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Duodenal GIST: Surgical treatment based on the location. A single center experience with review of the literature

Duodenal GIST: Lokasyona göre cerrahi tedavi. Literatür derlemesi ile tek merkez deneyimleri

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Abstract

Aim: Gastrointestinal stromal tumors (GIST) are the most common digestive tract mesenchymal neoplasms, but only 1 to 5% of GISTs occur in the duodenum. Consequently, clinical manifestations, management and surgical treatment and their results remain poorly defined. The aim of this study is to expose the surgical experience in our institution, analyze surgical procedures according to the location of the tumor in the duodenum, and review the surgical management of GISTs in this anatomically complex region.

Methods: Patients with duodenal GISTs who were surgically treated with curative intention in our center during the last 5 years (January 2014 - December 2019) were included in this retrospective cohort study. Demographic data, clinical presentation, GIST location, diagnostic evaluation, oncologic treatment, surgical procedure, mortality and morbidity, pathological and morphological GIST characteristics, pathological risk category, follow up and survival were noted.

Results: Five patients diagnosed with duodenal GIST were operated in our center during the last 5 years. Four surgeries were performed with intent to cure and negative margins of resection. Only one was performed by laparoscopic approach. Limited resection R0 was done in all cases. None of the patients received neoadjuvant treatment before surgery. All patients were women with a mean age of 63 years (52-70 years). Clinical manifestations consisted of abdominal pain and upper gastrointestinal bleeding. One of the cases was incidentally diagnosed. There was no postoperative mortality. Mean length of stay was of 8 days (4-26 days). The median follow-up time was 33 months (6 months - 8 years). During the follow up, 2 patients passed away due non-GIST related causes, and one patient was operated for resectable peritoneum metastasis 29 months after the initial surgery.

Conclusion: Tumor biology is more important than the surgical procedure for oncologic results of duodenal GIST. GIST located in duodenum with surgical indication is a challenge for the surgeon due to the complex duodenum anatomy.

Keywords: Gastrointestinal stromal tumor, Duodenum, Surgery procedures

Öz

Amaç: Gastrointestinal stromal tümörler (GIST) en yaygın sindirim yolu mezenkimal neoplazileridir, ancak GIST'lerin sadece% 1-5'i duodenumda görülür. Klinik belirtiler, yönetim, cerrahi tedavi ve bunların sonuçları tam olarak tanımlanmamıştır. Bu çalışmanın amacı, kurumumuzdaki cerrahi deneyimi ortaya koymak, duodenumdaki tümörün konumuna göre cerrahi prosedürleri analiz etmek ve anatomik olarak karmaşık olan bu bölgedeki GIST'lerin cerrahi yönetimini gözden geçirmektir.

Yöntemler: Son 5 yılda (Ocak 2014 - Aralık 2019) merkezimizde küratif amaçla cerrahi olarak tedavi edilen duodenal GIST'li hastalar bu retrospektif kohort çalışmaya dahil edildi. Demografik veriler, klinik tablo, GIST yeri, tanısal değerlendirme, onkolojik tedavi, cerrahi prosedür, mortalite ve morbidite, patolojik ve morfolojik GIST özellikleri, patolojik risk kategorisi, takip ve sağkalım not edildi.

Bulgular: Merkezimizde son 5 yılda duodenal GIST tanısı alan 5 hasta ameliyat edildi. İyileştirme amaçlı ve negatif rezeksiyon sınırları ile dört ameliyat yapıldı. Sadece biri laparoskopik yaklaşımla yapıldı. Tüm vakalarda sınırlı rezeksiyon R0 yapıldı. Hiçbir hasta ameliyattan önce neoadjuvan tedavi almadı. Tüm hastaların ortalama yaşı 63 yıldı (52-70 yıl) ve hepsi kadındı. Klinik belirtiler karın ağrısı ve üst gastrointestinal kanamadan oluşuyordu. Vakalardan biri tesadüfen teşhis edildi. Postoperatif mortalite olmadı. Ortalama hastanede kalış süresi 8 gündü (4-26 gün). Ortanca takip süresi 33 aydı (6 ay - 8 yıl). Takip sırasında 2 hasta GIST dışı nedenlerle kaybedildi ve bir hasta ilk ameliyattan 29 ay sonra rezektabl periton metastazı nedeniyle ameliyat edildi.

