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Analysis of Postoperative Recurrence in Stage I–III Midgut Neuroendocrine Tumors

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Abstract

Background: Surgery represents the only curative treatment for stage I–III midgut neuroendocrine tumors (NETs). At present, there are very limited data on the risk of postoperative recurrence. The optimal modality, duration and frequency of surveillance have not been well established. In this work, we investigated the long-term risk of recurrence, peak timing of recurrence, and potential predictors of relapse in patients with stage I–III midgut NETs.

Methods: We retrospectively evaluated 129 patients with stage I–III midgut NETs who were seen at the Moffitt Cancer Center between 2000 and 2010 following an R0/R1 resection. Disease-free survival (DFS) was estimated using the Kaplan-Meier method. Demographic, clinical, and pathological features were assessed as potential predictors of recurrence. All statistical tests were two-sided.

Results: After a median postoperative follow-up of 81 months (range = 1–295 months), recurrence was diagnosed in 40 out of 129 patients (31.0%, 95% confidence interval [CI] = 23.0% to 39.0%). Liver, mesentery, and pelvic lymph nodes were the main sites of relapse. The median DFS was 138 months (95% CI = 117 to 223 months). Resection of 17 or fewer lymph nodes predicted relapse ($P = .01$) and shorter DFS ($P = .04$). Among patients who relapsed, the cumulative risks of recurrence at one, five, and 10 years were 15.0% (95% CI = 3.9% to 26.1%), 50.0% (95% CI = 34.5% to 65.5%), and 85.0% (95% CI = 73.9% to 96.0%). No recurrence was observed among patients (n = 6) with stage I tumors, whereas similar rates of relapse were noted in patients with stage II or III NETs (n = 118).

Conclusions: An annual surveillance interval may allow early detection of recurrence. Given the apparent decline in recurrence after eight years from surgery, a decade-long duration of active surveillance may be proposed.

Neuroendocrine tumors (NETs) of the small intestine and proximal colon, also known as midgut carcinoid tumors, represent the most common type of gastrointestinal NET (1). Their incidence has increased substantially in recent years (2). Midgut NETs tend to progress indolently and produce serotonin among other vasoactive substances. In patients with distant metastases, this hormonal output often results in the malignant carcinoid syndrome (3). Analyses of the Surveillance, Epidemiology, and End Results (SEER) database suggest that the majority of patients present initially with tumors that are either local or metastatic to locoregional lymph nodes (4). Symptoms related to intraluminal and mesenteric tumors include abdominal pain, bleeding, or nausea/vomiting. Mesenteric lymph node metastases often produce a dense fibrotic reaction that can tether surrounding bowel and mesenteric vessels, resulting in bowel obstruction or ischemia. Occasionally, tumors of the ileocecum are discovered incidentally on colonoscopy, while mesenteric masses may also be detected incidentally on imaging studies. Surgical resection, typically via right hemicolectomy or partial small bowel resection with lymphadenectomy, represents the standard of care for most patients with early-stage disease (3). While surgery is potentially curative, there are limited data on

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the risk of postoperative recurrence, and therefore very little evidence upon which to base guidelines for long-term surveillance. One reason for the dearth in literature on recurrence risk is the need for long-term follow-up: tumors can metastasize more than 10 years after primary tumor resection (5,6).

In the past, the ability to predict recurrence was also limited by the absence of a commonly accepted staging classification. However, in 2007, the European Neuroendocrine Tumor Society (ENETS) developed a tumor/node/metastasis (TNM)-based staging classification for small bowel NETs of the jejunum and ileum (7). This classification distinguished between tumors confined to the submucosa and smaller than 1 cm (stage I), tumors invading the muscularis propria or subserosa or larger than 1 cm (stage II), tumors invading the visceral peritoneum (serosa) or other organs (stage IIIA), and tumors metastatic to locoregional lymph nodes (stage IIIB). This staging system was subsequently adopted by the American Joint Committee on Cancer (AJCC) for the 7th edition of its staging manual (8). Both ENETS and the AJCC have also adopted a grading classification proposed in 2010 by the World Health Organization (WHO) that distinguishes between low-grade tumors (0–1 mitoses per 10 high-powered fields, or Ki-67 index $\leq$ 2%), intermediate-grade tumors (mitotic rate 2–20 per 10 high-powered fields, or Ki-67 index 3%–20%), and high-grade tumors (mitotic rate >20 per 10 high-powered fields, or Ki-67 index > 20%) (9). Most small bowel NETs are low grade (10).

