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ORIGINAL ARTICLE – PANCREATIC TUMORS

Limited Resection Versus Pancreaticoduodenectomy for Duodenal Gastrointestinal Stromal Tumors? Enucleation Interferes in the Debate: A European Multicenter Retrospective Cohort Study

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ABSTRACT

Background. The optimal surgical procedure for duodenal gastrointestinal stromal tumors (D-GISTs) remains poorly defined. Pancreaticoduodenectomy (PD) allows for a wide resection but is associated with a high morbidity rate.

Objectives. The aim of this study was to compare the short- and long-term outcomes of PD versus limited resection (LR) for D-GISTs and to evaluate the role of tumor enucleation (EN).

Methods. In this retrospective European multicenter cohort study, 100 patients who underwent resection for D-GIST between 2001 and 2013 were compared between PD ($n = 19$) and LR ($n = 81$). LR included segmental duodenectomy ($n = 47$), wedge resection ($n = 21$), or EN ($n = 13$). The primary objective was to evaluate disease-free survival (DFS) between the groups, while the secondary objectives were to analyze the overall morbidity and mortality, radicality of resection, and 5-year overall survival (OS) and recurrence rates between groups. Furthermore, the short- and long-term outcomes of EN were evaluated.

Results. Baseline characteristics were comparable between the PD and LR groups, except for a more frequent D2 tumor location in the PD group (68.3% vs. 29.6%; $p = 0.016$). Postoperative morbidity was higher after PD (68.4% vs. 23.5%; $p < 0.001$). OS ($p = 0.70$) and DFS ($p = 0.64$) were comparable after adjustment for D2 location and adjuvant therapy rate. EN was performed more in American Society of Anesthesiologists (ASA) stage III/IV patients with tumors < 5 cm and was associated with a 5-year OS rate of 84.6%, without any disease recurrences.

Conclusions. For D-GISTs, LR should be the procedure of choice due to lower morbidity and similar oncological outcomes compared with PD. In selected patients, EN appears to be associated with equivalent short- and long-term outcomes. Based on these results, a surgical treatment algorithm is proposed.

Gastrointestinal stromal tumor (GIST) is the most common type of mesenchymal tumor of the gastrointestinal tract and is most frequently located in the stomach (60–70%) and small intestine (20–30%). Duodenal GISTs (D-GISTs) account for 5% of all GISTs.[1] The standard treatment for localized GIST is complete R0 surgical excision, avoiding tumor rupture.[2–4] Because of their

anatomic location, the optimal surgical procedure for D-GISTs remains poorly defined. Although limited resection (LR) such as a segmental duodenal resection, atypical lateral (wedge) resection, or enucleation (EN) may be technically feasible, anatomical considerations may render LR more difficult to perform due to the proximity of other critical structures, including the duodenal papilla and pancreas. As such, pancreaticoduodenectomy (PD) may be warranted in a subset of patients;[3–10] however, PD is associated with significant short- and long-term morbidity, especially for this specific indication.[11–13] In recent literature, several authors compared PD with LR for D-GISTs.[14–24] The results of these studies are in favor of offering an LR when possible rather than PD because of lower postoperative morbidity and equivalent long-term oncological results. However, in those small-size studies, the postoperative follow-up is often limited and patients are usually not comparable regarding comorbidities, tumor size, and tumor location within the duodenum.[14–17] To our knowledge, the role of EN for D-GISTs has not yet been evaluated in other studies. In a recent multicenter study of the French EsoGastric Tumors (FREGAT) Working Group network, the oncological safety of this approach has been suggested for esophageal GISTs of limited size (< 6.5 cm) without mucosal ulceration.[25] Whether or not the findings of this study could also apply to D-GISTs remains to be defined.

Consequently, the aim of this study was to evaluate (1) the postoperative course and oncological outcome of LR versus PD for patients with non-metastatic D-GISTs, and (2) the feasibility and short- and long-term outcomes of EN for D-GISTs.

METHODS

Study Design and Population

In this observational cohort study, data from 1413 consecutive adult patients treated for histopathologically confirmed GIST in 61 French-speaking European centers between 2001 and 2013 were collected retrospectively through a dedicated website (http://www.chirurgie-viscerale.org). Data on patient demographics, clinical presentation, initial work-up, operative technique, histopathology, postoperative course, and oncological outcomes were gathered and analyzed. When missing, additional data were obtained by means of e-mail exchanges or phone calls with the collaborating centers. Patients were not included if the surgical and/or tumor data required for the analysis were missing.

Overall, 109 patients treated for a D-GIST were recorded in the database. The criteria for inclusion in this study were (1) D-GIST; (2) no distant metastasis; (3) with surgical treatment; and (4) no other progressive malignancy at the time of surgery. An overview of the study population and reasons for exclusion are shown in Fig. 1. Among the remaining population (n = 100), patients who underwent EN (n = 13), wedge resection (n = 21), and segmental resection (n = 47) were grouped together in an LR group (n = 81) and compared as a whole with the PD group (n = 19). Additionally, outcomes from the subgroup of patients who underwent EN were analyzed separately. This study was registered at researchregistry.com (UIN6164). Ethics Committee approval was not required due to the retrospective observational nature of this study.

