates complications requiring surgical, endoscopic, or radiologic interventions that do not require general anesthesia. Grade IIIb classification denotes complications requiring intervention(s) performed under general anesthesia. Grade IVa classification encompasses single organ dysfunction (including dialysis) and grade IVb classification includes multiorgan dysfunction. A grade V classification indicates death of the patient.[10]

Survival was measured from the date of histologic diagnosis to either the date of death or the date of last follow-up (April 16, 2012). The date of death was confirmed by the US government's Social Security Death Index record database (http://www.genealogybank.com). Patients were censored for statistical purposes if they were living as of April 16, 2012. The date of death was recorded in absolute terms.

Expected survival (actuarial survival) was calculated for each patient based on their sex, race, and age at the date of diagnosis (rounded to the nearest 5 and used as "current age" for analyses). The actuarial survival reflects how long a person without an NET could expect to live according to the US National Center for Health Statistics, Table 105: Life Expectancy by Sex, Age, and Race: 2008.[11] This was directly compared with the patient's actual survival.

The data from our chart review were entered into a Microsoft Excel spreadsheet (version 97, 2003). These data were analyzed and survival rates were calculated in

MedCalc (v11.2.1) using the Kaplan-Meier survival analysis method, with death as the outcomes parameter.[12]

RESULTS

Demographics

Of the 189 patients, 80 (42%) were male and 109 (58%) were female. One hundred and seventy-six (93%) were Caucasian and 13 (7%) were classified as "other." Mean age ± SD at surgery (n = 229) was 59 ± 10 years. Median age at surgery was 59 years (range 31 to 81 years). Primary NET locations were 95 (50%) ileum, 38 (20%) terminal ileum, 5 (3%) jejunum, and 51 (27%) small bowel (not otherwise specified).

Primary tumor size, nodal status, and metastases

All 189 patients were analyzed for the size of their primary tumor, the extent of nodal involvement, and the location of their distant metastases. These results are displayed in Table 1.

Table 1. Tumor Characteristics: Primary Tumor Size and Nodal Metastasis Information and the Location of Distant Metastases and Resection Status for All Patients in this Study (n = 189)

Characteristic	n
Primary tumor size	
Unknown	11
≤1 cm	15
1.1−1.9 cm	30
≥2 cm	64
Multiple	69
Nodal metastasis	
Unknown	4
Negative/no nodes	8
1−9 positive nodes	30
≥10 nodes or a mesenteric mass	147
Distant metastasis	
Liver metastases, resected	61
Liver metastases, not resected	1
Other* metastases, resected	17
Other* metastases, not resected	3
Both liver and other metastases, resected†	105
Both liver and other metastases, not resected‡	2

*Other, extrahepatic metastases.
†At least one attempt was made at resection of metastases.
‡No attempt was made at resection of metastases.

Preoperative evaluation

All patients (n = 189) were evaluated to determine the incidence of preoperative comorbid conditions. Five percent (5%) of patients reported no conditions other than NET. Hypertension was the most prevalent comorbid condition (107 of 189 [57%]), followed by heart conditions (43 of 189 [23%]). Heart conditions were subdivided into arrhythmia (n = 16), valvular (n = 17), and arterial (n = 10). Osteoarthritis/arthritis was present in 33 (17%) patients, hypothyroidism in 26 (14%) patients, asthma in 16 (9%) patients, hyperlipidema in 15 (8%) patients, diabetes in 14 (7%) patients, and osteoporosis in 13 (7%) patients.

We also evaluated preoperative carcinoid-related symptoms for all patients before each surgery (n = 229). The majority of patients presented with diarrhea (74%) and flushing (64%). In contrast, only 9% of patients presented with wheezing. In our patient cohort, 86% of patients were believed to have carcinoid syndrome (Table 2). Seventy-nine percent of patients (181 of 229) were on somatostatin analog therapy, either lanreotide (Somatuline Depot, Ipsen Pharma Biotech) or octreotide (Sandostatin, Novartis Pharmaceuticals) before surgery.