In order to help counsel patients on risk of postoperative recurrence and to aid in development of surveillance guidelines, we searched a retrospective database for all patients with pathologically confirmed jejunal, ileal, or ileocecal NETs, identifying patients who presented without evidence of distant metastases (stage I–III). The primary goal of our study was to determine stage-based recurrence risk and to ascertain the peak timing of recurrence. In doing so, we hoped to answer the following questions: which patients benefit from postoperative surveillance?; what tests should be performed?; what is the appropriate duration of surveillance?; and what is the appropriate frequency?

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Methods

Patients

We searched a retrospective database of patients with midgut NETs seen at our institution (H. Lee Moffitt Cancer Center, Tampa, FL) between January 2000 and December 2010. Within this group, we identified patients who underwent R0/R1 surgical resection for tumors lacking both radiographic and intraoperative evidence of synchronous distant metastases (stage I–III). Patients who were lost to follow-up immediately after the surgery, patients with unresectable mesenteric lymph nodes, and patients with mixed adenoneuroendocrine carcinomas (including goblet cell carcinoids) were excluded. In order to limit referral bias, we also excluded patients who had undergone surgery and subsequently developed metastatic disease prior to referral to our institution.

The following information was collected by review of patient medical records: demographics, date of initial diagnosis, date of surgery, presenting symptoms, surgery characteristics, initial tumor stage according to the ENETS/AJCC classification (7), location of primary tumor, presence of a functional hormonal syndrome at diagnosis, elevation of tumor markers such as chromogranin A (CgA) and 5-hydroxindoloacetic acid (5-HIAA), and follow-up data, including date and site of recurrence or date of last contact without recurrence. Pathological information including tumor grade by WHO 2010 criteria (9), tumor size and uni- or multifocality, extent of parietal invasion, clearance of margins and presence of perineural or lymphovascular invasion were obtained by review of surgical pathology reports. The NET diagnosis was considered incidental when patients were being worked up for signs and symptoms unrelated to their midgut NET. Institutional approval was obtained for this study.

Statistical Analysis

Descriptive statistics were used for patient demographics. The association between recurrence risk and patients' clinicopathological features was evaluated by χ^2 or Fisher's test, as appropriate. Factors showing a *P* value of .2 or less at univariate analysis were introduced in a multivariable logistic regression model, in which variables were selected using backward stepwise elimination with statistical significance at a *P* value of .05 or less. Receiver operating characteristics (ROC) curve analysis was used to set the optimal cutoff point for possible predictors of relapse. DeLong's test was used to compare the area under the ROC curves (AUC) (11). Disease-free survival (DFS) was calculated from date of surgery (R0/R1) until evidence of macroscopic recurrence by imaging or surgical exploration, or death. Time to progression (TTP) was calculated from date of surgery until evidence of recurrence. Overall survival (OS) was measured from date of initial diagnosis until death from any cause or last known follow-up. All time-to-event functions were estimated by the Kaplan-Meier method and compared by the log-rank test. Multivariable analysis was performed using Cox proportional hazards regression. The assumption of proportionality was verified by log-log plot. Only variables with a *P* value of .2 or less at univariate analysis were included in the Cox model. Exact 95% confidence intervals were calculated for each proportion of interest. All tests were two-sided, and statistical significance was declared at a *P* value of .05 or less. Statistical analysis was conducted using MedCal statistical software 12.7 (MedCalc Software bvba, Ostend, Belgium).

A potential confounding factor in an institutional survival analysis is the immortal time bias, also known as left truncation bias. For the purpose of this study, immortal time bias refers to the span of time in the observation period of a cohort during which relapse could not have occurred (12). Therefore, here we defined immortal time bias as the interval of time between diagnosis and the original presentation to our institution. To mitigate this bias, we carried out separate analyses for patients who were seen at the Moffitt Cancer Center within 12 months of their diagnosis.