Pretreatment Work-Up and Surgical Approach

Pretreatment investigations were standardized according to the guidelines of the European Society for Medical Oncology (ESMO) that were applicable at the time of surgical treatment.[4] The surgical approach (LR/PD) was determined according to the size and location of the tumor and/or involvement of the head of the pancreas, at the discretion of the operating surgeon. Reconstruction after PD was achieved using a pancreaticojejunostomy or pancreaticogastrostomy according to surgeon and center preferences. LR included segmental resection of the duodenum, local wedge resection, or EN (excision of the tumor without mucosal disruption). In general, following LR, the duodenal defect was closed primarily whenever possible or by means of a Roux-en-Y duodenojejunostomy if primary closure was not feasible. Margin status was ascertained based on the final pathologic assessment. Perioperative care was based on the usual practices of the individual surgeons.

Postoperative Course

Postoperative morbidity was categorized into surgical complications (including anastomotic leak, intra-abdominal abscess, surgical site infection and bleeding necessitating blood transfusions, reoperation, and others) and medical complications (including urologic, pulmonary, cardiovascular, thromboembolic, neurologic complications, and others). The severity of complications was assessed according to the Clavien–Dindo (CD) classification and only grade II or higher complications were considered for the analysis of overall morbidity. Grade III/IV complications (severe complications) were assessed likewise.[13]

Histopathologic Analysis

The final diagnosis of GIST was based on histologic and immunohistochemical analysis, with selective use of

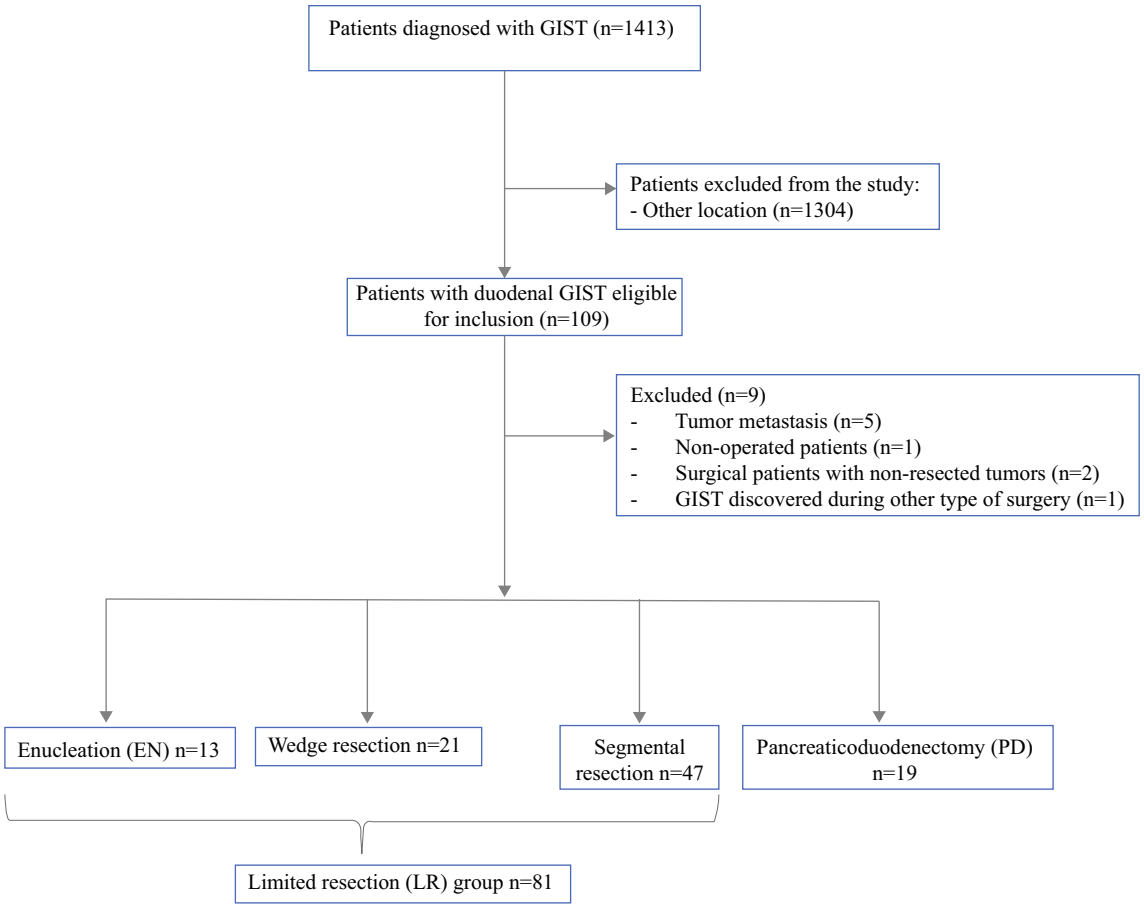

FIG. 1 Study population. *GIST* gastrointestinal stromal tumor

mutational analysis in doubtful cases. Tumor histopathology was studied to determine size (cm) and mitotic index (mitoses/5 mm^2). Risk of recurrence was evaluated according to the modified National Institutes of Health Criteria, the Armed Forces Institute of Pathology (AFIP), and the TNM stage from the 7th edition of the International Union Against Cancer.[12,26,27] Resections were designated R0 if complete removal was obtained, both macroscopically and microscopically, and R1 in the case of a microscopically positive resection margin.