Sonuç: Tümör biyolojisi, duodenal GIST'nin onkolojik sonuçları için cerrahi işlemden daha önemlidir. Duodenumda görülen, cerrahi rezeksiyon endikasyonu olan GIST, karmaşık duodenum anatomisi nedeniyle cerrah için zordur.

Anahtar kelimeler: Gastrointestinal stromal tümör, Duodenum, Cerrahi işlemler

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Introduction

Gastrointestinal stromal tumors (GIST) originate in the interstitial cells of Cajal, which are mesenchymal cells located in the myenteric plexus of the gastrointestinal wall. Around 80-85% of these tumors have mutations in the gene encoding Tyrosine Kinase Protein Receptor (c-KIT) and 5-7% in the Platelet Derived Growth Factor Receptor Alpha (PDGFREA) gene. Remaining 10-15% of GISTs do not present with KIT / PDGFRA detectable mutations (*wild type GIST*) [1].

GISTs are the most common mesenchymal neoplasms in the gastrointestinal tract, although they represent less than 1% of digestive tumors. The main locations for GISTs are stomach (60-70%), small intestine (20-30%), colon and esophagus (<5%). They are less frequently seen in the peritoneum, mesentery and omentum [2]. Presentation in duodenum is rare (1-5% of all GIST), however, GISTs represent 30% of all primary duodenal tumors [3].

The ideal treatment for GIST is surgical excision with an intact psuedocapsule and negative surgical margins. Surgical excision with wide margins and lymphadenectomy are not generally indicated because GISTs do not extend further than the submucosal layer or present with lymphatic invasion [4].

Unlike other locations where surgical treatment is established, the clinical manifestations, diagnosis and treatment are not well defined in duodenal GISTs, since they are based on case reports or studies with limited sample sizes [5].

The purpose of this study is to analyze the results of duodenal GISTs operated in our center during the last 5 years and review the surgical management of GISTs in this anatomically complex region.

Materials and methods

This is a retrospective analysis of patients with duodenal GISTs surgically treated with curative intention in our center during the last 5 years (January 2014 - December 2019). Incidentally diagnosed cases in surgical specimen during another surgery and initially metastatic cases were excluded.

Demographic data, clinical presentation, GIST location, diagnostic evaluation, oncologic treatment, surgical procedure, mortality and morbidity, pathological and morphological GIST characteristics, pathological risk category, follow up and survival were noted.

Risk assessment was calculated according to the *Armed Forces Institute of Pathology* (AFIP) [1] and TNM 8th edition classifications [6]. Low risk GISTs were smaller than 2 cm and had less than 5 mitosis / 50 high power fields (HPF), intermediate risk GISTs presented with a size between 2 and 5 cm and more than 5 mitosis /50 HPF or more than 10 cm but less than 5 mitosis / 50 HPF, and high risk GISTs were >5cm in size with more than 5 mitosis / 50 HPF.

All operations were performed with curative intention following the current guidelines [7]. Surgeries were classified based on the duodenal location (first, second, third or fourth duodenal portion).

Postoperative complications were categorized according to the Clavien-Dindo classification [8].

Follow up protocol included physical examination, blood test and imaging every 6 months until 5 years of follow up, then yearly afterwards for low-risk GIST, every 3-4 months for high-risk GIST until 3 years, then every 6 months until 5 years, and annually after 5 years of follow up.

Results

Five patients diagnosed with duodenal GISTs were operated in our center during the last 5 years. Four of them had curative intention surgery with clear margins, one of the surgeries had palliative intention, which was reason for exclusion.

Patients' demographic and disease characteristics are presented in Table 1. All patients were female with a mean age of 63 years (52-70 years) at the time of surgery. Clinical manifestations included abdominal pain and upper gastrointestinal bleeding. One of the cases was incidentally diagnosed. All cases of duodenal GISTs were detected with abdominal computed tomography (Figure 1-4).