Results

Demographics and Tumor Characteristics

Demographic variables and clinicopathological characteristics of 129 patients included in the study are listed in Table 1. The majority of patients (110/129, 85.3%) were referred to our institution within one year of their diagnosis. The median age at diagnosis was 57 years (range = 33–85 years). The diagnosis was incidental in 39.5% of patients. Presence of the carcinoid syndrome was documented in 17 patients (13.2%) at baseline. The majority of patients (86.0%) had ileal primaries, and multifocal tumors were detected in 30.2% of cases. Right hemicolectomy and partial small bowel resection were performed in 53.5% and

Table 1. Patient demographics and tumor characteristics

Characteristics	No. of patients (%) (n = 129)
Age at diagnosis, y	
Median	57
Range	33–85
Sex	
Male	61 (47.3)
Female	68 (52.7)
Race	
White	106 (82.2)
Black	13 (10.1)
Hispanic	3 (2.3)
Asian	1 (0.8)
Unknown	6 (4.6)
Incidental diagnosis	
Yes	51 (39.5)
No	64 (49.6)
Unknown	14 (10.9)
Carcinoid syndrome	
Yes	17 (13.2)
No	112 (86.8)
Tumor location	
Jejunum	6 (4.7)
Ileum	111 (86.0)
Right colon and appendix	4 (3.1)
Unknown	8 (6.2)
Tumor multifocality	
Yes	39 (30.2)
No	85 (65.9)
Unknown	5 (3.9)
Type of surgery	
Right hemicolectomy	69 (53.5)
Partial small bowel resection	58 (45.0)
Unknown	2 (1.5)
Tumor size, cm	
Median	1.8
Range	0.3–7
Degree of parietal invasion	
Submucosa	6 (4.7)
Muscularis propria	32 (24.8)
Subserosa	19 (14.7)
Serosa/mesenteric fat	48 (37.2)
Unknown	24 (18.6)
Lymph node metastases	
N0	19 (14.7)
N1	99 (76.8)
Nx	11 (8.5)
Lymph nodes harvested	
≤17	83 (64.3)
>17	33 (25.6)
Unknown	13 (10.1)
Macroscopic mesenteric lymph nodes	
Yes	36 (27.9)
No	89 (69.0)
Unknown	4 (3.1)
Involvement of radial margins	
Yes	15 (11.6)
No	106 (82.2)
Unknown	8 (6.2)
Tumor stage	
I	6 (4.7)
IIA	12 (9.3)
IIB	2 (1.5)
IIIA	5 (3.9)
IIIB	99 (76.7)
Unknown	5 (3.9)
Tumor grade	
G1	107 (82.9)
G2	20 (15.5)
Unknown	2 (1.6)
Lymphovascular invasion	
Yes	70 (54.3)
No	13 (10.1)
Unknown	46 (35.6)
Perineural invasion	
Yes	53 (41.1)
No	20 (15.5)
Unknown	56 (43.4)
Follow-up, mo	
Median	81
Range	1–295
Recurrent disease	
Yes	40 (31.0)
No	89 (69.0)
Sites of recurrence	
Liver	21 (52.5)
Mesentery	11 (27.5)
Peritoneum	3 (7.5)
Pelvic lymph nodes	6 (15.0)
Others	9 (22.5)

45.0% of the patient population, respectively. The median tumor size was 1.8 cm (range = 0.3–7 cm), and more than three-quarters of patients (76.8%) had lymph node metastases and consequently stage IIIB tumors according to ENETS/AJCC criteria. The median number of lymph nodes harvested was 12 (range = 0–52). Grossly involved mesenteric lymph nodes were present in 27.9% of patients. Proximal and distal bowel margins were always free of disease, whereas radial margins were microscopically negative in 82.2% of the cohort. The majority of tumors (82.9%) were G1, and lymphovascular and perineural invasion were described in 54.3% and 41.1% of cases, respectively. Before surgery, CgA and 5-HIAA were available only in 19 and 26 cases, respectively, and were elevated in 26.3% and 30.8% of patients.

Recurrence Rates and Characteristics

After a median postoperative follow-up of 81 months (range = 1–295 months), recurrence was diagnosed in 40 of 129 patients (31.0%, 95% confidence interval [CI] = 23.0% to 39.0%) (Table 1). Among patients who relapsed, the cumulative rates of recurrence at one, three, five, and 10 years were 15.0% (95% CI = 3.9% to 26.1%), 37.5% (95% CI = 22.5% to 52.5%), 50.0% (95% CI = 34.5% to 65.5%), and 85.0% (95% CI = 73.9% to 96.0%), respectively. As shown in Figure 1, the risk of recurrence substantially declined eight years after surgery among relapsing patients. Nearly all recurrences were detected within 12 years of surgery, with the exception of one patient, whose primary tumor had the largest diameter recorded in this cohort (7 cm). No relapse was observed among patients (n = 6) with stage I tumors. Among patients with stage II–IIIA tumors (n = 19), one-, three-, five-, and 10-year cumulative relapse rates were 10.5% (95% CI = 0.0% to 24.3%), 21.1% (95% CI = 2.8% to 39.4%), 21.1% (95% CI = 2.8% to

