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REVIEW ARTICLE – GASTROINTESTINAL ONCOLOGY

A Systematic Review and Meta-analysis Comparing Pancreaticoduodenectomy Versus Limited Resection for Duodenal Gastrointestinal Stromal Tumors

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ABSTRACT

Purpose. This study was designed to compare the clinical outcomes of patients who underwent limited resection (LR) versus pancreaticoduodenectomy (PD) for duodenal gastrointestinal stromal tumors (GISTs).

Methods. A systematic review of the literature was performed to identify studies analyzing the clinical outcomes of LR and PD for duodenal GISTs.

Results. Eleven studies were included, of which 7 that compared 162 patients who underwent LR versus 98 patients who underwent PD were suitable for meta-analysis. Patients who underwent PD were more likely to have tumors which were large (≥ 5 cm) [76.0 vs. 36.6 %, odds ratio (OR) 5.49, 95 % confidence interval (CI) 1.8–16.76], with high mitotic count ≥5/50 high-power field (HPF) (33.7 vs. 18.5 %, OR 2.23, 95 % CI 1.22–4.08), classified as high risk (60.3 vs. 32.0 %, OR 3.23, 95 % CI 1.65–6.34), and which were located at D2 (80.5 vs. 28.6 %, OR 10.33, 95 % CI 5.22–20.47) compared with LR. PD was associated with a higher postoperative morbidity rate than LR [48.3 vs. 20.7 %, relative risk (RR) 2.34, 95 % CI 1.61–3.42]. LR was not associated with an increased local recurrence rate, had a better DFS [hazard ratio (HR) 2.07, 95 % CI 1.07–4.01], and lower rate of distant metastasis (8.9 vs. 25.8 %, OR 0.28, 95 % CI 0.13–0.59) compared with PD.

Conclusions. LR should be the procedure of choice for duodenal GIST whenever technically feasible, because it is associated with good oncologic outcomes and lower morbidity compared with PD. The oncologic outcome of GIST is more likely to be dependent on tumor biology rather that the type of surgical resection. The use of Imatinib in patients with duodenal GIST may potentially allow a proportion of patients who would otherwise require a PD to undergo LR instead.

Gastrointestinal stromal tumors (GISTs) represent the commonest mesenchymal tumors in the digestive tract,[1] with a reported incidence of 10–20 per million.[2] They occur most frequently in the stomach (60–70 %), followed by small intestine (20–25 %), large intestine (5 %), and oesophagus (<5 %).[3,4] They also rarely have been reported to arise from outside the gut wall and these are termed extragastrointestinal stromal tumors.[5] Duodenal GISTs are a relatively uncommon entity, comprising 3–5 % of all GISTs.[2,6,7] Although they can arise in any part of the duodenum, most are reported to arise from the second portion.[6,8,9]

The mainstay of treatment of primary localized GIST is complete surgical resection with clear margins, avoiding tumor rupture or spillage,[9–11] which can increase the risk of disease recurrence and peritoneal dissemination. In most instances, this can be achieved via limited resection without formal organ resection or lymphadenectomy.[12] Wide margins and regional lymphadenectomy are not routinely required, because GISTs unlike carcinomas rarely invade into adjacent organs or demonstrate lymphatic infiltration.[13–16]

Presently, the optimal management of duodenal GIST remains poorly defined.[15] This is because unlike other sites

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in the digestive tract, such as the stomach or small bowel, where complete resection would entail a relatively straightforward surgical procedure, wide resections of tumors in the duodenum would almost always entail a pancreaticoduodenectomy (PD) due to the complex anatomy around the pancreatoduodenal region.[15] Many surgeons remain cautious about performing routine PD for GIST despite the decreasing mortality rates, because it is still associated with a high morbidity rate.[15] Hence, in addition to PD various surgical options which entail a more limited resection (LR) have been described for the management of duodenal GISTs, including pancreas-sparing duodenectomy, segmental duodenectomy, and local resection.[17–24] Presently, most surgeons would perform a LR for duodenal GISTs if technically feasible. This is based on the clinical experience with gastric GISTs, whereby limited wedge resections as opposed to formal gastrectomies have become widely accepted.[12] However, unlike the stomach, adequacy of margins and oncologic clearance is a real concern for duodenal GISTs. The choice of LR versus PD is dependent on factors, such as tumor size, location (proximity to the ampulla of Vater), invasion or adherence to adjacent organs, and patient's overall fitness.