Table 1: Patients' demographics and disease characteristics

Characteristics	Duodenal location			
	D1	D2	D3	D4
Age (years)	52	70	57	69
Sex	Female	Female	Female	Female
Size (cm)	3	4	5	14
Mitosis	<5	0	>5	>5
Clinical presentation	Anemia	Incidental finding	Abdominal Pain	Abdominal Pain
Recurrence risk	Low	Low	Intermediate	High
Neoadjuvant treatment	No	No	No	No
Adjuvant treatment	No	No	No	Yes
Diagnosis	CT/ endoscopy	CT/ endoscopy	CT/ endoscopy	CT
Follow up (months)	6	14	51	100

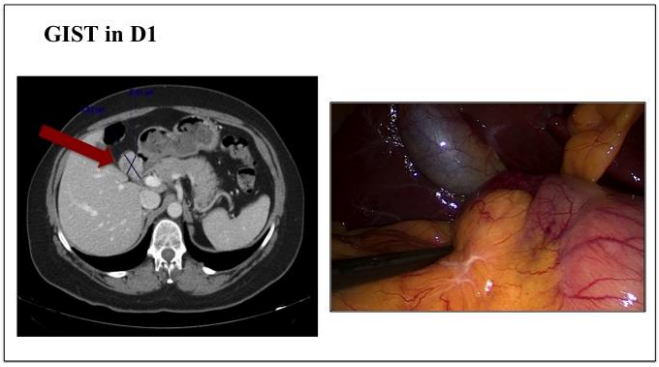

Figure 1: CT images of duodenal GIST depending on duodenal location, GIST in D1 (First duodenal portion), Arterial CT and tumor image during laparoscopic surgery

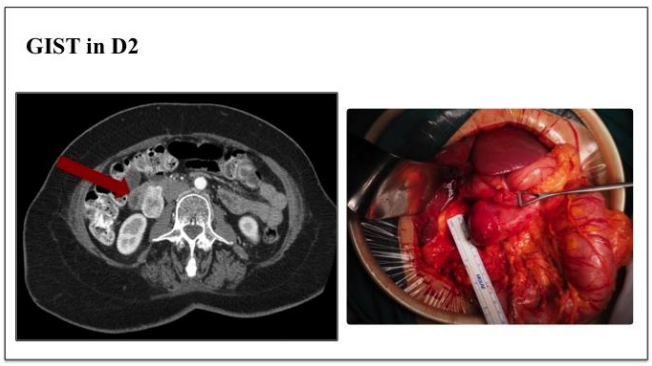

Figure 2: GIST in D2-infrapapillary portion (Second duodenal portion). Arterial CT and tumor image during open surgery

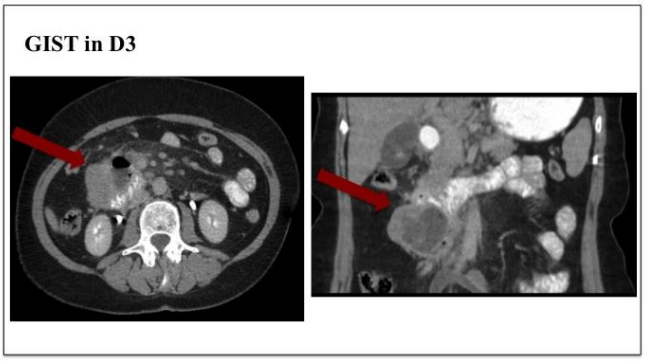

Figure 3: GIST in D3 (Third duodenal portion) CT in arterial and venous phases

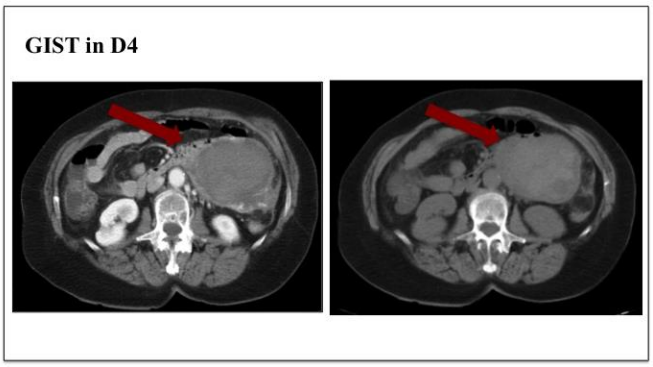

Figure 4: GIST in D4 (Fourth duodenal portion), CT in arterial and venous phases

Only one surgery was performed by laparoscopic approach. Limited resection R0 procedure was performed in all cases without capsule break. Details of the surgical procedure are described in Table 2 and Figure 5. Histopathological findings of our series are shown in Table 3.

There was no postoperative mortality. Morbidity was based on Clavien-Dindo classification, also described in Table 2. Mean length of stay was of 8 days (4-26 days).