Perioperative Treatment and Follow-Up

All cases were discussed during multidisciplinary team meetings. Decisions regarding the need for neoadjuvant and adjuvant tyrosine kinase inhibitors (TKIs) were made at the discretion of the local multidisciplinary teams in accordance with national and European guidelines.[3,4] Regular follow-up with clinical examination and computed tomography (CT) scan was recommended for at least 5 years, with frequency depending on the recurrence risk according to the European guidelines.[4] Disease recurrence was categorized as locoregional or distant. Mixed recurrences included concomitant locoregional and distant relapses.

Study Endpoints

The primary objective of this study was to compare the disease-free survival (DFS) between LR and PD, while the secondary objectives were to analyze the overall morbidity and mortality, radicality of resection, 5-year overall survival (OS), and 5-year recurrence in the LR and PD groups. An additional secondary objective was to evaluate the oncological results of the EN subgroup, as well as the related overall postoperative morbidity and mortality.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as median and range. The distribution of the continuous variables was verified graphically and by means of the Shapiro–Wilk test. A Chi-square test or Fisher's exact test was used to compare categorical data between groups, a Cochran–Armitage trend test for ordered categorical

TABLE 1 Baseline characteristics and therapeutic data

	Overall [n = 100]	LR group [n = 81]	PD group [n = 19]	p value	EN group [n = 13]
Age < 60 years	52 (52.0)	40 (49.3)	12 (63.2)	0.28	4 (30.8)
Male	55 (55.0)	44 (54.3)	11 (57.9)	0.78	6 (46.2)
ASA score > 2	18 (18.0)	16 (19.8)	2 (10.5)	0.51	5 (38.5)
Tumor location				**0.016**	
D1	13 (13.0)	12 (14.8)	1 (5.3)		4 (30.8)
D2	37 (37.0)	24 (29.6)	13 (68.3)		6 (46.2)
D3	32 (32.0)	28 (34.6)	4 (21.1)		2 (15.4)
D4	18 (18.0)	17 (21.0)	1 (5.3)		1 (7.7)
Cause of diagnosis				0.78	
Symptomatic	71 (71.0)	58 (71.6)	13 (68.4)		3 (23.1)
Incidental	29 (29.0)	23 (28.4)	6 (31.6)		10 (76.9)
Biopsy	55 (55.0)	39 (48.1)	16 (84.2)	**0.005**	4 (30.8)
Mucosal ulceration on diagnostic endoscopy[a]	34/60 (56.7)	28/47 (59.6)	6/13 (46.2)	0.39	7/8 (87.5)
Neoadjuvant therapy	6 (6.0)	4 (4.9)	2 (10.5)	NA	0 (0.0)
Elective surgery	92 (92.0)	75 (92.6)	17 (89.5)	0.65	12 (92.3)
Laparotomy	95 (95.0)	76 (93.8)	19 (100.0)	0.59	11 (84.6)
Tumor breach or perforation	3 (3.0)	2 (2.5)	1 (5.3)	0.47	1 (7.7)
Median operating time, min (median [range])	224 [60–502]	190 [60–480]	350 [190–502]	< **0.001**	180 [90–240]
Estimate blood loss, mL (median [range])	50 [0–1800]	0 [0–1600]	100 [0–1800]	0.050	0 [0–0]
Intraoperative transfusion	5 (5.0)	2 (2.5)	3 (15.8)	**0.046**	0 (0.0)
Adjuvant therapy	31 (31.0)	21 (25.9)	10 (52.6)	**0.023**	0 (0.0)

Data are expressed as n (%) unless otherwise specified

LR limited resection, *PD* pancreaticoduodenectomy, *ASA* American Society of Anesthesiologists, *NA* not applicable, *EN* enucleation

[a]Missing data in 10 patients, among 70 patients assessed by endoscopy

variables, and a Mann–Whitney test was used for non-gaussian continuous variables. Follow-up data included the date of the most recent follow-up or 11 October 2016**,** the censoring date. The 3- and 5-year OS and DFS were estimated using the Kaplan–Meier method. The Cox proportional hazard regression model was performed to estimate the hazard ratio (HR) and its 95% confidence interval (CI) for PD versus LR group comparison. The DFS analysis was adjusted for D2 location and adjuvant therapy in the PD versus LR group comparison. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA) and a p value < 0.05 was considered statistically significant.

RESULTS

Pancreaticoduodenectomy (PD) Versus Limited Resection (LR)

Baseline Demographics and Pre-Therapeutic Data An overview of baseline demographics and pre-therapeutic data is illustrated in Table 1. Median age was 60 years (range 28–107), and overall median follow-up after surgery was 63.2 months (interquartile range 40.6–86.5). Demographic characteristics and the American Society of Anesthesiologists (ASA) score did not differ significantly between the PD and LR groups. D-GISTs were discovered incidentally in 29% of cases, either by abdominal CT (n = 24) or by means of an endoscopy (n = 5). In symptomatic patients, the most common presenting symptoms were anemia (n = 48), gastrointestinal (most often externalized) bleeding (n = 31), abdominal pain (n = 24), asthenia (n = 23), weight loss (n = 12), anorexia (n = 10), and presence of an abdominal mass (n = 9); none presented with jaundice. Diagnostic modalities and the nature of presenting symptoms did not differ significantly between both groups (p = 0.39). The tumor location was significantly different between groups (p = 0.016); in the PD group, the tumor was most frequently located at the second part of the duodenum (68.3%), whereas in the LR group, the two most frequent locations were the third (34.6%) and second parts of the duodenum (29.6%). A diagnostic biopsy was performed in 55% of cases, either endoscopically (n = 50),