Intraoperative evaluation

The type of procedure performed was evaluated for all 229 operations. The most common surgical procedures performed were liver resections (n = 166 [72%]), mesenteric mass dissections (n = 129 [56%]), primary tumor resections (n = 118 [52%]), and "other" lymph node dissections (n = 118 [52%]). Other commonly performed procedures include cholecystectomy (n = 97 [42%]), oophorectomy (n = 32 [14%]), and peritoneal stripping (n = 17 [7%]).

In this study, all patients had their primary tumor resected. Approximately one third of the patients had an R0 (complete) resection, one third had R1 (tumor cells remain in resected margins), and one third had an R2 (incomplete) resection. Patients that had incomplete, R2, resection tended to have undergone serial cytoreductive procedures.

Forty-eight percent (48%) of patients had their primary resected at an outside institution before their debulking surgery at our institution. Intraoperative local chemotherapy (gelfoam soaked in 5-FU) was used in 112 (49%) patients, lymphatic mapping was performed in 74 (32%) patients, radiofrequency ablation in 70 (31%) patients, and neoprobe-assisted exploration was performed in 53 (23%) patients.[13]

Mean ± SD operative time was 380 ± 127 minutes (6.3 ± 2.3 hours). Median operative time was 380 minutes (6.3 hours) and operative times ranged from 87 minutes to 900 minutes (1.5 to 15 hours).

Intraoperative complications

Ninety-seven percent of operations (223 of 229) did not have any intraoperative complication noted in the

Table 2. Carcinoid Symptoms Present for All Patients in this Study before Surgery (n = 229)

	Reported flushing		Witnessed flushing		Diarrhea		Wheezing		Carcinoid syndrome	
	n	%	n	%	n	%	n	%	n	%
Yes	132	64	17	9	157	74	18*	9	182	86
No	73	36	162	91	55	26	172	91	30	14
Unknown	24		50		17		39		17	

*Includes 3 smokers.

operative report. For this study, only the surgical records were considered and anesthesia records were not reviewed, therefore, intraoperative "carcinoid crises" (excessively high or low blood pressure) were not included as a complication. There were 6 operations noted to have intraoperative complications: 2 operations were deemed highly difficult in the operative report by the attending surgeon, 1 patient required extensive adhesiolysis to gain access to the abdominal cavity, 1 patient had intra-abdominal spillage of succus from enterotomies, 1 patient had a perioperative myocardial infarction, and in 1 patient the first surgical attempt was aborted due to atenolol toxicity, which presented as profound bradycardia and hypotension on induction of anesthesia. A subsequent surgical attempt was successful. Also of note, 3 "cocoon-like" formations of densely adhered bowel were identified intraoperatively, preventing additional surgery.[14]

Ten percent of operations (24 of 229) required intraoperative blood transfusions. Twelve patients were reinfused with autologous blood (1 to 2 units). Ten patients received packed red blood cells: 7 of 10 patients received 1 unit, 2 of 10 patients received 2 units, and 1 of 10 patients received 3 units. One patient required 4 units of packed RBCs and 2 units of plasma, and 1 patient required 2 units of autologous blood and 2 units of packed RBCs.

Postoperative evaluation

For all 229 operations performed, mean ± SD stay in the ICU was 4 ± 3 days (range 0 to 23 days). Three patients died in the ICU on days 1, 4, and 11, respectively, and 2 patients spent the majority of their 41-day and 122-day hospital stays intermittently in the ICU. Twelve patients spent between 0 and 1 day in the ICU, 19 patients spent 2 days, 72 patients spent 3 days, and 57 patients spent 4 days in the ICU.

Mean ± SD total days in the hospital was 9 ± 10 days (range 1 to 122 days). There were 3 outliers with hospital stays of 41, 60, and 122 days. Thirty-four patients spent between 1 and 5 days in the hospital, 45 patients spent 6 days, 44 patients spent 7 days, and 78 patients spent between 8 and 12 days.