The median follow-up time was 33 months (6 months - 8 years). During the follow up, 2 patients passed away due to non-GIST related causes, and one patient was operated for resectable peritoneum metastasis 29 months after the initial surgery. This patient presented with disease progression during adjuvant treatment with Imatinib, ineligible for surgical treatment.

None of the patients received neoadjuvant treatment before surgery.

Table 2: Surgical procedures according to GIST location in the duodenum

Surgery	Duodenal location			
	D1	D2	D3	D4
Procedure	Segmental Duodenectomy	Segmental Duodenectomy	Local Resection	Segmental Duodenectomy
Anastomosis	End-to-side Duodenojejunal	Side-to-end Duodenojejunal	Side-to-side Duodenojejunal	End-to-end Duodenojejunal
Approach	Laparoscopy	Laparotomy	Laparotomy	Laparotomy
Duodenal Side	Antimesenteric Anterolateral	Antimesenteric Posterolateral	Antimesenteric Lateral	Antimesenteric Posterolateral
Size (cm)	3	4	5	14
Morbidity	No	Yes	Yes	No
Clavien-DIndo classification	-	IIIa (Intra-abdominal abscess)	II (Anemic syndrome)	-
Length of stay (days)	4	26	8	8
Recurrence (location)	No	No	No	Peritoneal
Time to recurrence (months)	-	-	-	29

D1: First duodenal portion, D2: Second duodenal portion, D3: Third duodenal portion, D4: fourth duodenal portion

Table 3: Histopathologic features according to GIST location in the duodenum

Histopathologic features	Duodenal location			
	D1	D2	D3	D4
Cell type	Fusocelular	Fusocelular	Fusocelular	Fusocelular
Atypia	No	Moderate	No	Severe
Necrosis	No	No	Yes	Yes
Resection margins	Clear	Clear	Clear	Clear
CD34	NA	Positive	NA	Positive
CD-117	Positive	Positive	Positive	Positive
Mutation	c-KIT exon 11	NA	NA	c-KIT exon 11
TNM classification	T2NxM0	T2NxM0	T2NxM0	T4NxM0

NA = not applicable, D1: First duodenal portion, D2: Second duodenal portion, D3: Third duodenal portion, D4: fourth duodenal portion