To date, there remains limited data supporting either LR or PD for duodenal GIST due to the rarity of these tumor and few studies have been performed to compare the outcomes of patients who have undergone LR versus PD for duodenal GISTs.[15] The study by Goh et al.[14] was the first study that attempted to compare the outcomes of patients undergoing limited LR versus PD.[15] The authors concluded that LR with clear margins is a viable treatment option, and PD should be reserved for cases where LR is not technically feasible. Since then, several larger retrospective multi-institution studies have attempted to address the short-term and long-term results of patients surgically treated with LR versus PD. However, the results of these studies remain limited by the small sample size. This systematic review aims to summarize the current literature on duodenal GIST and attempts to determine the optimal surgical approach for patients with duodenal GISTs by comparing the short- and long-term outcomes after LR and PD.

METHODS

A computerized search was performed of the PubMed database from January 1, 2000 to October 31, 2012 for studies comparing outcomes of patients with duodenal GISTs after LR or PD. The medical subject headings (MeSH) keywords "gastrointestinal stromal tumor," "gastrointestinal stromal tumour," "duodenum," "duodenal GIST," "duodenal resection," "pancreaticoduodenectomy," and combinations of these were used. The systematic review was performed in accordance to the PRISMA guidelines published in 2009.[25]

Eligibility Criteria and Study Selection

Two authors (AYC and YXK) independently screened the titles and abstracts. All abstracts were reviewed, and if the information from an abstract was deemed insufficient for evaluation, the full article was obtained. The inclusion criteria were as follows:

1. Original articles published in English;
2. Patients who underwent resection with curative intent for primary duodenal GISTs;
3. Comparative analyses of the outcomes between patients who underwent LR versus PD
4. Studies whereby separate clinicopathological data were available for patients with duodenal GISTs stratified by either PD or LR.

The exclusion criteria were:

1. Conference abstracts, case reports, editorials and expert opinions, molecular and histopathological studies, and reviews;
2. Studies with heterogenous data on various other pathologies, such as duodenal adenocarcinomas and neuroendocrine tumors, or consisting of GISTs arising from multiple sites besides the duodenum;
3. Series that did not specifically address the surgical approaches for duodenal GISTs or when separate clinicopathological data for either LR or PD were not available;

Of the short-listed studies, those that performed comparative analyses of the outcomes between patients who underwent LR versus PD and contained sufficient information on recurrence and morbidity rates were deemed suitable for meta-analysis. Finally, study cohorts containing patients with metastatic disease at presentation were excluded from this systematic review. The reference lists of identified papers were individually searched for other relevant studies.

Data Collection and Quality Assessment (Appendix 1 online).

Statistical Analysis and Clinical Outcomes (Appendix 2 online).[26,27]

RESULTS

The initial search produced a total of 165 titles, of which 18 case reports had no abstracts available. A total of 147 abstracts were reviewed, of which 12 were potential full-text articles that reported on the surgical treatment outcomes of duodenal GISTs.[11,15,28–37] A poster entitled "Gastrointestinal stromal tumors (GIST) of the duodenum: A French Sarcoma Group (FSG) retrospective review of 90 patients (pts)" was considered for inclusion in this review, but no formal publication could be found (Appendix 1

