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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Presentation and Management of Gastrointestinal Stromal Tumors of the Duodenum: A Multi-Institutional Analysis

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ABSTRACT

Background. Duodenal gastrointestinal stromal tumors (GISTs) are a small subset of GISTs, and their management is poorly defined. We evaluated surgical management and outcomes of patients with duodenal GISTs treated with pancreaticoduodenectomy (PD) versus local resection (LR) and defined factors associated with prognosis.

Methods. Between January 1994 and January 2011, 96 patients with duodenal GISTs were identified from five major surgical centers. Perioperative and long-term outcomes were compared based on surgical approach (PD vs LR).

Results. A total of 58 patients (60.4 %) underwent LR, while 38 (39.6 %) underwent PD. Patients presented with gross bleeding ($n = 25$; 26.0 %), pain ($n = 23$; 24.0 %), occult bleeding ($n = 19$; 19.8 %), or obstruction ($n = 3$; 3.1 %). GIST lesions were located in first ($n = 8$, 8.4 %), second ($n = 47$; 49 %), or third/fourth ($n = 41$; 42.7 %) portion of duodenum. Most patients ($n = 86$; 89.6 %) had negative surgical margins (R0) (PD, 92.1 vs LR, 87.9 %) ($P = 0.34$). Median length of stay was longer for PD (11 days) versus LR (7 days) ($P = 0.001$). PD also had more complications (PD, 57.9 vs LR, 29.3 %) ($P = 0.005$). The 1-, 2-, and 3-year actuarial recurrence-free survival was 94.2, 82.3, and 67.3 %, respectively. Factors associated with a worse recurrence-free survival included tumor size [hazard ratio (HR) = 1.09], mitotic count >10 mitosis/50 HPF (HR = 6.89), AJCC stage III disease (HR = 4.85), and NIH high risk classification (HR = 4.31) (all $P < 0.05$). The 1-, 3-, and 5-year actuarial survival was 98.3, 87.4, and 82.0%, respectively. PD versus LR was not associated with overall survival.

Conclusions. Recurrence of duodenal GIST is dependent on tumor biology rather than surgical approach. PD was associated with longer hospital stays and higher risk of perioperative complications. When feasible, LR is appropriate for duodenal GIST and PD should be reserved for lesions not amenable to LR.

Gastrointestinal stromal tumors (GISTs), defined as spindle cell tumors that are CD117 (c-kit protein) positive, are the most common mesenchymal tumors arising within the gastrointestinal (GI) tract. GISTs account for only 1–3% of all gastrointestinal tumors.[1–4] While GISTs can arise throughout the entire GI tract, GISTs are most commonly found in the stomach (50–60 %), small intestine (20–30 %), and colorectum (10 %).[4] Duodenal tumors compromise a small and rare subset with an overall frequency of 3–5 %, while comprising about 6–21 % of surgically resected GISTs.[5,6] Previous reports have demonstrated that GISTs of different anatomic sites have different clinical, histological, and immunohistochemical characteristics; perhaps more importantly, some studies have found that anatomic location is an important prognostic factor independent of tumor diameter and mitotic rate, which are the two main risk factors most often associated with recurrence and metastases.[4,7–10]

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Complete surgical resection remains the main curative treatment modality for primary GISTs regardless of the anatomic site.[2,4,6,11–13] Unlike carcinomas, GISTs typically do not infiltrate into adjacent structures and rarely metastasize to lymph nodes.[14] Because of their anatomic location, the optimal surgical procedure for duodenal GISTs remains poorly defined. Specifically, while local resection (LR) may be technically feasible, anatomical considerations may make LR more difficult due the proximity of other anatomical structures, including the duodenal papilla, pancreas, and the biliary and pancreatic ducts.[15–18] As such, pancreaticoduodenectomy (PD) may be warranted in a subset of patients.[18,19] While PD is generally safe and associated with low mortality, many surgeons remain cautious about performing PD for duodenal GISTs as it remains a complex procedure associated with significant short- and long-term morbidity.[20] Furthermore, as GISTs rarely demonstrate lymphatic and submucosal spread, it is unclear whether extensive lymphadenectomy or radical resection is relevant to long-term survival in duodenal GIST patients.