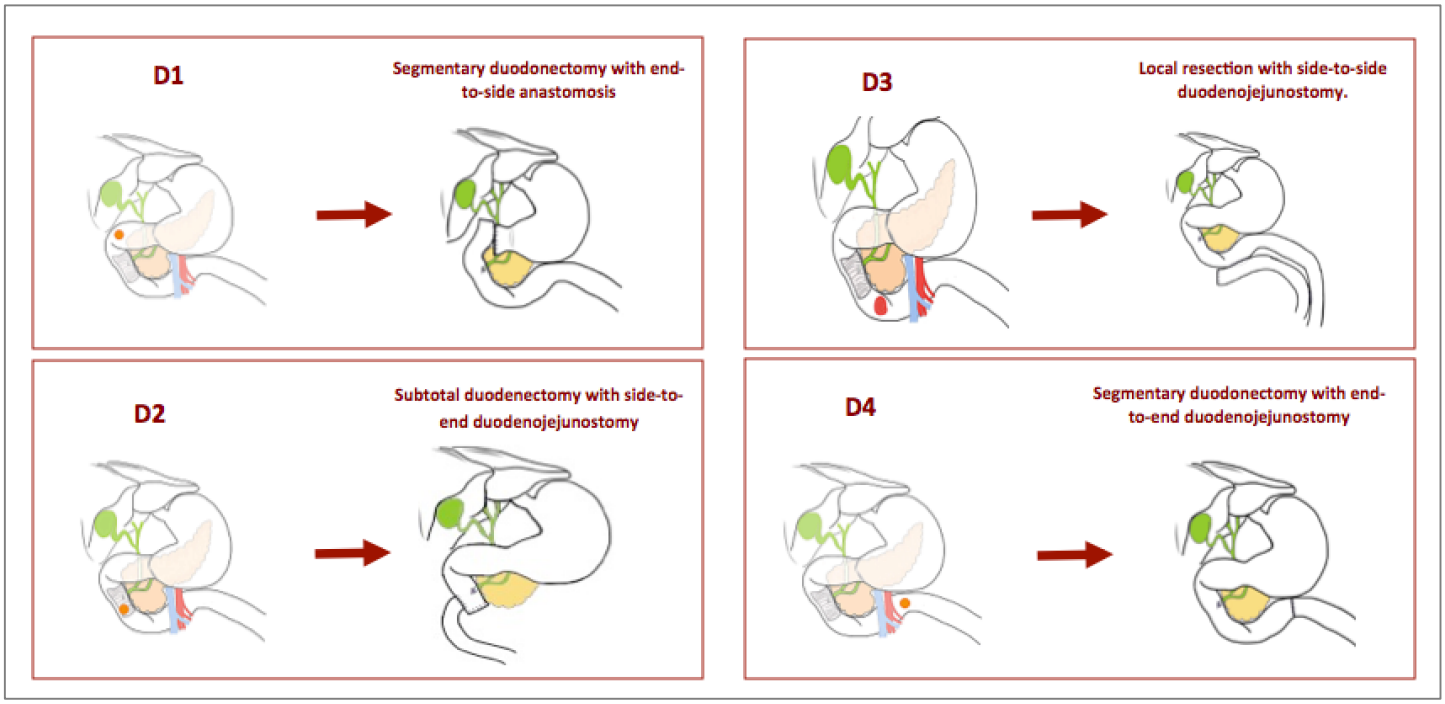

Figure 5: D1 (First duodenal portion): GIST in D1 with resected area marked. Surgical procedure: segmental duodenectomy with end-to-side anastomosis. D2 (Second duodenal portion): GIST in D2 (infrapapillary) with resected area marked. Surgical procedure: subtotal duodenectomy with side-to-end duodenojejunostomy. D3 (Third duodenal portion): GIST in D3 with resected area marked. Surgical procedure: local resection with side-to-side duodenojejunostomy. D4 (Fourth duodenal portion): GIST in D4 with resected area marked. Surgical procedure: segmental duodenectomy with end-to-end duodenojejunostomy.

Discussion

The most common duodenal portion affected by GIST is the second part, followed by the third and first parts [3,9]. This is in coherence with our results (40% GISTs were located in the second part of the duodenum).

In our series, all our patients were females, with a mean age of 63 years (52-70 years), which is also consistent with the literature [7,10]. Most patients had clinical manifestations such as hemorrhage and abdominal pain, which are the most common presentation of duodenal GISTs [9,10].

Contrast-enhanced abdominal and pelvic computed tomography (CT) scan is the investigation of choice for staging and follow-up. GISTs are hypervascular tumors appearing as well-defined endophytic or exophytic masses on contrast enhanced images, the tumor is strongly enhanced in the arterial phase and this enhancement may last until the delayed venous phase [9]. In our study, all patients were diagnosed by CT.

The differential diagnosis includes other soft tissue tumors including leiomyoma adenocarcinoma, leiomyoma, leiomyosarcoma, fibrosing mesenteritis, lipoma, mesenteric lymphangioma, plexiform neurofibromatosis, ectopic pancreas, Brunner's gland cyst, schwannoma, vascular tumors, and neuroendocrine tumors [9,11].

Upper endoscopy should be the first procedure of choice, it can even be therapeutic as the most frequent clinical manifestation of duodenal GIST is bleeding [11]. Duodenal GIST usually shows as a submucous elevated lesion. Endoscopy also allows exploration of the first and second duodenal parts. Endoscopic biopsies usually do not provide enough material for GIST diagnosis due to its location in the submucous layer. Endoscopic ultrasound assessment (EUS) is a better tool to define GIST-suspicious lesions, which are round or oval shaped, hypoechogenic, and originate from muscular propria. EUS allows localizing the lesion with precision and its relationship with surrounding structures (pancreatic head, ampulla of Vater) [7,9].

In our series, EUS was not performed because it was not available. Upper endoscopy was performed in tumors located in D1, D2 and D3, biopsy confirming the diagnosis in half of the cases.

There are many histopathologic and biological factors associated with prognostic value (tumor line, cell density, ulceration, mucous layer invasion, necrosis, cell atypia, KIT/PDGFRA mutation). However, it is difficult to distinguish the real importance of these factors because relevant studies include small number of patients and are usually retrospective in design [12].

In the published series, the recurrence risk is low and very low in 50-64% of cases [10,13]. The disease-free survival and the disease-specific survival of duodenal GISTs are significantly worse than those of gastric GISTs [10].