radiologically ($n = 4$), or surgically ($n = 1$). The number of patients who underwent a preoperative biopsy was significantly higher in the PD group (84.2% vs. 48.1%; $p = 0.005$). Among the 70 patients who underwent endoscopy as part of the preoperative assessment, data regarding endoscopic findings were available in 60 patients; mucosal ulceration was noted in 56.7% of these cases, with no significant difference between the PD and LR groups (46.2% vs. 59.6%; $p = 0.39$).

Therapeutic Data Details considering therapeutic data are shown in Table 1. Six patients received neoadjuvant TKI treatment, of whom two were included in the PD group. The median duration of neoadjuvant treatment was 8 months (1–18). Re-evaluation after neoadjuvant treatment demonstrated a partial response in three cases, stable disease in two cases, and disease progression in one case. Only five patients in the LR group underwent laparoscopic surgery, of whom two were converted to laparotomy. In the LR group, 47 patients underwent segmental resection (58%), 21 patients had a wedge resection (25.9%), and 13 D-GISTs were removed by EN (16%). Tumor breach was identified in two patients during surgical exploration. In one patient in the LR group, tumor perforation occurred intraoperatively during segmental duodenectomy. The median operating time was significantly longer in the PD group than in the LR group (350 min [190–502] vs. 190 min [60–480]; $p < 0.001$]. Blood loss tended to be higher in the PD group ($p = 0.050$), with a required transfusion rate that was six times higher ($p = 0.046$) compared with the LR group. Intraoperatively, resection was considered curative in all patients. Adjuvant TKI therapy was more frequently prescribed in the PD group (52.6% vs. 25.9%; $p = 0.023$).

Postoperative Outcomes The in-hospital and 30-day mortality rate was 0% in both groups, while the 90-day mortality rate was 1% due to one patient dying of pneumonia, which occurred after discharge from the hospital on day 38. As shown in Table 2, the overall morbidity risk was significantly higher in the PD group (68.4% vs. 23.5%; $p < 0.001$). This increased complication risk in the PD group included both surgical ($p < 0.001$) and medical complications ($p = 0.047$). Patients in the PD group were affected by higher rates of reoperation (26.3% vs. 3.7%; $p = 0.006$) and severe complications (CD grade > 2; 26.3% vs. 6.2%; $p = 0.020$). The median length of stay was also significantly prolonged in the PD group (23 days [5–103] vs. 13 days [5–50]; $p < 0.001$).

Histopathology Data Details considering the histopathological data can be found in Table 2. Only four patients were found to have a microscopic incomplete resection (R1), all of whom were in the LR group; two patients underwent an EN and two patients had a segmental resection. The number of R1 resections was too low to conclude any statistically significant difference between groups. In the overall population, the median tumor size was 4 cm (1–28), with a median mitotic index of 2 (0–50). In the PD group, tumor size, as well as the mitotic index, were not significantly higher compared with the LR group. There were no statistically significant differences in Joensuu score or modified AFIP scores, or in pTNM classification, between both groups ($p = 0.21$, $p = 0.41$, and $p = 0.39$, respectively). Molecular analysis of the resected specimen was performed in 40 patients; no mutation was detected in 9 patients, 29 patients had a KIT mutation (exon 11, 22 patients; exon 9, 6 patients; exon 13, 1 patient), and two patients had a mutation in platelet-derived growth factor-α (PDGFRα; exon 12, 1 patient; exon 18, 1 patient).

Long-Term Oncological Results The long-term oncological results are summarized in Table 3. OS rates between the LR and PD groups were comparable, with a 3- and 5-year OS rate of 95% versus 89% and 85% versus 89%, respectively (HR 1.28, 95% CI 0.36–4.54; $p = 0.70$) (Fig. 2a). The DFS rates of the LR and PD groups at 3 and 5 years were 95% versus 89% and 85% versus 89%, respectively. There was no significant difference in DFS (HR 1.24, 95% CI 0.47–3.28; $p = 0.67$] between the two groups, even after adjustment for location and adjuvant therapy (adjusted HR [aHR] 1.30, 95% CI 0.43–3.98; adjusted $p = 0.64$) (Fig. 2b). Disease recurrence occurred in 21 patients—17 patients in the LR group and 4 patients in the PD group. In the majority of cases, recurrence presented as metastatic disease (18/21, 86% of disease recurrence). Recurrence mode did not differ significantly between both groups ($p = 0.61$).