Given that duodenal GISTs are rare, the characteristics, prognosis, and optimal surgical management have not been well clarified. Currently, there are very few reports in the literature addressing the topic of duodenal GISTs, with most being small, single-institution series.[2,5,6,12] The objective of this study was to assess the efficacy of surgical therapy for duodenal GISTs in a large cohort of patients treated at five major centers. Specifically, we sought to define the benefit of surgery for patients with duodenal GISTs, as well as determine which factors were associated with prognosis. In addition, we examined the relative perioperative outcomes, as well as long-term outcomes for those patients with duodenal GISTs managed with LR versus PD.

PATIENTS AND METHODS

Patients

Using a multi-institutional database, patients with histologically proven duodenal GIST who underwent surgical resection with curative intent between January 1994 and January 2011 at one of five institutions (The Johns Hopkins University School of Medicine, Baltimore, MD; Washington University School of Medicine, St. Louis, MO; Emory University School of Medicine, Atlanta, GA; Duke University Medical Center, Durham, NC; Medical College of Wisconsin, Milwaukee, WI) were identified.[3] The institutional review board of each respective institution approved this study. Only patients with histologically confirmed duodenal GISTs who received their treatment at a study center were included.

Data Collection

Standard demographic and clinicopathologic data were collected, including sex, age, and primary tumor characteristics, as well as American Joint Commission on Cancer (AJCC) staging. Tumors were defined as GISTs based on a combination of histological evaluation (spindle cell or occasionally epithelioid tumors, similar to other GISTs) and CD117 (KIT) positivity. Data were collected on primary tumor location and size, as well as mitotic rate. Risk categories were assigned according to revised NIH criteria.[2,21] Data on treatment-related variables, such as type of surgery (LR vs PD) and adjuvant therapy, were also obtained. Operative procedures other than PD that were defined as limited resection included local wedge or segmental resection of duodenum. In general, following LR the duodenal defect was closed primarily when possible or with a Roux-en-Y duodenojejunostomy when primary closure was not possible. Margin status was ascertained based on final pathologic assessment. Data on operative morbidity and mortality were recorded. Complications were classified according to the Clavien–Dindo classification.[22] Data on the use of perioperative therapies including imatinib were also recorded. Dates of last follow-up and vital status were collected on all patients.

Statistical Analysis

Median values were used to describe continuous data, with discrete variables displayed as totals and frequencies. Comparisons of clinicopathologic characteristics between surgical groups were assessed using the chi-square test for dichotomous and categorical variables. Mann-Whitney *U* test was used to compare continuous variables. Cumulative event rates were calculated using the method of Kaplan and Meier, and survival curves were compared using the log-rank test. Recurrence-free survival (RFS) was determined as the time from operation to either biopsy-proven or radiologic evidence of disease recurrence. Overall survival (OS) was calculated from the date of operation to last follow-up time or death. Cox's proportional hazards regression model was used for multivariate modeling of RFS and OS. Statistical significance was defined as a 2-tailed *P* value less than 0.05. All data analyses were performed using SPSS version 17.0 for Microsoft Windows (LEAD Technologies, Inc., Chicago, IL) statistical software package.

RESULTS

Patient Demographics and Clinical Presentation

Characteristics of the 96 patients included in the current study are detailed in Table 1. The median age at presentation

was 59 years (range 27–84 years). Patients with duodenal GISTs presented in several different ways: gross bleeding ($n = 25$; 26.0 %), pain ($n = 23$; 24.0 %), occult bleeding ($n = 19$; 19.8 %), or obstruction ($n = 3$; 3.1 %). There were 26 patients (28 %) who were asymptomatic and had the duodenal GISTs incidentally discovered as part of a workup for unrelated reasons. GIST lesions were located in the first ($n = 8$, 8.4 %), second ($n = 47$; 49 %), or third/fourth ($n = 41$; 42.7 %) portion of the duodenum. Most patients presented with solitary/focal disease ($n = 88$; 91.6 %). The median size of the GIST on cross-sectional imaging was 4 cm (range 0.1–32 cm).

In comparing patients who underwent PD versus LR, many of the clinicopathological characteristics in the two cohorts were similar, including patient sex and median age (Table 2). Patients who ultimately underwent PD were, however, more likely to present with a larger tumor (median size: PD, 5.0 cm vs LR, 3.5 cm; $P = .002$) and more commonly presented with a tumor in the second portion of the duodenum (second portion: PD, 81.6 vs LR, 28.1 %; $P = 0.001$). In addition, while pain was the most common complaint among patients ultimately undergoing PD (pain: PD, 36.8 vs LR, 8.6%; $P = 0.003$), bleeding was the leading presenting symptom among patient who had an LR (bleeding: PD, 31.6 vs LR, 67.2 %; $P = 0.003$).