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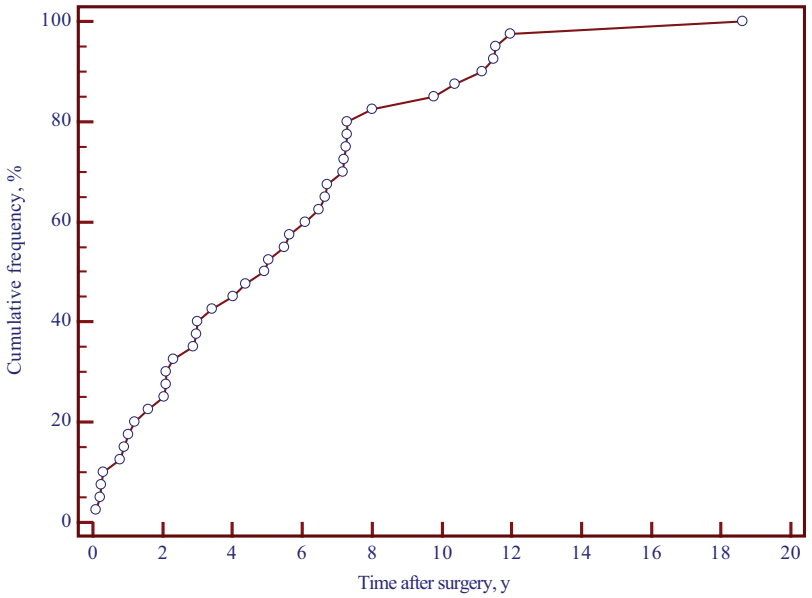

Figure 1. Frequency distribution of postoperative recurrence in relapsing stage I–III midgut NETs. Recurrences (**white circles**) are represented as a function of time.

39.4%), and 31.6% (95% CI = 10.7% to 52.5%), respectively, whereas recurrence rates of 4.0% (95% CI = 0.2% to 7.8%), 10.1% (95% CI = 4.2% to 16.0%), 15.1% (95% CI = 8.0% to 22.1%), and 26.3% (95% CI = 17.6% to 35.0%) were estimated for patients with stage IIIB (lymph node–positive) midgut NETs (n = 99). The majority of recurrences were metastatic, with liver (52.5%) and pelvic lymph nodes (15.0%) being the main sites of distant relapse (Table 1). Thirteen patients (32.5%) presented with locoregional recurrences (11 in the mesentery, two in the small intestine). All patients recurring in the mesentery had surgical margins free of disease. At the time of relapse, 19 of 40 patients (47.5%) were asymptomatic, whereas abdominal pain, new-onset/worsened diarrhea or flushing, and/or diaphoresis prompted further work-up in 32.5%, 22.5%, 12.5%, and 5.0% of patients, respectively. Disease recurrence was mainly diagnosed by computed tomography (80.0%) or magnetic resonance imaging (20.0%). These investigations were usually limited to the abdomen and pelvis (85.0%). As depicted in Figure 2, 5-HIAA levels at relapse were statistically significantly different when compared with their first value after curative surgery ($P < .001$). There was no difference between CgA levels after surgery and at relapse ($P = .08$).