Narcotic use was examined preoperatively and post recovery (3 to 6 months postoperatively) in 195 operations (status unknown for 21 operations). Eighty-one percent (158 of 195) of patients did not chronically take narcotics either pre- or postoperatively and 15% (29 of 195) of patients chronically used narcotics both pre- and postoperatively. Eight patients (4%) that had not previously taken narcotics began their use after surgery and 5 patients (3%) stopped taking narcotics after surgery.

Karnofsky performance scores were evaluated pre- and postoperatively. Preoperatively, mean ± SD Karnofsky score was 85 ± 12 (ranging from 50 to 100). Postoperatively, mean ± SD Karnofsky score was 86 ± 11 (ranging from 55 to 100).

Postoperative complications

Postoperative complications were identified and classified according to the grading system established by Dindo and colleagues.[10] Table 3 illustrates postoperative complications in our patient cohort. Excluded from this Table are patients that died (grade V) from complications due to surgery in a 150-day follow-up period. Before discharge, 110 patients had no complications and the majority of complications experienced were minor: 34 grade I, 51 grade II, and 21 grade III/IV. From discharge, complications were identified and categorized in 30-day increments. The majority of patients did not have any complications after hospital discharge. Of the total 229 operations performed on 189 patients, the death rate due to surgical complications was 7% (13 of 189).

Survival from histologic diagnosis

Mean survival from histologic diagnosis for all 189 patients was 236 months. The 5-, 10-, and 20-year survival rates from diagnosis were 87%, 77%, and 41%, respectively (Fig. 2).

Expected vs actual survival

Expected survival vs actual survival was compared for all 189 patients. The comparison for our patients' survival (actual survival) vs actuarial survival (expected survival) is displayed in Figure 3.

Table 3. Complications for All Operations in This Study Using the Dindo Surgical Complication Grading System

Complication grade	During hospital stay (before discharge) (n = 216)*	Discharge to 30-day complications (n = 175)*	30- to 60-Day complications (n = 185)*	60- to 90-Day complications (n = 187)*
0	110	149	177	177
I (minor)	34 (1 ID)	9	2	4
II	51 (1 IID)	14	3	2
IIIa	9	2	1	0
IIIb	3	1	2	3
IVa	8	0	0	1
IVb	1	0	0	0

*Excluding patients that died due to surgical complications (grade V) during a postoperative follow-up period of 150 days, n = 13. Also excluded patients with unknown complications.

DISCUSSION

Several recently published reports purport that, despite advancements in the understanding and management of small bowel NETs, survival rates have remained largely unchanged for the past 40 years.[1,6-8] Conversely, other authors believe the survival of these patients with NETs is improving and this change is attributed, in part, to an increase in the number of patients treated at specialized academic referral centers.[3,15,16] The conflicting survival results reported from a variety of centers, the current skepticism about the lack of progress in the care and management of small bowel NETs, and the lack of multi-institution or large, single-institution trials prompted us to undertake this study. The aim of this study was to determine whether surgical cytoreduction of well-differentiated, small bowel NETs in a specialty center with a multidisciplinary team approach to patient care positively affected survival.

Surgical treatment of NETs is the only potentially curative option. However, achieving a complete excision of the primary tumor and all associated metastases is rare. Debulking or cytoreductive surgical procedures are often undertaken with palliative intent or to help reduce disease burden and hopefully increase survival. Even in patients with advanced metastatic disease, surgical resection has been shown to increase survival.[6] Saxena and colleagues systematically reviewed clinical studies to determine the efficacy of resection of hepatic metastases in NET patients. They reported a 69% 5-year survival rate and a 47% 10-year survival rate and concluded that hepatic resection provides enhanced symptom control as well as increases survival.[17]