The case in our series with the worst prognosis (high recurrence risk) presented with tumoral progression in peritoneum, one of the most frequent locations for metastasis, together with the liver. The guideline of European Society of Medical Oncology (ESMO) proposes EUS evaluation and follow up for duodenal tumors <2cm, and excision if tumor growth is noticed or linked with symptomatology. In lesions ≥2cm, biopsy or excision is recommended due to worse prognosis if GIST [7].

The decision to obtain a biopsy should be based on the grade of suspected tumor type, and disease extension. Biopsy is needed before starting neoadjuvant treatment. The National Comprehensive Cancer Network (NCCN) guidelines suggest that EUS fine needle guided biopsy is better than percutaneous biopsy due to high bleeding risk and intra-abdominal dissemination. Percutaneous biopsy would be appropriate to confirm cases with metastasis [1,14].

The duodenal GIST cases analyzed in our series presented with a tumoral size ≥ 2 cm. Endoscopic biopsy confirmed diagnosis in 2 cases and the therapeutic procedure was limited resection with curative intention (R0) in all cases.

The published series describe 2 main surgical procedures: Limited resection (LR), which includes duodenectomy preserving pancreas, segmental duodenectomy or local excision with primary closure and duodenopancreatectomy (DP).

Selection of any of these options depends on tumor size, location in mesenteric or anti-mesenteric side in the duodenum and distance to essential structures (Vater's papilla).

In a revision of more than 300 cases [10], 66,3 % were treated with LR and 26% with DP. In multivariate analysis the technical procedure was not an independent prognostic factor.

Miettinen et al. [3] published a revision of duodenal GIST where 45% of cases were treated with segmental resection, 34% with local excision and the remaining 20% with DP. In the published series, between 20-80% of patients are treated with DP [2,15,16].

A meta-analysis suggests that LR is the best procedure for duodenal GIST whenever it is technically possible, due to its good oncologic results and low morbidity compared to DP [2]. When comparing both procedures, one should be cautious on account of proximity to essential structures such as the papilla of Vater, pancreas, mesenteric vessels, common biliary duct, and pancreatic duct, which can be a selection bias. The choice of the surgical approach should depend on the anatomical location and tumor size [17].

GISTs located on the anti-mesenteric side (lateral wall) in D2 and those not located in the periampullary region can be limitedly resected with local resection or segmental duodenectomy depending on the circumferential extension. Primary closure of the duodenal wall can be achieved through transverse suture, and if there is risk of duodenum lumen stenosis, side-to-end duodenojejunostomy or Roux-en-Y side-to-side duodenojejunostomy [9,18].

Tumors localized in D2, surrounding Vater's ampulla, and in the mesenteric border (medial wall) could be candidates for local resection with ampullectomy, duodenectomy with pancreatic preservation or cephalic duodenopancreatectomy depending on tumor size [19].

Options for GISTs located in lateral wall of D1, D3 or D4 are local resection or segmental duodenectomy with end-to-end / end-to-side / side-to-side anastomosis. If a large tumor is located on the medial wall, an aggressive surgery may be needed [9,11,20].

Limitations

We do not pretend to describe new or relevant aspects about the pathophysiology of the disease or its diagnosis. Our aim is to propose different surgical approaches with low morbidity in a complex anatomical location, such as the duodenum.

Some of the limitations include the retrospective design and the small sample size of this study. This happens because duodenal GISTs are uncommon tumors. It´s acknowledged that most of the publications are based on case reports or small sample studies, although there are available meta-analyses and systematic reviews that can help understand the current evidence in surgical treatment. Since it is an uncommon pathology, a review of these articles is necessary when facing these tumors.

We could not compare different surgical procedures (LR vs. DP) due to small sample size and because we did not have the chance to perform DP in our series.

Conclusion

The second duodenal portion is the most common location for duodenal GISTs. Placement in duodenal wall (mesenteric o anti-mesenteric side), tumor size and relation to critical structures in the duodenal-pancreatic anatomy are the most important key factors for surgical procedure selection. Tumor biology is more important than the surgical procedure for oncologic results of duodenal GIST. Surgical procedure (LR or DP) is not an independent prognostic factor.

GISTs located in duodenum with surgical indication are a challenge for the surgeon due to the complex duodenum anatomy. Our first option is limited resection with R0 margins in opposition to more aggressive options with high morbidity and mortality.

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