Of the 96 patients with duodenal GISTs who underwent surgery, 22 patients (22.9 %) received perioperative therapy with imatinib. Specifically, three patients (PD, $n = 0$ vs LR, $n = 3$) received preoperative neoadjuvant imatinib. Adjuvant imatinib was administered to 18 patients (18.8 %) (PD, $n = 6$ vs LR, $n = 12$). One patient received both preoperative and postoperative imatinib.

Details of Duodenal-Directed Surgery and Postoperative Course

Of the 96 patients with duodenal GISTs, 58 (60.4 %) underwent LR while 38 (39.6 %) underwent PD. Among the 58 patients who underwent LR, the duodenal defect was closed either primarily ($n = 47$; 81.0 %) or with a Roux-en-Y duodenojejunostomy reconstruction ($n = 11$; 19.0 %) (Table 3). At the time of duodenal GIST resection, 27 patients (28.1 %) underwent a concomitant procedure such as a colectomy ($n = 8$; 8.3 %), hepatectomy ($n = 3$; 3.1 %), or other ($n = 6$; 6.3 %); the need for a concomitant procedure was similar among patients undergoing PD (21.1 %) versus LR (31.0 %) ($P = 0.28$). One patient who underwent a PD for a duodenal GIST had a concomitant portal vein resection and reconstruction. Lymphadenectomy, defined as the harvesting of at least one lymph node, was performed in 43 patients (43.8 %) (PD, $n = 38$; 100 % vs LR, $n = 5$; 13.2 %).

TABLE 1 Demographics and tumor characteristics for patients with duodenal GIST ($n = 96$)

Variable	No. of patients (%)/ median (range)
Age (years)	59 (27–84)
Gender	
Male	53 (55.2 %)
Female	43 (44.8 %)
Ethnicity	
White	82 (85.4 %)
Black	8 (8.3 %)
Other	6 (6.3 %)
Symptoms on presentation	
Gross bleeding	25 (26.0 %)
Occult bleeding	19 (19.8 %)
Pain	23 (24.0 %)
Obstruction	3 (3.1 %)
Tumor size (cm)	4.0 (0.1–32.0)
Mitotic no.	
≤5 mitosis/50 HPF	79 (82.3 %)
6–10 mitosis/50 HPF	11 (11.5 %)
>10 mitosis/50 HPF	6 (6.2 %)
AJCC/UICC	
Stage I	56 (58.3 %)
Stage II	14 (14.6 %)
Stage III	13 (13.5 %)
Stage IV	13 (13.5 %)
NIH risk classification[23]	
Very low risk	8 (8.3 %)
Low risk	46 (47.9 %)
Intermediate risk	25 (26.0)
High risk	16 (16.7 %)
Unknown	1 (1.0 %)
Site	
D1	8 (8.3 %)
D2	47 (49.0 %)
D3/D4	41 (42.7 %)
Lymph nodal involvement	2 (2.1 %)
Margin status	
R0	86 (89.6 %)
R1	10 (10.4 %)
Synchronous metastasis	9 (9.4 %)

On final pathological analysis, the overwhelming majority of patients ($n = 86$; 89.6 %) had a negative surgical margin (R0); 10 patients (10.4 %) were noted to have microscopic disease at the margin (R1), and no patient had residual macroscopic disease (R2). The incidence of R0 margin was comparable among patients who underwent a PD (92.1 %) versus LR (87.9 %) ($P = 0.34$). Lymph node metastasis was rare ($n = 2$; 2.1 %). On assessment of

TABLE 2 Comparison between limited resection and pancreaticoduodenectomy procedure for duodenal GIST