TABLE 1 Summary of 11 studies reporting surgical outcomes of duodenal GISTs

Year of study (recruitment period)	Reference (NOS score)	Country	*N*	N-D2 LR-D2 PD-D2	Median age	Sex (F)	Size > 5 cm	Median size (range, cm)	Mitosis < 5	Mitosis > 5	Risk (low/int/high)	Median FU (range, mo)
2006 (2000–2005)	Winfield et al.[11] (6 points)	USA	8[a]	Total D2: 4	57	5	4	6.25 (3–22)	6	1	2/3/1 (1 unknown)	6 (0.5–60)
			LR: 2	LR: 1	(40–80)	LR: 1	LR: 0	LR: 3.5 (3.5)	LR: 2	LR: 0	LR: 1/0/0	
			PD: 5	PD: 3		PD: 4	PD: 4	PD: 6.5 (3–22)	PD: 4	PD: 1	PD: 1/3/1	
2008 (1992–2006)	Goh et al.[15] (8 points)	Singapore	14	NA	59	5	NA	8.5 (2.5–18.0)	NA	NA	5/3/6	42 (2–174)
			LR: 7		(42–77)						LR: 4/0/3	
			PD: 7								PD: 1/3/3	
2010 (2001–2008)	Tien et al.[28] (8 points)	Taiwan	25	Total D2: 13	66	9	13	5 (1.3–25)	17	8	11/5/9	18 (9–92)
			LR: 16	LR: 7	(44–75)	LR: 7	LR: 5		LR: 12	LR: 4	LR: 10/2/4	
			PD: 9	PD: 6		PD: 2	PD: 8		PD: 5	PD: 4	PD: 1/3/5	
2012 (1994–2011)	Johnston et al.[29] (8 points)	USA	96	Total D2: 47	59	43	NA	4 (0.1–32)	79	17	54/25/16	22 (NA)
			LR: 58	LR: 16	(27–84)	LR: 26		LR: 3.5	LR: 49	LR: 9	(1 unknown)	
			PD: 38	PD: 31		PD: 17		PD: 5.0	PD: 30	PD: 8		
2012 (2000–2011)	Colombo et al.[30] (8 points)	Europe/USA	84	Total D2: 21	58	45	NA	5 (1–19)	56	22	35/4/39	42 (2–135)
			LR: 56	LR: 6	(27–76)	LR: 31		LR: 5 (2–11)	LR: 41	LR: 11	LR: 28/3/21	
			PD: 28	PD:15		PD: 14		PD: 7 (1–19)	PD: 15	PD: 11	PD: 7/1/18	
2012 (NA)	Beham et al.[31] (7 points)	Germany	13	NA	71	6	8	8 (1.8–15)	7	6	5/0/8	NA
			LR: 8		(58–75)	LR: 3	LR: 4	LR: 7.25 (2.5–15)	LR: 5	LR: 3	LR: 4/0/4	
			PD: 5			PD: 3	PD: 4	PD: 8 (4–10)	PD: 2	PD: 3	PD: 1/0/4	
2010 (2000–2008)	Buchs et al.[32] (7 points)	Switzerland	7	Total D2: 2	51	NA	5	6.5 (2–10)	3	4	2/2/3	41 (18–85)
			LR: 5	LR: 1	(41–73)		LR: 3	LR: 5.5 (2–10)	LR: 3	LR: 2	LR: 2/2/1	
			PD: 2	PD: 1			PD: 2	PD: 6.75 (6.5–7)	PD: 0	PD: 2	PD: 0/0/2	
2009 (2000–2007)	Yang et al.[33] (7 points)	China	21	Total D2: 14	48	10	8	4 (2–13)	18	3	13/4/4	44 (19–101)
			LR: 12	LR: 5	(36–84)	LR: 5	LR: 3	LR: 3.85 (2–10)	LR: 12	LR: 0	LR: 9/3/0	
			PD: 9	PD: 9		PD: 5	PD: 5	PD: 5.1 (3–13)	PD: 6	PD: 3	PD: 4/1/4	
2012 (2002–2012)	Gendi et al.[34] (6 points)	Egypt	12	Total D2: 4	60.5	5	12	8 (5–16)	9	3	2/6/4	45 (15–78)
			LR: 12	LR: 4	(49–71)		LR: 12					
			PD: 0	PD: 0			PD: 0					
2010 (2001–2009)	Chung et al.[35] (6 points)	South Korea	9	Total D2: 4	52	3	1	3.5 (1.9–5.5)	9	0	7/2/0	22 (13–61)
			LR: 9	LR: 4	(45–73)		LR: 1					
			PD: 0	PD: 0			PD: 0					
2010 (1993–2008)	Miki et al.[36] (6 points)	Japan	7[b]	Total D2: 3	66	5	4	6.5 (3–15)	3	3	0/3/3	NA
			LR: 4	LR: 1	(39–75)	LR: 3	LR: 3	LR: 9 (3–15)	LR: 2	LR: 2	LR: 0/2/2	
			PD: 2	PD: 2		PD: 2	PD: 1	PD: 5.5 (4–7)	PD: 1	PD: 1	PD: 0/1/1	

NOS score Newcastle-Ottawa Scale score, with maximum of 4 for selection, 2 for comparability, 3 for outcome

N number, *LR* local resection, *PD* pancreaticoduodenectomy, *FU* follow-up, *NA* not available

[a] Resection was not performed in one patient secondary to the patient's severe cirrhosis and portal hypertension

[b] One patient deemed unfit for radical surgery

online).[38] No further studies were identified on evaluation of the reference lists of the short-listed studies. Based on the period of recruitment of patients and the institutions involved in each study, there were no overlapping cohorts of patients found among these 12 studies.