Enucleation Subgroup

Of the 100 patients included in the study, 13 underwent EN. An overview of the baseline and treatment characteristics of these patients is shown in Table 1. None of the patients in the EN group received neoadjuvant treatment or adjuvant therapy. Tumor breach was noted during surgical exploration in one patient, but no intraoperative tumor rupture occurred. Global morbidity and surgical and medical complication rates in the EN group were comparable with the general LR group (Table 2). One case of postoperative leak occurred, which was treated conservatively. As illustrated in Table 2, R1 resection was found in 2 of 13 patients in the EN group. In both of these patients, mucosal ulceration was noted during preoperative endoscopy. In the EN group, only two patients had a lesion > 5 cm in

TABLE 2 Postoperative outcome and histopathology data

	Overall [n = 100]	LR group [n = 81]	PD group [n = 19]	p value	EN group [n = 13]
Postoperative outcome					
Global morbidity	32 (32)	19 (23.5)	13 (68.4)	< **0.001**	3 (23.1)
Surgical complications	22 (22)	11 (13.6)	11 (57.9)	< **0.001**	2 (15.4)
Leak	14 (14)	6 (7.4)	8 (42.1)	**0.001**	1 (7.7)
Deep abscess	3 (3)	1 (1.2)	2 (10.5)	NA	
Bleeding	4 (4)	2 (2.5)	2 (10.5)	NA	
Medical complications	19 (19)	12 (14.8)	7 (36.8)	**0.047**	1 (7.7)
Urinary	2 (2)	0	2 (10.5)	NA	
Pulmonary	4 (4)	4 (4.9)	0	NA	
Cardiac failure	2 (2)	2 (2.5)	0	NA	
Thromboembolic	2 (2)	1 (1.2)	1 (5.3)	NA	
Neurologic	2 (2)	2 (2.5)	0	NA	
Reoperation	8 (8)	3 (3.7)	5 (26.3)	**0.006**	0 (0.0)
Clavien–Dindo grade > 2	10 (10)	5 (6.2)	5 (26.3)	**0.020**	0 (0.0)
Length of hospital stay, days (median [range])	13 [5–103]	13 [5–50]	23 [5–103]	< **0.001**	9 [5–19]
Histopathology data					
Resection rate				NA	
R0	96 (96.0)	77 (95.1)	19 (100.0)		11 (84.6)
R1	4 (4.0)	4 (4.9)	0 (0.0)		2 (15.4)
Tumor size, cm				0.16	
≤ 2	8 (8.0)	7 (8.6)	1 (5.3)		3 (23.1)
2–5	52 (52.0)	45 (55.6)	7 (36.8)		8 (61.5)
5–10	31 (31.0)	22 (27.2)	9 (47.4)		2 (15.4)
> 10	9 (9.0)	7 (8.6)	2 (10.5)		0 (0.0)
Mitotic index, n(/5 mm^2)				0.63	
≤ 5	78 (78.0)	63 (77.8)	15 (78.9)		13 (100.0)
6–10	11 (11.0)	8 (9.9)	3 (15.8)		0 (0.0)
> 10	11 (11.0)	10 (12.3)	1 (5.3)		0 (0.0)
Joensuu risk of recurrence				0.21	
Very low risk	10 (10.0)	8 (9.9)	2 (10.5)		3 (23.1)
Low risk	47 (47.0)	41 (50.6)	6 (31.6)		8 (61.5)
Intermediate risk	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)
High risk	43 (43.0)	32 (39.5)	11 (57.9)		2 (15.4)
Modified AFIP recurrence risk				0.41	
Very low risk	10	8 (9.9)	2 (10.5)		3 (23.1)
Low risk	48	42 (51.9)	6 (31.6)		8 (61.5)
Intermediate risk	17	11 (13.6)	6 (31.6)		2 (15.4)
High risk	25	20 (24.7)	5 (26.3)		0 (0.0)
pTNM				0.39*	
I	58	49 (60.5)	8 (42.1)		11 (84.6)
II	17	11 (13.6)	6 (31.6)		2 (15.4)
IIIA	4	3 (3.7)	1 (5.3)		0 (0.0)
IIIB	21	18 (22.2)	4 (21.1)		0 (0.0)

Data are expressed as n (%) unless otherwise specified

LR limited resection, *PD* pancreaticoduodenectomy, *AFIP* Armed Forces Institute of Pathology, *NA* not applicable, *EN* enucleation

*Tested after pooled IIIA and IIIB

TABLE 3 Long-term oncological results of local resection versus pancreaticoduodenectomy

	Non-adjusted HR (95% CI)	*p* value	Adjusted[a] HR (95% CI)	*p* value
Overall survival	1.28 (0.36–4.54)	0.70	NA	NA
Disease-free survival	1.24 (0.47–3.28)	0.67	1.30 (0.43–3.98)	0.64
Disease recurrence	1.33 (0.45–3.97)	0.61	NA	NA

HRs are expressed for the pancreaticoduodenectomy group, with the limited resection group as reference

HR hazard ratio, *CI* confidence interval, *NA* not applicable due to the low number of events