Variable	Limited duodenal resection ($N = 58$)	Pancreaticoduodenectomy ($N = 38$)	P value
Demographics			
Median age (years)	59 (34–84)	58 (27–77)	0.32
Female gender	26 (44.8 %)	17 (44.7 %)	1
Symptoms			0.003
Gross bleeding	19 (32.8 %)	7 (18.4 %)	
Occult bleeding	20 (34.5 %)	5 (13.2 %)	
Pain	5 (8.6 %)	14 (36.8 %)	
Obstruction	2 (3.4 %)	1 (2.6 %)	
Tumor factors			
Median tumor size (cm)	3.5 (0.1–32.0)	5.0 (1.1–13.0)	0.002
Mitotic no.			0.79
≤5 mitosis/50 HPF	49 (84.5 %)	30 (78.9 %)	
6–10 mitosis/50 HPF	6 (10.5 %)	5 (13.2 %)	
>10 mitosis/50 HPF	3 (5.3 %)	3 (7.9 %)	
Site			0.001
D1	5 (8.8 %)	3 (7.9 %)	
D2	16 (28.1 %)	31 (81.6 %)	
D3/D4	37 (63.8 %)	4 (10.5 %)	
Lymph node metastasis	0	2 (12.5 %)	0.29
Distant metastases	2 (3.4 %)	6 (15.8 %)	0.03
Positive margin	7 (12.3 %)	3 (8.1 %)	0.52
Operative details			
Lymphadenectomy	10 (17.2 %)	32 (84.2 %)	0.001
Portal vein resection	0	1 (2.6 %)	0.21
Concomitant procedure	18 (31.0 %)	9 (23.7 %)	0.43
Outcomes			
Length of hospitalization (days)	7 (1–39)	11 (5–36)	0.001
Complications (any)	17 (29.3 %)	22 (57.9 %)	0.005
Major complications	2 (3.4 %)	9 (23.7 %)	0.006
Recurrence	7 (12.1 %)	11 (28.9 %)	0.04
Median time to recurrence (months)	30 (22–81)	19 (4–35)	0.02

histological grade, most tumors were classified as low grade ($n = 79$; 82.3 %) having <5 mitosis/50 HPF. In addition, most patients (70; 72.9 %) were classified as AJCC stage I ($n = 56$; 58.3 %) or stage II ($n = 14$; 14.6 %) (Table 1). Based on the NIH risk stratification schema, 54 patients (56.3 %) exhibited very low ($n = 8$; 8.3 %) or low ($n = 46$; 47.9 %) risk prognostic criteria.[21] There were no differences in histological grade, AJCC staging, or NIH risk stratification comparing patients with duodenal GISTs resected by PD versus LR (Table 2).

The median length of stay was 8 days (range, 1–39 days). Median length of stay was longer among patients who underwent PD (11 days) versus LR (7 days) ($P = 0.001$). There was a postoperative death within 90 days of surgery for a mortality of 1.0 %. A total of 39 patients experienced a postoperative complication for a morbidity of 40.6 %. Most complications were mild ($n = 27$, 28.1 %) grade I–II complications, while a few were more serious grade III–V that required an intervention ($n = 12$; 12.5 %). Patients who underwent PD were more likely to experience a postoperative complication (PD, 57.9 % vs LR, 29.3 %) ($P = 0.005$); the incidence of grade III/IV complications was also higher among patients undergoing PD (PD, 23.7 % vs LR, 3.4 %) ($P = 0.006$).

Recurrence and OS

With a median follow-up of 22 months, median RFS had not been reached. At last follow-up, 18 patients (18.8 %) had recurred after a median disease-free interval

TABLE 3 Treatment details and outcomes after resection of duodenal GIST

Variable	No. of patients (%)/ median (range)
Medical therapy	
Gleevec	22 (22.9 %)
Neoadjuvant	3 (3.1 %)
Adjuvant	18 (18.8 %)
Both	1 (1 %)
Sutent (adjuvant)	2 (2.1 %)
Operative details	
Extent of resection	
Limited duodenal resection (LR)	58 (60.4 %)
Primary anastomosis	47 (49.0 %)
Roux-en-Y comparable anastomosis	11 (11.5 %)
Pancreaticoduodenectomy (PD)	38 (39.6 %)
Lymphadenectomy	42 (43.8 %)
Portal vein resection	1 (1.0 %)
Concomitant procedure	27 (28.1 %)
Treatment of metastases	
Chemotherapy	2 (2.1 %)
Resection	7 (7.3 %)
Other	1 (1.0 %)
Perioperative outcomes	
Length of hospitalization (days)	8 (1–39)
Complications (30 days)	39 (40.6 %)
Grade I	11 (11.5 %)
Grade II	16 (16.7 %)
Grade III (A & B)	9 (9.4 %)
Grade IV (A & B)	2 (2.1 %)
Grade V	1 (1 %)
Mortality (90 days)	1 (1 %)
Long-term outcomes	
Recurrence	18 (18.8 %)
Local	2 (2.1 %)
Distant	12 (12.5 %)
Both	4 (4.2 %)
Site of recurrence	
Liver	15 (15.6 %)
Lung	0
Peritoneal	1 (1.0 %)
Local/regional	6 (6.3 %)
Time to recurrence (months)	24 (4–81)
Treatment of recurrence	
Resection	8 (8.3 %)
Chemotherapy	12 (12.5 %)
Other	2 (2.1 %)