Of these 12 studies, the study by Kamath et al.[37] was excluded from the systematic review, because data such as the baseline demographics, tumor characteristics, or clinical outcomes of the patients as stratified by the type of surgery performed (LR vs. PD) were not available.[37] Hence, 11 studies were included in this systematic review (Appendix 3 online) and are summarized in Table 1.[11,15,28–36] Of these 11 included studies, 7 had sufficient data for performing a meta-analysis comparing LR versus PD. Two studies were excluded from further meta-analysis, because they contained only patients who underwent LR of duodenal GIST.[34,35] The two studies by Winfield et al. and Miki et al. did not contain sufficient data to study the impact of surgical outcomes stratified by the type of resection and also were excluded from further meta-analysis.[11,36]

Study, Patient, and Tumor Characteristics

All 11 studies were retrospective case series. There were nine single-centre and two multi-centre studies, with patients recruited from centers in the United States, Italy, Germany, Switzerland, Poland, Egypt, China, Taiwan, Japan, South Korea, and Singapore, over a time period extending from 1992 to 2011. The number of patients per study ranged from 7 to 96, with a total of 294 patients who underwent surgical resection for localized primary duodenal GIST. The study characteristics, data on patient and tumor features, and the study quality are summarized in Table 1.

In total, 189 patients were treated via LR and 105 patients via PD. The summary and pooled comparison of the baseline characteristics of the LR and PD groups are shown in Table 2.

Meta-analyses

Baseline Characteristics Seven of the 11 studies had sufficient data for meta-analysis; 162 patients were treated via LR, and 98 patients via PD. Comparison of the baseline characteristics of the LR and PD groups is summarized in Table 3. Of the 98 tumors arising from the second part of the duodenum (D2), 62 (63.3 %) were treated via PD, whereas the 36.7 % of D2 tumors underwent LR. In contrast, among the 105 tumors arising from the first, third, and fourth parts of the duodenum, only 14.3 % required PD, whereas 85.7 % underwent LR. Patients who underwent PD were more likely to have large (≥5 cm) tumors (76.0 vs. 36.6 %, OR 5.49, 95 % CI 1.8–16.76), tumors with high mitotic count ≥5/50 HPF (33.7 vs. 18.5 %, OR 2.23, 95 % CI 1.22–4.08), high-risk tumors (60.3 vs. 32.0 %, OR 3.23, 95 % CI 1.65–6.34), and tumors located at the second part of the duodenum (80.5 vs. 28.6 %, OR 10.33, 95 % CI 5.22–20.47) compared with LR.

Operative Outcomes PD was associated with a higher risk of postoperative morbidity, including both minor and major complications, than LR (48.3 vs. 20.7 %, RR 2.34; 95 % CI 1.61–3.41; $n = 5$ studies; $I^2 = 0$ %; Table 3, Fig. 1, Appendix 4 online).

Oncological Outcomes Patients who underwent LR were more likely to have positive margins compared with those who underwent PD (16.3 vs. 5.1 %, $P = 0.0547$), although this only approached statistical significance (Fig. 2, Appendix 5 online). There was no significant difference in local recurrence between LR and PD. Patients who underwent PD were significantly more likely to develop distant recurrence compared with LR (25.8 vs. 8.9 %, RR 2.9, 95 % CI 1.55–5.43). With regard to disease-free survival (DFS), 2 of the 7 pooled studies showed better DFS for LR over PD,[30,32] with hazard ratios of 2.34 (1.03–5.33) and 62.8 (2.89–1363) respectively (Fig. 2c). In this analysis, the hazard ratio (HR) was used at the summary effect measure for DFS, a time-to-event outcome. Pooled analysis showed that PD was associated with a worse DFS (HR 1.85, 95 % CI 1.09–3.15; $n = 5$ studies; $I^2 = 0$ %).

Role of Imatinib Five studies ($n = 228$) reported the use of preoperative and/or postoperative imatinib.[15,29–31,33] There was no significant difference in the frequency of use of imatinib between the LR versus PD groups (Appendix 6 online).

DISCUSSION

Patients with duodenal GISTs may present with a wide variety of clinical symptoms.[39] These may range from an incidental lesion detected during radiological imaging or a surgical emergency due to perforation or severe gastrointestinal hemorrhage with resultant hemodynamic compromise. The clinical presentation is dependent on tumor size, presence of mucosal ulceration, location in relation to the Ampulla of Vater, and involvement of adjacent organs. Bleeding has been reported to be the most common presenting symptom, followed by abdominal pain, abdominal mass, intestinal obstruction, or biliary obstruction.[28,30] Gross hemorrhage from the digestive tract, including hematemesis and melena, was reported in

TABLE 2 Comparison of baseline characteristics of patients who underwent LR versus PD (pooled data from 11 studies)