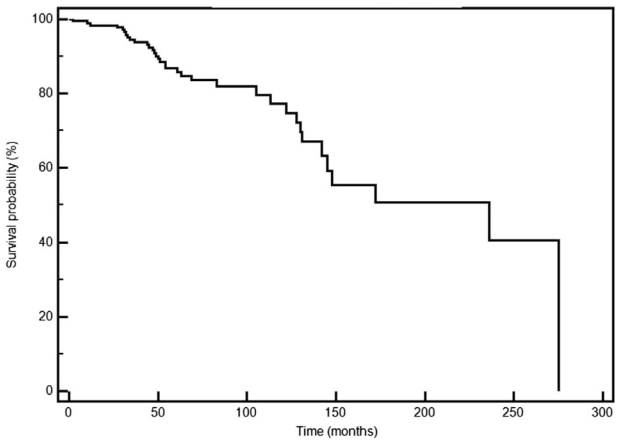

Figure 2. Survival from date of histologic diagnosis of neuroendocrine tumor for all patients in this study (n = 189), mean survival of 236 months.

The rarity of small bowel NETs implies that only a small number of cases are usually reported from a single institution. During a 20-year time frame, Massachusetts General Hospital saw only 58 patients with jejunal or ileal NETs.[18] Other single-institution studies have reported similar small series, and often the total number of patients in such trials is <200.[3,16,18-24]

In this study, we evaluated 189 patients with stage IV, well-differentiated NETs with small bowel primaries undergoing cytoreductive surgery and multidisciplinary management at our center. A total of 229 operations were performed, ranging from 1 to 4 surgical procedures performed per patient. One hundred and forty-five (77%) patients were cytoreduced only once at our institution. The remaining 44 (23%) patients underwent 2 or more cytoreductive procedures. Arguments against surgical cytoreduction cite a high recurrence rate (94% at 10 years).[6] However, our high survival rates (77% at 10 years) support the use of surgical cytoreduction even with the potential for recurrent disease.

Cytoreduction of NETs is associated with a low operative mortality, generally reported at <5.3%.[6] In this study, we observed a 0% mortality rate intraoperatively and a 3% mortality rate in a 30-day postoperative follow-up period. Intraoperative complications were rare (3%) as was the need for intraoperative blood transfusions (10%). In a 30-day follow-up period from the date of

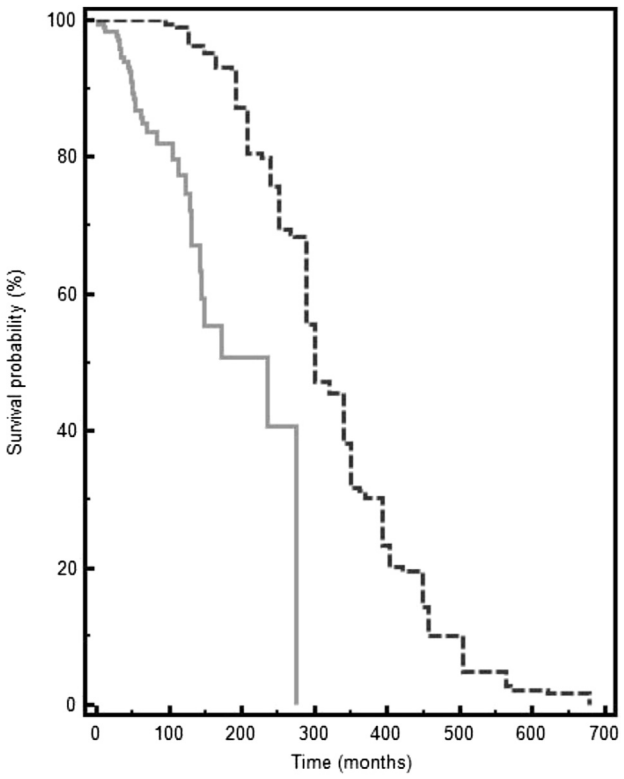

Figure 3. Actuarial survival for patients in this study with stage IV, midgut neuroendocrine tumors compared with expected survival without a neuroendocrine tumor diagnosis (n = 189). Gray line, survival in our clinic of patients with stage IV small bowel neuroendocrine tumors; dashed line, expected survival, general population.

discharge, 85% of patients had no complications and 13% had minor complications.