of 24 months (range, 4–81 months) (Figs. 1, 2). Among the 18 patients with recurrence, the pattern of recurrence was distant metastasis in 12 patients (12.5 %) compared with local recurrence in two patients (2.1 %), and synchronous local and distant metastases in four patients (4.2 %). Site of distant metastases was primarily liver ($n = 15$; 15.6 %) (Table 3). The 1-, 2-, and 3-year actuarial RFS for the entire cohort was 94.2, 82.3, and 67.3 %, respectively. Several factors were associated with a worse RFS. Specifically, tumor size >5 cm (HR = 1.09) and mitotic count >10 mitosis/50 HPF (HR = 6.89) were associated with an increased risk of recurrence (all $P < 0.05$) (Table 4). In addition, both AJCC stage and NIH risk classification were associated with disease-free survival. Patients with duodenal GIST who were AJCC stage I, II, and III/IV disease had a median RFS that was not reached, 81 months, and 31 months, respectively ($P = 0.008$). Similarly, median survival was not reached for patients with very low/low NIH risk classification versus 81 months for patients with intermediate risk classification and 27 months for patients who were classified as high risk ($P = 0.05$). Among all patients, those who underwent PD tended to have a shorter median time to recurrence (19 months) compared with patients treated with LR (30 months) ($P = 0.02$). Of note, however, there was no difference in the 5-year actuarial RFS following PD and LR for duodenal GIST tumors >3 cm (5-year RFS: PD, 53.9 % vs LR, 47.3 %; $P = 0.21$).

Disease-specific death following resection of duodenal GIST was somewhat uncommon. Overall 1-, 3-, and 5-year actuarial survival was 98.3, 87.4, and 82.0 %, respectively. Receipt of PD versus LR was not associated with OS. Probably because death was a relatively uncommon event, only one factor was noted to be associated with this event. Specifically, the presence of synchronous metastatic disease at the time of presentation was predictive of a worse long-term survival (HR = 5.50; $P = 0.04$).

DISCUSSION

GISTs are the most common mesenchymal tumors arising within the gastrointestinal (GI) tract and account for 1–3% of all gastrointestinal tumors.[1–4] While the clinicopathological features and frequency of duodenal GISTs have been reported previously in case reports and series, only two small studies have addressed the effect of operative methods and survival after surgery.[5,23–25] In this study we focused on management and outcomes of patients with duodenal GISTs using a large, multicenter cohort of patients. The current study is important because we define the presentation of patients presenting with duodenal GIST, as well as identify factors associated with RFS. In addition, we demonstrate that tumor-specific factors including tumor size, number of mitosis, and NIH risk classification were more strongly associated with outcome rather than the