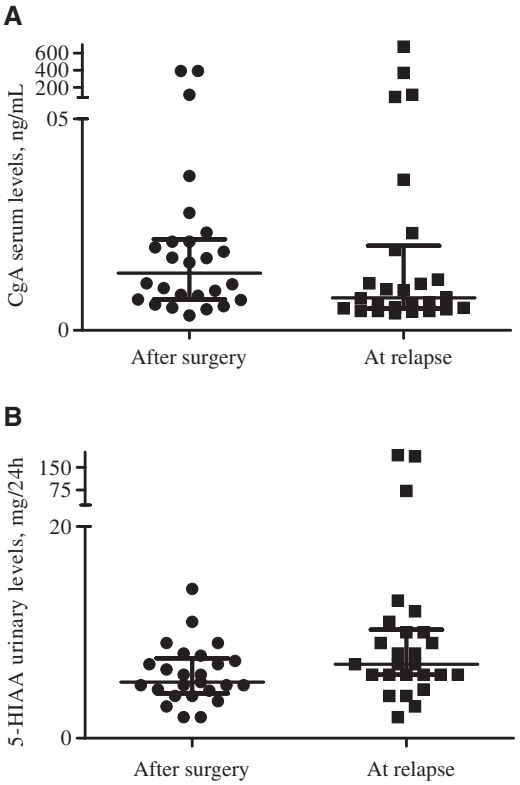

Figure 2. Tumor markers and recurrence detection. Differences in **(A)** median chromogranin A serum concentrations and **(B)** median urinary 5-HIAA after surgery and at relapse were calculated by Wilcoxon matched pairs signed-rank test. Paired row values, median change, and interquartile range are represented. All statistical tests were two-sided. CgA = chromogranin A; 5-HIAA = 5-hydroxyindoleacetic acid.

Predictors of Recurrence

As detailed in Table 2, the number of lymph nodes excised at the time of surgical resection was the only clinic-pathologic feature predictive of relapse in univariate analysis. However, the relative homogeneity of the study cohort and the consequent presence of subgroups with small numbers may have limited our ability to detect statistically significant differences, as suggested by wide confidence intervals around recurrence rates. To identify the optimal cutoff number of harvested lymph nodes capable of predicting relapse, ROC curve analysis was performed (Figure 3). In our cohort, a lymph node threshold of 17 or fewer distinguished between relapsing and nonrelapsing patients with a sensitivity of 88.2% (95% CI = 72.5% to 96.7%) and a specificity of 35.4% (95% CI = 25.1% to 46.7%), with an AUC of 0.63 (95% CI = 0.54 to 0.72, $P = .01$). By univariate analysis, a number of harvested lymph nodes of 17 or fewer statistically significantly predicted recurrence ($P = .01$). After adjusting for variables that showed a P value of less than .20 in univariate analysis (incidental diagnosis, N stage, tumor size), dissection of more than 17 lymph nodes remained associated with reduced

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Table 2. Univariate analysis of potential predictors of recurrence

Characteristics	Recurrence rate (95% CI), %	P*	Median DFS (95% CI), mo	P†
Age at diagnosis, y		.98		.72
20–40	25.0 (7.1 to 59.1)		NR (11 to NR)	
40–60	31.8 (21.8 to 43.8)		138 (124 to 139)	
>60	30.9 (20.3 to 44)		117 (86 to 223)	
Sex		.71		.83
Male	32.8 (22.3 to 45.3)		134 (87 to 223)	
Female	29.4 (19.9 to 41.1)		NR (96 to NR)	
Race		.22		.06
White	31.1 (23.1 to 40.5)		144 (124 to 223)	
Black	46.1 (23.2 to 70.8)		87 (36 to 117)	
Hispanic, Asian, unknown	11.1 (2.0 to 43.5)		NR (139 to NR)	
Incidental diagnosis		.17		.33
Yes	37.5 (26.7 to 49.7)		NR (87 to NR)	
No	21.6 (12.5 to 34.6)		124 (87 to 144)	
Unknown	35.7 (16.3 to 61.2)		NR (96 to NR)	
Carcinoid syndrome		.78		.79
Yes	35.3 (17.3 to 58.7)		134 (86 to 134)	
No	30.4 (22.6 to 39.4)		139 (117 to 223)	
Tumor location		.58		.33
Ileum	32.4 (24.4 to 41.6)		138 (96 to 223)	
Others	22.2 (9.0 to 45.2)		NR (87 to NR)	
Tumor multifocality		.30		.09
Yes	30.8 (18.6 to 46.4)		139 (68 to 223)	
No	32.9 (23.9 to 43.5)		134 (96 to 144)	
Type of surgery		.70		.33
Right hemicolectomy	29.0 (19.6 to 40.6)		138 (96 to 144)	
Partial small bowel resection	32.8 (22.1 to 45.6)		139 (87 to 223)	
Tumor size, cm		.07		.08
<1	19.2 (8.5 to 37.9)		124 (124 to 125)	
1–2	34.8 (22.7 to 49.2)		87 (68 to 138)	
2–4	37.2 (24.3 to 52.1)		134 (87 to 144)	
>4	60.0 (23.1 to 88.2)		223 (3 to NR)	
Unknown	0 (0 to 30)		NR (NR to NR)	
Degree of parietal invasion		.49		.26
Submucosa	16.7 (3.0 to 56.3)		NR (134 to NR)	
Muscularis propria	31.3 (18.0 to 48.6)		96 (87 to 139)	
Subserosa	47.4 (27.3 to 68.3)		144 (36 to NR)	
Serosa/mesenteric fat	29.2 (18.2 to 43.2)		124 (87 to 223)	
Lymph node metastases		.20		.65
N0	15.8 (5.5 to 37.6)		NR (NR to NR)	
N1	32.3 (23.9 to 42.0)		138 (96 to 223)	
Nx	45.4 (21.3 to 72.0)		NR (24 to NR)	
Lymph nodes harvested		.01		.03
≤17	36.1 (26.6 to 46.9)		134 (87 to 144)	
>17	12.1 (4.8 to 27.3)		NR (87 to NR)	
Macroscopic mesenteric lymph nodes		.39		.64
Yes	33.3 (20.2 to 49.7)		139 (87 to 223)	
No	31.5 (22.7 to 41.7)		134 (96 to 144)	
Tumor stage		.58		.40
I	0 (0 to 39)		NR (NR to NR)	
II	35.7 (16.3 to 61.2)		NR (25 to NR)	
III	31.7 (23.6 to 41.2)		138 (96 to 223)	
Tumor grade		.88		.25
G1	31.8 (23.7 to 41.1)		138 (117 to 223)	
G2	30.0 (14.5 to 51.9)		81 (66 to 96)	
Involvement of radial margins		.50		.33
Yes	33.3 (15.2 to 58.3)		139 (41 to NR)	
No	32.1 (23.9 to 41.5)		134 (96 to 144)	
Lymphovascular invasion		.78		.55
Yes	32.9 (23.0 to 44.5)		139 (87 to 144)	
No	23.1 (8.2 to 50.3)		87 (87 to 88)	
Unknown	30.4 (19.1 to 44.8)		138 (117 to 223)	