Baseline characteristic	No. of studies[a]	First author	No. of patients	Total	LR	PD
Gender						
Male	9 studies	Winfield, Tien, Johnston, Colombo, Beham, Yang, Gendi, Chung, Miki	273 patients	142	93 (52.5 %)	49 (51.0 %)
Female				131	84 (47.5 %)	47 (49.0 %)
Presence of symptoms						
Symptomatic	7 studies	Winfield, Tien, John, Col, Gendi, Chung, Miki	234 patients	188	125 (80.6 %)	63 (79.7 %)
Asymptomatic				46	30 (19.4 %)	16 (20.3 %)
Location						
D2	9 studies	Winfield, Tien, Johnston, Colombo, Yang, Buchs, Gendi, Chung, Miki	237 patients	112	45 (29.4 %)	67 (79.8 %)
Others (D1/3/4)				125	108 (70.6 %)	17 (20.2 %)
Size	8 studies	Winfield, Tien, Beham, Yang, Buchs, Gendi, Chung, Miki	99 patients			
<5 cm				43	35 (52.2 %)	8 (25.0 %)
≥5 cm				56	32 (47.8 %)	24 (75.0 %)
Mitotic count	10 studies	Winfield, Tien, Johnston, Colombo, Beham, Yang, Buchs, Gendi, Chung, Miki	274 patients			
<5 (/50HPF)				207	144 (80.9 %)	63 (65.6 %)
≥5 (/50HPF)				67	34 (19.1 %)	33 (34.4 %)
Mitotic count	9 studies	Winfield, Tien, Johnston, Beham, Yang, Buchs, Gendi, Chung, Miki	196 patients			
≤5 (/50HPF)				151	103 (81.8 %)	48 (68.6 %)
6–10 (/50HPF)				25	15 (11.9 %)	10 (14.3 %)
>10 (/50HPF)				20	8 (6.3 %)	12 (17.1 %)
Risk category	10 studies	Winfield, Goh, Tien, Colombo, Beham, Yang, Buchs, Gendi, Chung, Miki	159 patients			
Very low/low				82	67 (63.2 %)	15 (28.3 %)
High				77	39 (36.8 %)	38 (71.7 %)
Risk category	10 studies	Winfield, Goh, Tien, Colombo, Beham, Yang, Buchs, Gendi, Chung, Miki	191 patients			
VL/low/int				114	87 (69.0 %)	27 (41.5 %)
High				77	39 (31.0 %)	38 (58.5 %)
Presence of complications	8 studies	Goh, Tien, Johnston, Colombo, Beham, Buchs, Gendi, Chung	260 patients			
All complications				79	36 (21.1 %)	43 (48.3 %)
No complications				181	135 (78.9 %)	46 (51.7 %)
Presence of complications	8 studies	Goh, Tien, Johnston, Colombo, Beham, Buchs, Gendi, Chung	229 patients			
Minor complications				48	27 (16.7 %)	21 (31.3 %)
No complications				181	135 (83.3 %)	46 (68.7 %)
Presence of complications	8 studies	Goh, Tien, Johnston, Colombo, Beham, Buchs, Gendi, Chung	212 patients			
Major complications				31	9 (6.2 %)	22 (32.4 %)
No complications				181	135 (93.8 %)	46 (67.6 %)
Local recurrence	7 studies	Goh, Colombo, Beham, Yang, Buchs, Gendi, Chung	160 patients			
Local recurrence: yes				7	3 (2.8 %)	4 (7.8 %)
Local recurrence: no				153	106 (97.2 %)	47 (92.2 %)
Distant recurrence	8 studies	Goh, Johnston, Colombo, Beham, Yang, Buchs, Gendi, Chung	256 patients			
Distant recurrence: yes				37	14 (8.4 %)	23 (25.8 %)
Distant recurrence: no				219	153 (91.6 %)	66 (74.2 %)
All recurrence	9 studies	Goh, Johnston, Colombo, Beham, Yang, Buchs, Gendi, Chung, Miki	262 patients			
All recurrence: yes				55	24 (14.0 %)	31 (34.1 %)
All recurrence: no				207	147 (86.0 %)	60 (65.9 %)
Margin positivity	6 studies	Winfield, Johnston, Colombo, Buchs, Gendi, Chung	185 patients			
Positive margin: yes				19	16 (13.2 %)	3 (4.7 %)
Positive margin: no				166	105 (86.8 %)	61 (95.3 %)

TABLE 2 continued

Baseline characteristic	No. of studies[a]	First author	No. of patients	Total	LR	PD
Neoadjuvant treatment	8 studies	Winfield, Goh, Johnston, Colombo, Beham, Yang, Gendi, Chung	256 patients			
Preop imatinib: yes				16	10 (6.1 %)	6 (6.5 %)
Preop imatinib: no				240	154 (93.9 %)	86 (93.5 %)
Adjuvant treatment	9 studies	Winfield, Goh, Johnston, Colombo, Beham, Yang, Gendi, Chung, Miki	262 patients			
Postop imatinib: yes				57	38 (22.6 %)	19 (20.2 %)
Postop imatinib: no				205	130 (77.4 %)	75 (79.8 %)