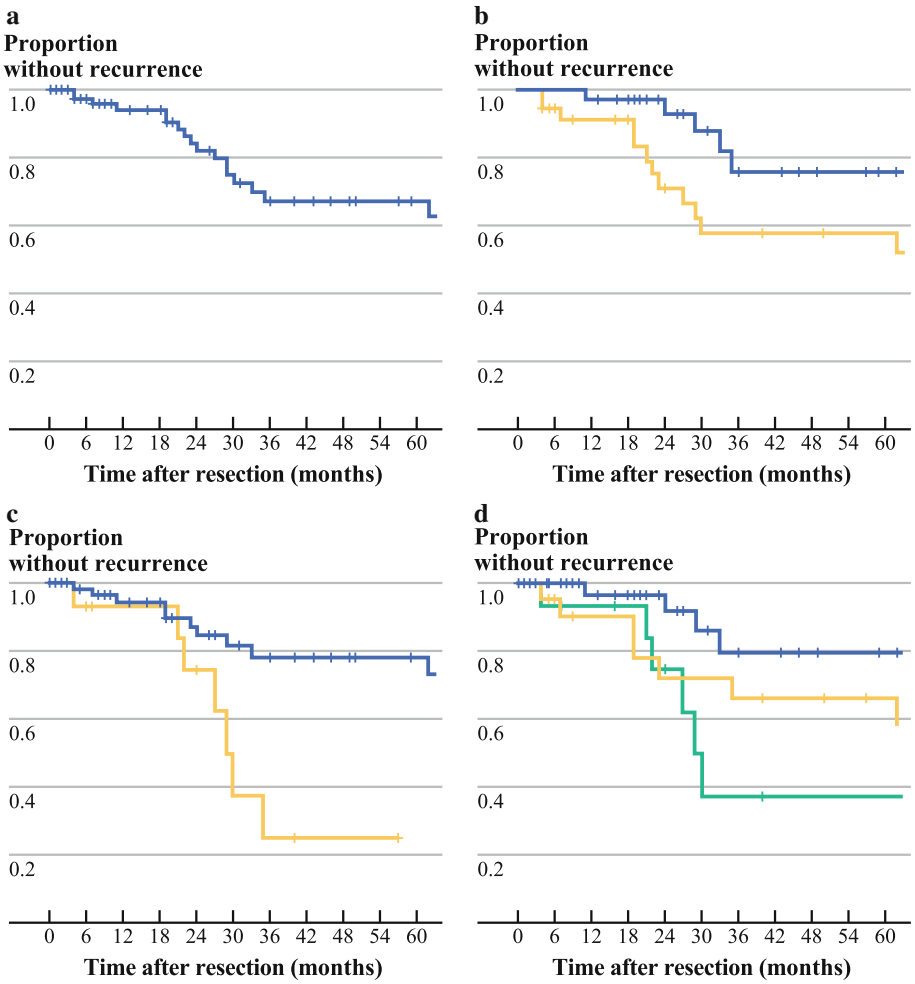

FIG. 1 Recurrence-free survival of 96 patients after resection of duodenal GIST. **a** 82.3 % at 2 years and 67.3 % at 3 and 5 years. **b** Stratified by tumor size: <5 cm (*blue line*): median survival not reached vs ≥5 cm (*yellow line*): 81 months ($P = 0.03$). **c** Stratified by mitotic index: ≤5 mitosis/50 HPF (*blue line*): median survival not reached vs ≥5 mitosis/50 HPF (*yellow line*): 29 months ($P = 0.004$). **d**. Stratified by NIH risk classification. Low risk (*blue line*), median survival not reached vs intermediate risk (*yellow line*), 81 months, vs high risk (*green line*), 29 months ($P = 0.05$)

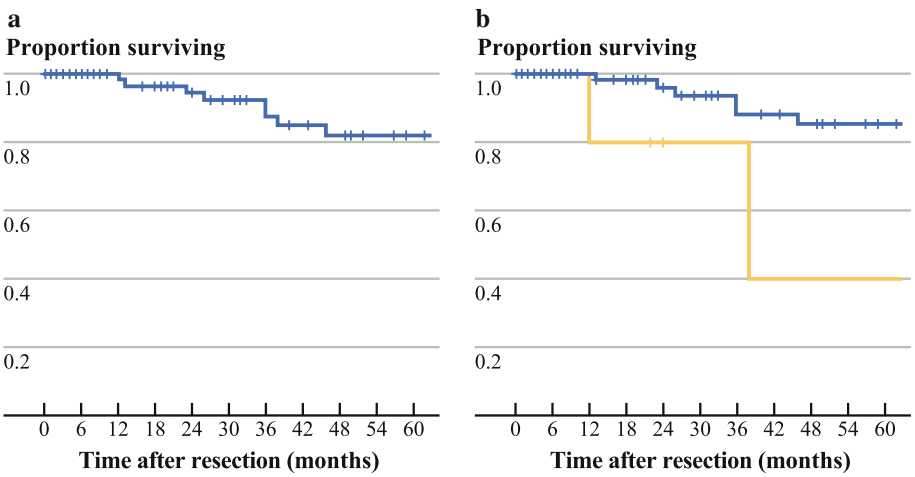

FIG. 2 Overall survival of 96 patients after resection of duodenal GIST. **a** Overall 1-, 3-, and 5-year actuarial survival was 98.3, 87.4, and 82.0 %, respectively. **b** Stratified by metastatic disease: no metastases (*blue line*): median survival not reached vs metastases present (*yellow line*): median 38 months ($P = 0.02$)

specific surgical approach. In addition to having the same incidence of R0 resection, patients who underwent PD versus LR also had the same long-term OS. While patients who underwent PD did have a somewhat shorter disease-free survival when all patients were examined, after controlling for tumor size, the difference in disease-free survival disappeared. In summary, our data strongly suggest that biological factors—rather than surgical approach—dictate outcome among patients with duodenal GISTs. As such, both PD and LR are acceptable surgical strategies, and