(continued)

Table 2. (continued)

Characteristics	Recurrence rate (95% CI), %	P*	Median DFS (95% CI), mo	P†
Perineural invasion		.24		.31
Yes	34.0 (22.7 to 47.4)		144 (78 to 144)	
No	15.0 (5.2 to 36.0)		124 (96 to NR)	
Unknown	33.9 (22.9 to 47.0)		139 (117 to 223)	

*Calculated by χ^2 or Fisher's exact test, as appropriate. Both tests were two-sided. CI = confidence interval; DFS = disease free survival; NR = not reached.
†Calculated by two-sided log-rank test.

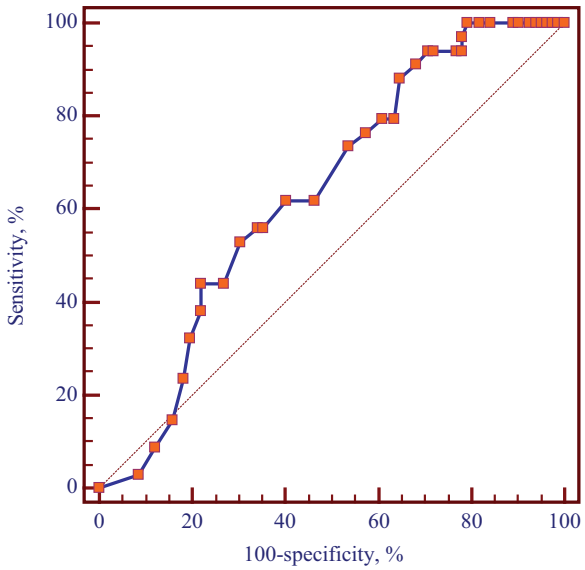

Figure 3. Lymph node count and tumor recurrence. Receiver operating characteristic curve showing the relationship between sensitivity and false-positive rate.

risk of tumor recurrence in multivariable analysis (odds ratio = 0.21, 95% CI = 0.06 to 0.80, $P = .02$).

We also evaluated a lower lymph node threshold of 12 based on data on minimal adequate evaluation in colorectal cancer (14). On univariate analysis, a number of harvested lymph nodes of less than 12 was associated with increased tumor recurrence in a statistically significant fashion ($P = .04$).