D2 s part of the duodenum, *HPF* high-power field, *VL* very low, *int* intermediate

[a] Number of studies of nine with information on baseline characteristics

26–71 % of patients.[29,33] The incidence of asymptomatic duodenal GISTs is reported to range from 9.5 to 40 % [28,30] and occur most commonly in the second part of the duodenum.[28–30] In the largest published study to date involving 156 pathological specimens of duodenal GISTs, 42 (26.9 %) tumors were located in D2.[6]

The cornerstone of curative treatment for GIST entails complete surgical resection with clear margins.[4,12] This usually can be achieved via a LR rather than a radical resection for GISTs in most locations, such as the stomach.[12] However, the optimal resection method for duodenal GISTs remains controversial [29] mainly due to the complex anatomy around the pancreatoduodenal region, which limits the resection margin achievable with LR.[15] Some investigators support the selective use of LR when technically possible, whereas others propose almost always performing a PD.[29] Proponents of routine PD argue that an aggressive surgical approach is almost always required to obtain clear surgical margins in this region and hence achieve good long-term oncologic outcomes.[15,29,30] On the other hand, advocates of selective LR suggest that LR is simpler to perform, less demanding if performed laparoscopically, is associated with decreased perioperative morbidity and better quality of life, and most importantly, does not compromise on oncological outcomes.[40,41] Furthermore, it is frequently impossible to distinguish GIST from other benign submucosal tumors preoperatively and it would be inappropriate to subject patients with benign submucosal tumors to a PD.[15]

To date, several studies have attempted to resolve this controversy, but these were all limited by a small sample size due to the rarity of duodenal GIST.[15,28–33] The present systematic review has attempted to overcome this limitation by pooling the results of 7 studies analyzing 260 patients. In the present study, the background characteristics of patients with GISTs treated via PD differed from LR. GISTs that were treated via PD were more likely to be larger, had higher mitotic counts, and to be located in D2. This observation is not surprising and can be attributed to selection bias. Patients with larger tumors located at D2 are more likely to undergo PD, because it is technically more difficult or sometimes even impossible to achieve clear resection margins with LR in these tumors.[29] Not unexpectedly, the assumption that PD is associated with an increased perioperative morbidity compared with LR was confirmed in this review.

Positive margins are a well-known risk factor of relapse after surgically resection of GIST.[4,29,42] In this study, although there was a higher proportion of positive surgical margins associated with LR, this only approached statistical significance and did not translate to an increase in local recurrence in this analysis. This finding could possibly be due to a Type 2 error due to the relatively small sample size. LR also was found to be associated with a lower recurrence rate, better DFS, and lower rate of distant metastasis compared with PD. This observation may be explained by selection bias that resulted in larger and higher-risk tumors being subjected to PD rather than LR and is unlikely due to the type of resection.[30] This finding is consistent with that of previous studies, which demonstrated that tumor biology and not resection type was the main determinant of oncologic outcome after surgical resection of GIST.[29]

The findings in this study may have important implications on the potential use of imatinib as neoadjuvant therapy for duodenal GISTs. Imatinib has been proposed as a neoadjuvant treatment to downstage GISTs, which would otherwise require extensive surgery.[43] Its use in patients with duodenal GIST may potentially allow a proportion of patients who would otherwise require a PD to undergo LR instead.[29]

TABLE 3 Comparison of baseline characteristics of patients who underwent LR versus PD (from the 7 studies in the meta-analysis)