[a]Adjusted for D2 localization and adjuvant therapy

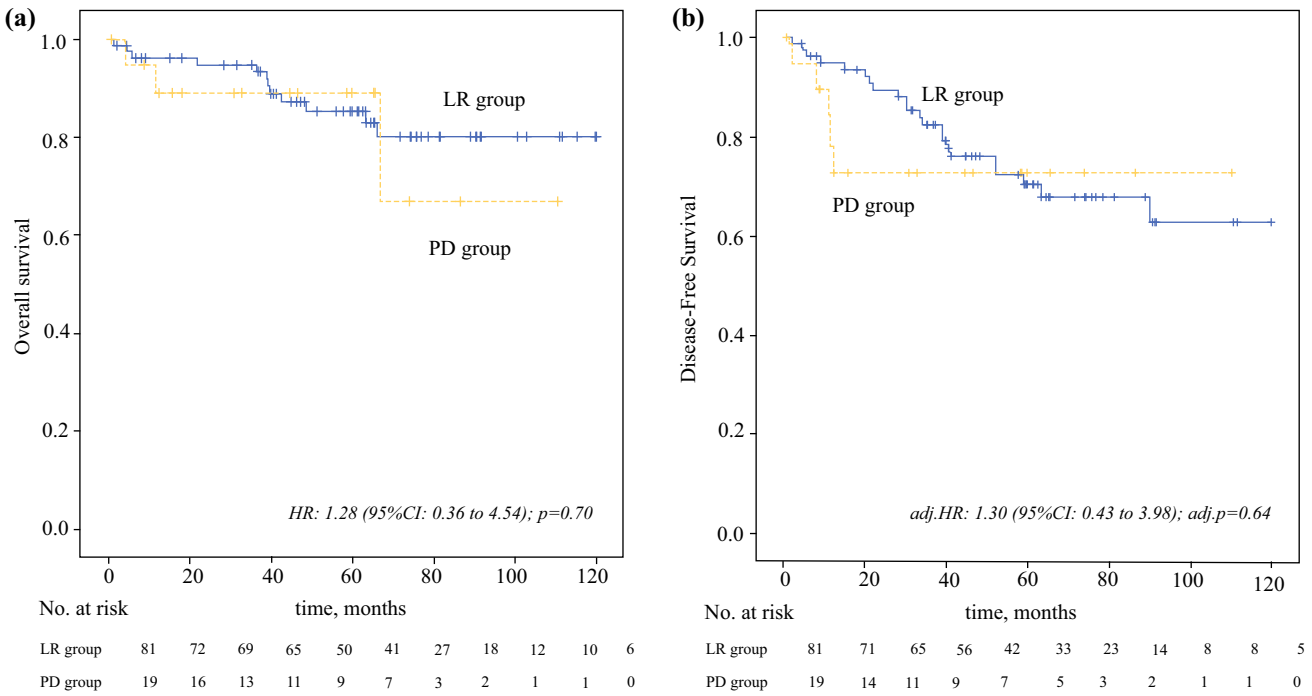

FIG. 2 Kaplan–Meier curve of the long-term oncological results of LR versus PD. **a** Overall survival; **b** disease-free survival. *LR* limited resection, *PD* pancreaticoduodenectomy, *HR* hazard ratio, *CI* confidence interval, *adj.* adjusted

diameter. Lesions in all other patients were ≤ 3.5 cm in diameter. According to both the Joensuu and AFIP classifications, 84.6% of EN patients were classified as having either low or very low risk of recurrence. Three deaths occurred in the EN group—two during the first year and one after 5 years; however, none were disease-related (pulmonary disease, cardiac insufficiency, and cerebrovascular incident). As such, the survival rate in the EN group was similar after 3 and 5 years (84.6%). Finally, in the EN group, no disease recurrence was noted.

DISCUSSION

The surgical management of duodenal GIST is considered as complex due to the anatomical constraints related to the organ. Several surgical procedures have been described in this context. In addition to the radical gesture of PD, other procedures with LR have been proposed, such as segmental and wedge resection, as well as EN. However, the different indications and results of these specific techniques remain poorly understood.[10,11,15–17,28–36] In this multicentric retrospective study, we observed that LR, when feasible, provides equivalent oncological results (OS, DFS, and risk of recurrence) compared with PD. Moreover, LR is associated with a reduced operating time and transfusion rate, as well as reduced morbidity and length of hospital stay. It should be noted that all R1 resections occurred in the LR group (n = 4). However, any statistical analysis was not applicable due to these low numbers. In our series, the tumor was most commonly located at the level of the second (37%) and third part (32%) of the duodenum, which is in accordance with other reports.[16,17,35,37,38] The majority of D-GISTs in our study, as well as in most other reports, had a low or very low risk

of recurrence according to Joensuu's classification (57%), suggesting a better prognosis of GIST located at the level of the duodenum compared with the small intestine.[16] However, a case-control study by Zhang et al. showed that, after pairing, the prognosis between these two locations seems to be similar.[14] Nineteen percent of patients in this study underwent PD. This rate is among the lowest when compared with other reports (10–40%),[18–25] which might suggest a more conservative attitude of European surgeons in general and French surgeons in particular who participated in this study.