Disease-Free Survival

DFS was measured from time of resection until the earliest evidence of relapse, death from any cause, or last clinical contact. The median DFS was 138 months (95% CI = 117 to 223 months) (Figure 4A). The five- and 10-year DFS rates were 81.6% (±3.8%) and 59.5% (±5.9%). There was no difference between TTP and DFS because no death was recorded before tumor recurrence. As illustrated in Figure 4B, patients who underwent resection of more than 17 lymph nodes had a superior DFS as compared with those who were subjected to dissection of 17 or fewer lymph nodes (median DFS = 134 months vs not reached, respectively, $P = .04$). In multivariable analysis, statistical significance was retained after controlling for race, tumor multifocality, and tumor size ($P = .04$). All remaining clinical-pathologic factors were not statistically significantly associated with changes in DFS (Table 2).

Immortal Time Bias

To mitigate the immortal time bias, patients who were seen at our institution within 12 months of their diagnosis (n = 109, 84.5%) were analyzed separately (data not shown). The median DFS of patients referred within 12 months of diagnosis was 134 months (95% CI = 87 to 144 months), whereas the median DFS was not reached (95% CI = 223 months to not reached) in patients referred after 12 months ($P = .01$).

Overall Survival

Five deaths occurred among the 129 patients in this cohort. Of the four deaths recorded among relapsing patients, two deaths were known to be directly related to progressive metastatic disease, one was possibly related to disease progression, and one was not tumor related (data not shown). Of the two deaths clearly attributable to progressive metastatic disease, one occurred nine years after initial surgery and seven years after metastatic relapse, while the other was recorded 12 years after initial surgery and seven years after relapse. All the remaining 36 patients with relapsed disease were alive at the time of data cutoff. Among relapsing patients, the 10-year and 15-year OS rates were 92.9% (±5.0%) and 74.0% (±13.3%).

Discussion

Data on risk of recurrence after resection of stage I–III midgut NETs are scarce. Retrospective series (5,6) have been limited by small size, relatively short median follow-up, and inclusion of patients who recurred prior to referral to the institution conducting the study. These factors can lead to either overestimation or underestimation of recurrence risk. Yet accurate information on probability of recurrence is critically important for several reasons: postoperative surveillance guidelines need to draw upon these data to develop recommendations on timing and duration of follow-up evaluations, adjuvant studies require estimates of baseline risk of recurrence, and patients seek accurate information on their personal risk of recurrence after surgery.

Past multi-institutional series have demonstrated that the large majority of patients presenting with midgut NETs have evidence of lymph node involvement on surgical resection. Metastatic recurrence rates in these patients have been reported to be roughly 50%, with an increase in risk associated with more distant mesenteric lymph node metastases and multifocal primary tumors (which are often associated with gross lymphadenopathy) (5,6,13).

Our database of 129 patients who underwent resection of stage I–III midgut NETs represents, to our knowledge, the largest single or multi-institutional series to examine this specific population. Results of our analysis show that 76.8% of patients

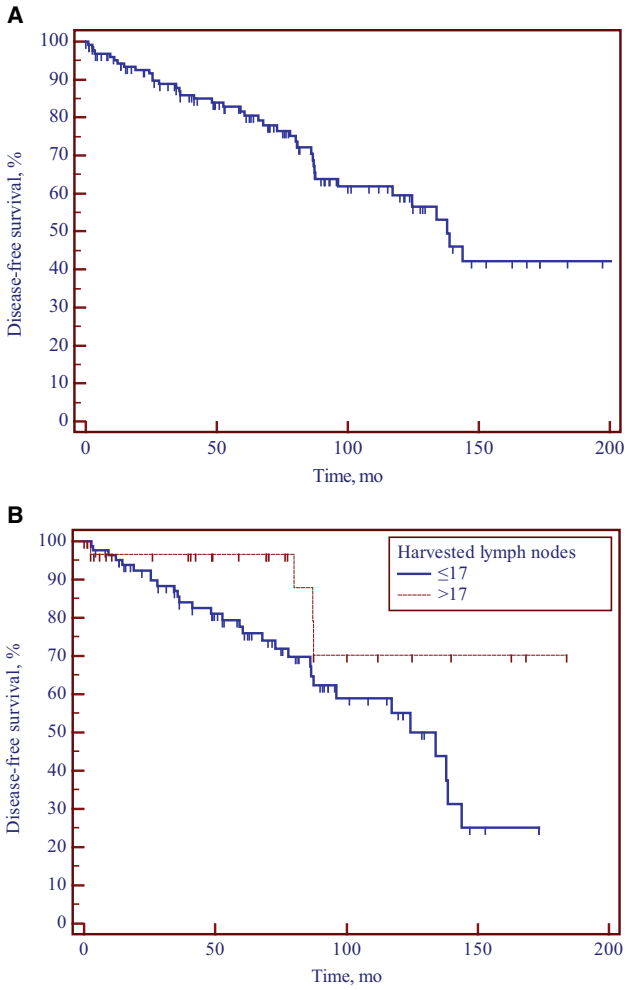

Figure 4. Kaplan-Meier estimates of disease-free survival (DFS). **A)** DFS in the overall population. **B)** DFS by number of harvested lymph nodes.