TABLE 4 Analysis of factors associated with recurrence-free and overall survival after resection of duodenal GIST

Variable	Recurrence-free survival		Overall survival	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age	0.96 (0.92–1.00)	0.050	0.97 (0.92–1.03)	0.35
Female gender	0.64 (0.25–1.67)	0.36	2.23 (0.57–8.69)	0.25
Tumor size	1.09 (1.00–1.19)	0.050	0.94 (0.75–1.19)	0.61
Mitotic no.				
≤5 mitosis/50 HPF	Reference group		Reference group	
6–10 mitosis/50 HPF	2.46 (0.66–9.08)	0.17	1.83 (0.39–8.64)	0.45
>10 mitosis/50 HPF	6.89 (2.04–23.3)	0.002	1 (0–∞)	0.99
AJCC/UICC				
Stage I	Reference group		Reference group	
Stage II	2.99 (0.79–11.28)	0.11	0.33 (0.04–2.85)	0.32
Stage III	4.85 (1.36–17.29)	0.015	1.10 (0.21–5.71)	0.91
Stage IV	7.21 (1.59–32.68)	0.010	4.68 (0.86–25.53)	0.07
NIH risk classification				
Very low to low risk	Reference group		Reference group	
Intermediate to high risk	3.23 (1.06–9.88)	0.039	0.71 (0.20–2.50)	0.59
NIH risk classification				
Very low to low risk	Reference group		Reference group	
Intermediate	2.69 (0.80–9.05)	0.11	0.59 (0.14–2.53)	0.48
High risk	4.31 (1.22–15.3)	0.024	1.01 (0.19–5.20)	0.99
Site				
D1	Reference group		Reference group	
D2	0.36 (0.08–1.68)	0.19	3.65 (0.65–20.6)	0.14
D3/D4	0.27 (0.05–1.42)	0.12	0.46 (0.10–2.08)	0.31
Metastatic disease	3.32 (0.96–11.65)	0.06	5.50 (1.10–27.53)	0.038
Margin status				
R0	Reference group		Reference group	
R1	3.09 (0.68–14.05)	0.15	0.05 (0.00–1.67)	0.79
Extent of resection				
Limited resection	Reference group		Reference group	
Whipple	2.38 (0.92–6.17)	0.08	1.10 (0.31–3.86)	0.89
Lymphadenectomy	1.85 (0.73–4.71)	0.20	0.81 (0.23–2.89)	0.75
Concomitant procedure	1.25 (0.44–3.52)	0.68	2.38 (0.63–9.07)	0.21

the approach should be dictated by the location of the lesion within the duodenum and the ability to achieve an R0 margin.

The clinical presentations of duodenal GIST can be variable, according to their size and the existence of mucosal ulceration. Similar to previous reports, in the current study, patients with duodenal GISTs most commonly presented with gastrointestinal bleeding, epigastric pain, and rarely intestinal obstruction.[5,6,15–17,19,26] We noted that patients who ultimately required a PD were more likely to present with larger tumors that caused pain. In contrast, patients who ultimately required LR more often presented with bleeding. In general, GISTs have been noted to most frequently involve the second portion of the duodenum, followed by the third portion, fourth portion, and first portion.[5] While we also noted that most duodenal GISTs were located in the second portion of the duodenum (49.0 %), we did find a high incidence of lesions in both the third and fourth portion of the duodenum (42.7 %). Perhaps, as expected, tumors in the second portion of the duodenum were much more likely to require a PD. As such, while one should always be prepared for a PD, this seems particularly likely when the tumor is found in this location.

The finding that most patients had a tumor with a low mitotic count (82.3 %) is consistent with those reported by others (72–78 %).[5,6,15] Interestingly, the proportion of patients within the different NIH risk categories

(high, intermediate, low, very low) was dissimilar to previous reports that examined small bowel GISTs in general. In the current series, most duodenal GISTs were classified as very low/low risk (54 %), while many other surgical series have reported much lower proportions of very low/low risk patients for small bowel tumors using the NIH risk stratification criteria.[10,27–34] Differences in the pathologic interpretation leading to a misclassification bias, referral bias, or actual difference in the incidences of risk categories among different patient populations are potential explanations for these differences. However, when looking at studies that specifically focused on duodenal GISTs, the incidence of very low/low risk patients was similar, suggesting that duodenal GISTs may belong in a better prognostic category than other small bowel GISTs.[15,18,24]