Baseline characteristics	Studies[a]	Patients	Total	LR	PD	*p* value
Gender	5 studies					0.772
Male	(Tien, Johnston, Colombo, Beham, Yang)	239 patients	126	78 (52.0 %)	48 (53.9 %)	
Female			113	72 (48.0 %)	41 (46.1 %)	
Presence of symptoms	3 studies					0.930
Symptomatic	(Tien, Johnston, Colombo)	200 patients	159	102 (79.7 %)	57 (79.2 %)	
Asymptomatic			41	26 (20.3 %)	15 (20.8 %)	
Location	5 studies					**<0.001**
D2	(Tien, Johnston, Colombo, Yang, Buchs)	203 patients	98	36 (28.6 %)	62 (80.5 %)	
Others (D1/3/4)			105	90 (71.4 %)	15 (19.5 %)	
Size	4 studies					**0.0028**
<5 cm	(Tien, Beham, Yang, Buchs)	66 patients	32	26 (63.4 %)	6 (24.0 %)	
≥5 cm			34	15 (36.6 %)	19 (76.0 %)	
Mitotic count	6 studies					**0.0088**
<5 (/50 HPF)	(Tien, Johnston, Colombo, Beham, Yang, Buchs)	240 patients	182	123 (81.5 %)	59 (66.3 %)	
≥5 (/50 HPF)			58	28 (18.5 %)	30 (33.7 %)	
Mitotic count	5 studies					0.119
≤5 (/50 HPF)	(Tien, Johnston, Beham, Yang, Buchs)	162 patients	126	82 (82.8 %)	44 (69.8 %)	
6–10 (/50 HPF)			19	10 (10.1 %)	9 (14.3 %)	
>10 (/50 HPF)			17	7 (7.1 %)	10 (15.9 %)	
Risk category	6 studies					**<0.001**
Very low/low	(Goh, Tien, Colombo, Beham, Yang, Buchs)	138 patients	71	57 (64.0 %)	14 (28.6 %)	
High			67	32 (36.0 %)	35 (71.4 %)	
Risk category	6 studies					**<0.001**
Very low/low/int	(Goh, Tien, Colombo, Beham, Yang, Buchs)	158 patients	91	68 (68.0 %)	23 (39.7 %)	
High			67	32 (32.0 %)	35 (60.3 %)	
Complications	6 studies					**<0.001**
All complications	(Goh, Tien, Johnston, Colombo, Beham, Buchs)	239 patients	74	31 (20.7 %)	43 (48.3 %)	
No complications			165	119 (79.3 %)	46 (51.7 %)	
Complications	6 studies					**0.009**
Minor complications	(Goh, Tien, Johnston, Colombo, Beham, Buchs)	208 patients	43	22 (15.6 %)	21 (31.3 %)	
No complications			165	119 (84.4 %)	46 (68.7 %)	
Complications	6 studies					**<0.001**
Major complications	(Goh, Tien, Johnston, Colombo, Beham, Buchs)	196 patients	31	9 (7.0 %)	22 (32.4 %)	
No complications			165	119 (93.0 %)	46 (67.6 %)	
Recurrence—local	5 studies					0.261
Local recurrence: yes	(Goh, Colombo, Beham, Yang, Buchs)	139 patients	7	3 (3.4 %)	4 (7.8 %)	
Local recurrence: no			132	85 (96.6 %)	47 (92.2 %)	
Recurrence—distant	6 studies					
Distant recurrence: yes	(Goh, Johnston, Colombo, Beham, Yang, Buchs)	235 patients	36	13 (8.9 %)	23 (25.8 %)	**<0.001**
Distant recurrence: no			199	133 (91.1 %)	66 (74.2 %)	
Recurrence (local/distant)	6 studies					**<0.001**
All recurrence: yes	(Goh, Johnston, Colombo, Beham, Yang, Buchs)	235 patients	52	21 (14.4 %)	31 (34.8 %)	
All recurrence: no			183	125 (85.6 %)	58 (65.2 %)	
Positive margin	3 studies					**0.0547**
Positive margin: yes	(Johnston, Colombo, Buchs)	157 patients	19	16 (16.3 %)	3 (5.1 %)	
Positive margin: no			138	82 (83.7 %)	56 (94.9 %)	
Preoperative imatinib	5 studies					0.955

TABLE 3 continued

Baseline characteristics	Studies[a]	Patients	Total	LR	PD	*p* value
Preop imatinib: yes	(Goh, Johnston, Colombo, Beham, Yang)	228 patients	16	10 (7.1 %)	6 (6.9 %)	
Preop imatinib: no			212	131 (92.9 %)	81 (93.1 %)	
Postoperative imatinib	5 studies					0.623
Postop imatinib: yes	(Goh, Johnston, Colombo, Beham, Yang)	228 patients	46	27 (19.1 %)	19 (21.8 %)	
Postop imatinib: no			182	114 (80.9 %)	68 (78.2 %)	