presented with lymph node–positive disease. This is similar to a rate of 79% observed in a multi-institutional French study of 100 patients (5). The median follow-up of 81 months allows us to evaluate long-term risk of recurrence with reasonable accuracy, although estimates of cumulative recurrence risk after five years are limited by large confidence intervals due to small numbers. Among all patients, the recurrence rate in our series was 31.0% (95% CI = 23.0% to 39.0%). Among lymph node–positive patients (n = 99), the long-term recurrence rate was 32.3%, with a 95% confidence interval of 23.1% to 41.5%. This is also in accordance with the prior 100-patient series (5) which revealed a 42% (95% CI = 32% to 52%) cumulative rate of recurrence (median follow-up = 57.5 months). An interesting finding in our study is that patients with stage I tumors (n = 6) had no evidence of recurrence, suggesting that such patients may be able to forgo surveillance or undergo a relatively low-intensity postoperative surveillance schedule. However, larger series of stage I patients are needed to draw firmer conclusions regarding recurrence risk.

The rate of recurrence in our database was relatively steady over an eight-year period, with a subsequent dropoff. It is uncertain whether this finding reflects a true decline in recurrence after eight years or a statistical artifact (only 25% of patients had surveillance beyond eight years). We conclude from these data that surveillance for recurrence does not need to be particularly frequent during the initial years after surgery. Indeed, an annual surveillance interval will likely allow early detection of most patients with metastatic disease. It is hard to recommend an outer limit for duration of surveillance given the fact that recurrences can occur after 10 years. However, given the apparent decline in recurrence after eight years, a decade-long duration of active surveillance will likely enable detection of most recurrences. In our series, the small number of patients with baseline elevated 5-HIAA or CgA hinders reliable conclusions regarding the role of tumor markers in the postoperative surveillance of patients with midgut carcinoid. While CgA did not appear to be a robust tumor marker for detection of metastatic recurrence, urine 5-HIAA levels did increase at the time of diagnosis of recurrence. However, it is difficult to ascertain whether measurement of urine 5-HIAA adds diagnostic value beyond cross-sectional imaging.

Among the clinical-pathologic features evaluated in this study, only the number of harvested lymph nodes statistically significantly predicted recurrence in both univariate ($P = .01$) and multivariable analysis ($P = .02$). While ROC analysis identified 17 lymph nodes as most predictive of recurrence, even removal of 12 lymph nodes was associated with a statistically significant reduction in recurrence risk. Consistent with the evidence that removal of mesenteric lymph node metastases positively impacts survival in patients with midgut NETs (15), our data suggest that an appropriate lymphadenectomy, rather than simple segmental bowel resection, is preferable in midgut NETs. With respect to other pathological prognostic factors, the statistical power of our study is limited by relatively small numbers of patients with grade 2 and lymph node–negative tumors. In our analysis, we were only able to confirm two deaths that were clearly attributable to disease progression. Given the median age of diagnosis (57 years) and very long survival of patients with early detection of metastatic disease on surveillance, it is unclear to what extent a diagnosis of early-stage midgut NET impacts overall life expectancy. It is likely that competing causes of death exceed NET-related deaths in this population. This has important implications regarding adjuvant therapy trials as it would be difficult to demonstrate that delay in recurrence impacts survival.

The main limitation of our study is incomplete follow-up, either due to loss of patients from the practice (patients undergoing surveillance at other institutions or choosing to forgo surveillance), or due to the fact that some patients were diagnosed within the past decade and therefore have not completed a 10-year course of surveillance. Therefore, it is possible that our recurrence rate of 31.0% represents an underestimation of the true long-term recurrence rate. An ideal estimation of recurrence risk would require a prospective database with a fixed surveillance schedule and a very long duration of follow-up.

Note

The authors declare no conflicts of interest.

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