Complete surgical resection with clear surgical margins including adjacent organs as necessary remains the main curative treatment modality for GIST.[4,11] Choice of surgical procedure for duodenal GIST generally is customized mainly to the size, location, and extent of disease. Additionally, as local and regional lymph node involvement is infrequent in GIST, routine lymph node dissection is not advocated.[4,35] In patients in whom the GIST is located near the ampulla of Vater, medial wall of the 2nd/3rd portion of the duodenum, or if the pancreas is involved then PD is most likely necessary. However, there remains some controversy regarding the optimal method for the resection of duodenal GIST with some investigators supporting the selective use of LR versus others who almost always perform a PD. Supporters of PD suggest an aggressive surgical approach is almost always required for complete removal of the tumor when it is located in the duodenum.[5,11,15–17] Additionally, proponents of PD feel that while LR may be simpler to perform, there is a risk of subsequent anastomotic leakage or stenosis and perhaps even earlier tumor recurrences compared with PD.[11,15–17,19] Advocates of LR tout that the operation contributes to a better quality of life and also has the added benefits of preservation of the pancreas and continuity of the GI tract.[15–17,19] Whether LR is an adequate alternative to PD has until now only been addressed in several small series.[5,11,19,36] In the current multi-institutional series, we noted that among patients presenting with a duodenal GIST over one-third (39.6 %) could be treated with a local surgical procedure that avoided a PD. Several criteria were associated with an increased likelihood of requiring PD versus LR (i.e., larger tumors, D2 location). Of note, PD was also associated with an increased length of stay as well as increased perioperative morbidity. Collectively, these data indicate that LR may be a feasible option for a significant subset of patients who present with duodenal GIST.

In the current series, the 1- and 3-year disease-free survival was 94.2 and 67.3 %, respectively. Previous studies had noted a 3-year disease-free survival for duodenal GIST that ranged from 50 to 95 %.[18,25] In comparison, the 3-year survival for other small bowel GIST has been noted to be lower at 40 %.[27,33] The reason for the improved outcome for patients with duodenal GIST is probably multifactorial and may be secondary to earlier presentation, smaller tumors, and a lower NIH risk classification. Factors associated with RFS did include several of these very factors such as AJCC staging and NIH risk classification. In contrast, margin status was not associated with overall or disease-free survival. The reason for this was probably related to the fact that the overwhelming majority of patients had an R0 resection—making margin status difficult to evaluate as a prognostic factor. It is important to note that other studies have reported that the relapse rate for resection of GIST was 5 % among those who had complete resection versus close to 90 % among those with an unresected or incompletely resected tumor.[11,12]

Imatinib mesylate (Gleevec), and other tyrosine kinase inhibitors, have played a key role in the management of GISTs, both as neoadjuvant therapy and in patients with recurrent and metastatic disease.[37–39] The role of a tyrosine kinase inhibitor as neoadjuvant therapy has been advocated as a means to downstage tumors that would otherwise require more extensive surgery.[38–42] RTOG 0132 suggested that neoadjuvant imatinib may play a significant role in tumor shrinkage and facilitate complete resection or decrease the morbidity of resection.[41] A summary of several trials involving imatinib therapy revealed a complete response rate in 1–6 %, partial response in 45–67 %, and stable disease in 16–33 %.[40,43] In the current study, less than a handful of patients received neoadjuvant imatinib ($n = 3$), while about 20 % of patients received adjuvant imatinib. Imatinib was mostly used in patients with larger tumor size, high-grade tumors, and those with a high NIH risk classification, suggesting the use of tyrosine kinase inhibitors in our cohort was predominantly used in higher-risk patients as recommend.[44] Of note, the three patients in the current study who received neoadjuvant imatinib were able to undergo LR. Use of neoadjuvant imatinib for GISTs involving the duodenum may potentially allow a proportion of patients who might otherwise require a PD to undergo LR instead, and should therefore be considered for patients with GISTs in the 2nd part of the duodenum and for those patients with large tumors.

In conclusion, our observations strongly suggest that recurrence of duodenal GIST is primarily dependent on tumor biology, including size and mitotic index rather than surgical approach. PD was associated with longer hospital stays and higher risk of perioperative complications. As the largest series published to date, our data demonstrated no differences in OS among patients with duodenal GISTs

undergoing PD versus LR. Collectively, our data therefore suggest that attempts at downsizing duodenal tumors may be beneficial, preventing patients from undergoing a more extensive operation, while still preserving comparable outcomes for patients with duodenal GISTs.

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