One of the most obvious limitations to this study was the presence of entry-level bias and the fact that the data were not level one. Due to the nature of this investigation, our data could not be randomized and entry-level bias could not be avoided. However, the size and construct of our study resulted in strong level-2 data.

In general, the majority of NET patients referred for surgery are those with localized disease or metastatic disease confined to one lobe of the liver that can be resected or ablated easily. Therefore, it is this cohort of patients that is included in retrospective survival studies. This leads to substantial selection bias in these studies, as these patients already have a relatively good prognosis and are bound to have better survival rates than the general population of patients with NETs.[25] Although an innate selection bias is unavoidable when performing retrospective surgical survival analysis, Bergesuen and colleagues compared hospital-based studies with population-based studies and found that 66% of patients with small bowel NETs had distant metastases at their initial presentation to the referral hospital compared with 27% in the general population. Their study suggests that patients with more extensive disease have a greater chance of being referred to a specialty center, implying that specialty center–based reports might have an innate bias toward worse survival rates.[3]

Dr Jeffrey Norton reported that aggressive surgery for metastatic NETs is controversial and it is difficult to prove its efficacy because there is usually a lack of long-term follow-up and too few patients.[25] In this study, we evaluated 189 patients with widespread metastatic disease (57% of our patients had metastatic disease to the liver and at least one other extrahepatic location). Follow-up survival statistics were calculated out to 20 years. In a previous study of 84 patients not included in this review, 67% of the patients we operated on were referrals that had previously been deemed unresectable, and 72% of our surgical patients had multilobar liver disease.[26] Surgery was performed on all of the patients in this study. Due to the diffuse nature of their disease, 100% (R0) resection was not possible in most patients. The goal of these operations was to decrease tumor burden as much as possible in an effort to prolong survival.

Norton and colleagues stated that "conventional contraindications to surgical resection such as superior mesenteric vein invasion and nodal or distant metastases should be redefined in patients with advanced neuroendocrine tumors" and that surgical debulking "even in patients with extensive disease" should be considered.[27] We believe our data support this claim, as all patients in this study had diffuse metastatic disease, 177 patients had nodal involvement, 72% of patient underwent liver resections, and 56% underwent mesenteric resections. Calculations were performed to determine the expected survival of our patient cohort had they never had an NET develop. Mean survival between the 2 groups had a difference of only 5 years, implying that, on average, having a stage IV, small bowel NET (when properly managed) decreases a person's life expectancy by approximately 5 years (Fig. 3). These data, coupled with a 10-year survival rate of 77%, demonstrate that surgical cytoreduction is warranted. Additional studies should be performed to evaluate the impact of other effective adjuvant therapies. However, we believe that there is overwhelming evidence in support of surgical cytoreduction. We also believe that future prospective randomized studies will pose an ethical dilemma if they do not include surgical cytoreduction.

A proactive and aggressive surgical approach to the management of this "indolent" disease provides a tremendous increase in the survival of patients with these

malignancies. Based on the results of the current study, we believe that a change in treatment philosophy from passive to active and from conservative to aggressive is warranted. The survival rates seen in this study are objectively higher than other study's survival rates and should prompt future research in this field.

Author Contributions

Study conception and design: Boudreaux, Wang, Diebold, Frey, Anthony, Uhlhorn, Woltering
Acquisition of data: Boudreaux, Wang, Diebold, Frey, Anthony, Uhlhorn, Ryan, Woltering
Analysis and interpretation of data: Boudreaux, Diebold, Ryan, Woltering
Drafting of manuscript: Woltering
Critical revision: Woltering, Diebold

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Discussion

DR B MARK EVERS (Lexington, KY): I would like to congratulate the authors for a nice presentation and for continuing to lead the way in defining the role of aggressive surgical management in patients with stage IV neuroendocrine tumors. Over the years, Drs Boudreaux, Wang, and Woltering have led the way to change the treatment paradigm of neuroendocrine tumors from a passive "wait and see" approach to a more aggressive multidisciplinary approach in which cytoreductive surgery should be an important consideration in the treatment strategy of these patients.