Regarding the pre-therapeutic data, the tumor was more frequently located in the second part of the duodenum in the PD group compared with the LR group. Indeed, the presence of the biliopancreatic junction and the close relationship between the pancreatic head and the duodenum at this level renders LR technically difficult to perform, except in cases of an antimesenteric location of the tumor. As expected, the preoperative biopsy rate was higher in the PD group due to the high morbidity rate and risk associated with the surgical procedure. As would be expected, the inherently more invasive technique of PD was associated with a significantly increased operating time and transfusion rate. In accordance with findings in other reports, PD was associated with a higher rate of postoperative complications, both medical and surgical in nature.[10,11,16–24,28–36] This in turn resulted in an extended length of hospital stay in the PD group. With regard to long-term oncological outcomes, LR was associated with an equivalent OS and adjusted DFS, without any measurable statistically significant difference in the R0 resection rate, or risk of recurrence between the two groups, and despite a higher rate of adjuvant TKI therapy in the PD group ($p = 0.023$). Moreover, since no differences were found in the mode of disease recurrence between PD and LR, the oncological safety of an LR technique for D-GISTs is demonstrated. However, it should be noted that despite the fact that this study can benefit from a relatively long median follow-up (63.2 months), it is known that a significant amount of disease recurrences (10–30%) are discovered more than 5 years after the initial surgical treatment.[22]

An overview of the literature comparing outcomes after PD or LR for D-GISTs is shown in Table 4. Regarding overall morbidity and survival, other studies including large numbers of patients reported results that are comparable with the findings in our study.[16,17,35] The majority of the authors report equivalent or inferior long-term oncologic outcomes in the PD group.[14] In these studies, the surgical technique could not be identified as an independent prognostic factor.[16,17,30] A recent meta-analysis by Shen et al. showed that PD was associated with a worse long-term prognosis.[39] However, Shen et al. emphasize that this should be considered as a correlation and not as a causal relationship since patients who underwent PD were selected based on infaust prognostic factors (D2 localization, high-degree of mitosis, and high-risk classifications).

The strength of this study is that it comprises one of the largest study populations in the literature. Furthermore, we believe that the quality of this study lies in the fact that the DFS analysis was adjusted for D2 location and adjuvant therapy in the PD versus LR group comparison. As such, a potential selection bias of the surgical technique at baseline was maximally corrected. Despite the fact that this study is among the largest in the literature, an analysis by means of propensity score matching was not feasible because of the lack of statistical power.

EN has only rarely been discussed in the surgical management of D-GIST.[40] Our results suggest that EN could offer an interesting alternative for well-defined D-GISTs. In this study, EN was mainly proposed in elder and frail patients, probably because the surgical strategy was tailored in terms of the estimated medical risk. The majority of enucleated tumors were located in the proximal duodenum (46.2% D2; 30.8% D1) and could therefore offer a valid alternative for PD in cases of a tumor diameter < 5 cm. EN was associated with a low grade of morbidity without the need for surgical re-intervention, and a reduced length of hospital stay. Moreover, with no disease recurrence or disease-related deaths in the EN group, this technique appears to result in acceptable long-term outcomes. These findings have been incorporated in a surgical treatment algorithm for D-GISTs, as proposed in Fig. 3. A major French retrospective analysis and literature review by the FREGAT Working Group has demonstrated that EN is safe and feasible in esophageal GIST with a tumor diameter ≤ 6.5 cm and in the absence of mucosal ulceration on endoscopy.[25] In this study, in the two patients in the EN group who had an R1 resection, mucosal ulceration was identified during preoperative endoscopic evaluation. Mucosal ulceration has been described as a negative prognostic factor. In their study on esophageal GIST, Blum et al. identified two recurrences out of four ENs,[41] with both patients having signs of ulcerations on preoperative endoscopy. Although a low level of evidence is provided, mucosal ulceration is considered as a contraindication for EN in esophageal GIST.[25]

The main limitation of this study, besides its retrospective nature, is the fact that the rate of mutation analysis in this study is quite low at 40%. Nevertheless, this rate is still higher than the mutation analysis rate in other studies reporting on outcomes from comparable inclusion periods, and has to be seen within the context of an era when mutation analysis was not yet recommended in a standardized fashion.[42] A second limitation of this study is that although D2 location and tumor size are presumed to be the

TABLE 4 Literature overview of studies comparing outcomes after PD and LR for D-GIST

Studies (year)	Time of inclusion	No. of patients	LR/PD	Morbidity (LR/PD) (%)	Follow-up (months) (median [range])	OS (%)
Dubois et al. (current study)	2001–2013	100	81/19	23.5/68.4%	63.2 [40.6–86.5]	89/89 (5 years)
Zhang et al.[19]	1999–2016	52	37/14	10.8/21.4 (CD $\geq$ 2)	36 [6–138]	89.1 (5 years)
Lee et al.[22]	2000–2017	118	73/45	24.5/24.4 (in-hospital) 1.9/15.6 (late)	46 [3.9–167.9]	91.9/96.2 (5 years)
Liu et al.[18]	2010–2016	37	22/9	NA	NA	NA
Shi et al.[23]	2005–2015	61	45/16	33.3/56.3	NA	NA
Lee et al.[37]	1994–2014	60	37/23	24/70	38 [21–72]	72/76 (5 years)
Chen et al.[21]	2005–2016	64	41/23	31.7/69.6	36 [5–102]	80.5/31.7 (5 years)
Sugase et al.[20]	1990–2014	25	16/9	31/33	NA	89/45 (5 years)
Crown et al.[24]	2000–2015	15	7/8	14/62	NA	NA
Chung et al.[28]	2001–2014	21	21/0	14.3	52 [5–125]	NA
Duffaud et al.[17]	1993–2002	105	82/23	18/26	36 [2–250]	86.5 (5 years)
Beham et al.[29]	NA	13	8/5	NA	NA	66 (months)
Zhou et al.[30]	2006–2012	48	34/14	11.8/35.7	36 [0–81]	NA
Hoeppner et al.[31]	2002–2011	9	8/1	NA	45 [6–111]	NA
Bourgouin et al.[32]	2000–2012	17	11/6	29/50	34	NA
Yang et al.[33]	1999–2011	22	13/9	15.4/88.9	67.5 [3–118]	80.6 (5 years)
Liang et al.[34]	1998–2006	28	18/10	NA	61 [23–164]	64.5 (months)
Colombo et al.[35]	2000–2011	84	56/28	9/36	42 [2–135]	89 (at 5 years)
Johnston et al.[16]	1994–2011	96	58/38	29.3/57.6	22 [4–81]	82 (5 years)
Kamath et al.[36]	1999–2011	41	30/11	20	18 [0–144]	74 (5 years)
Tien et al.[11]	2001–2008	25	16/9	12.5/44	18 [9–92]	NA
Goh et al.[10]	1992–2006	15	7/7	NA/43	42 [2–174]	NA