Bold values indicate $p < .05$

[a] Number of studies of seven with information on baseline characteristics

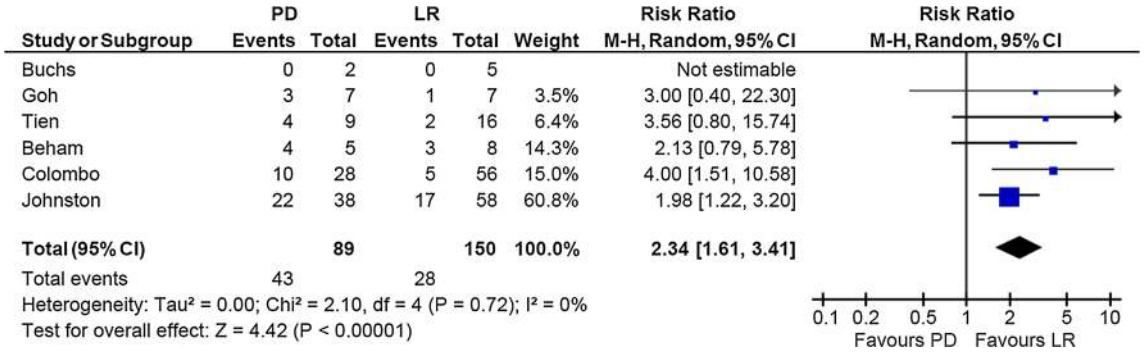
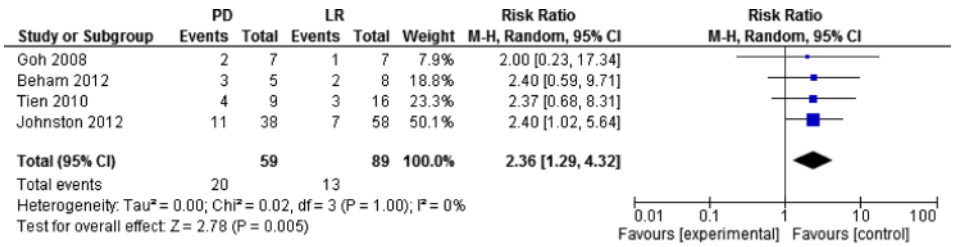


FIG. 1 Forest plot: overall complication rates

(a)

Outcome		Local recurrence			Distant metastases			Recurrence (local and distant)		
Study	Median follow-up time (months)	No. of patients with outcome/ No. of patients per arm		Odds Ratio (95% CI)	No. of patients with outcome/ No. of patients per arm		Odds Ratio (95% CI)	No. of patients with outcome/ No. of patients per arm		Odds Ratio (95% CI)
		LR	PD		LR	PD		LR	PD	
Goh	42	0/7	0/7	N/A	1/7	2/7	2.40 (0.09, 165)	1/7	2/7	2.40 (0.09, 165)
Johnston	22	-	-	-	2/58	6/38	5.25 (0.86, 55.2)	7/58	11/38	2.97 (0.92, 10.0)
Colombo	42	2/56	3/28	3.24 (0.34, 40.4)	9/56	9/28	2.47 (0.74, 8.20)	11/56	12/28	3.07 (1.00, 9.35)
Beham	Not reported	1/8	1/5	1.75 (0.02, 157)	1/8	3/5	10.5 (0.42, 627)	2/8	3/5	4.50 (0.25, 87.6)
Yang	44	0/12	0/9	N/A	0/12	1/9	N/A	0/12	1/9	N/A
Buchs	41	0/5	0/2	N/A	0/5	2/2	N/A	0/5	2/2	N/A

(b)



(c)

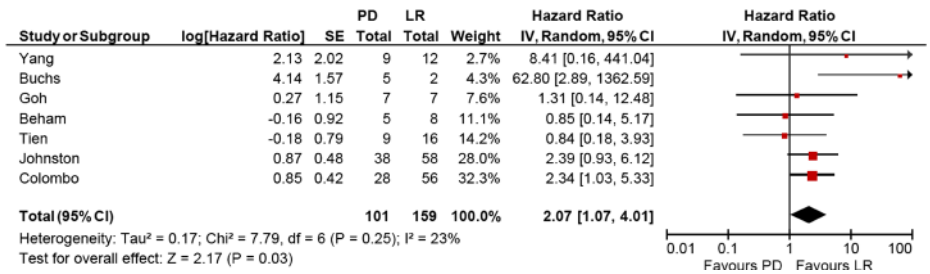


FIG. 2 **a** Rates of recurrence among patients who underwent LR versus PD. **b** Overall disease recurrence (local and/or systemic). **c** Forest plot of disease-free survival

CONCLUSIONS

The results of the present systematic review suggest that LR should be the procedure of choice for duodenal GIST whenever technically feasible, because it is associated with good oncological outcomes and lower morbidity compared with PD. The oncological outcome of GIST is more likely to be dependent on tumor biology rather that the type of surgical resection. However, patients should be carefully selected for LR, because this may be associated with a higher incidence of positive surgical margins. The use of neoadjuvant imatinib in patients with duodenal GIST may potentially allow a proportion of patients who would otherwise require a PD to undergo LR instead.

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