LR limited resection, *PD* pancreaticoduodenectomy, *OS* overall survival, *CD* Clavien–Dindo, *NA* not applicable, *D-GIST* duodenal gastrointestinal stromal tumor

main determinants for the decision of PD versus LR as the optimal surgical strategy, more details regarding the anatomical relationship of the tumor (relative to papilla, common bile duct, etc.) could not be retrieved from the database. Additionally, the authors acknowledge that although the rate of neoadjuvant TKI therapy is quite low at 6%, no further details regarding this patient group are known. However, to date, no randomized controlled trials have demonstrated any effect of neoadjuvant TKI therapy on the indication of surgical approach.[43,44] Moreover, since more patients in the PD group received neoadjuvant therapy, excluding this patient group would only further reinforce the results and message of this study.

CONCLUSIONS

The results of this study suggest that in the surgical management of D-GIST, LR is preferred over PD whenever feasible considering the anatomical relations of the tumor. LR for D-GIST is associated with a reduced morbidity rate and provides long-term oncological results that are at least equivalent to PD. For D-GIST without endoscopic signs of mucosal ulceration, EN could serve as a potential alternative for PD, segmental resection, or wedge resection. However, future studies regarding this subject, including long-term results and larger patient cohorts, are required. Based on the findings of this study, we propose a surgical treatment algorithm for D-GISTs.

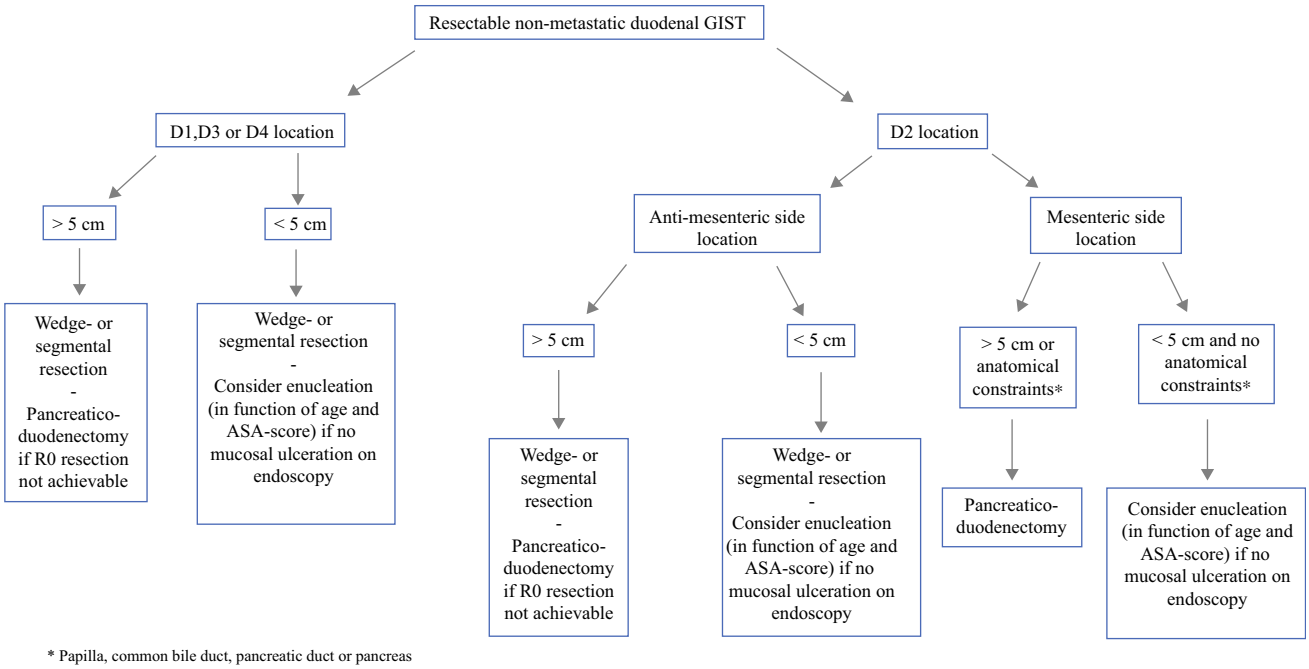

FIG. 3 Proposed algorithm for the treatment of resectable, non-metastatic duodenal GISTs. *GIST* gastrointestinal stromal tumor, *ASA* American Society of Anesthesiologists

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