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A single-center study and a review of the literature



Ann Ital Chir, 2022; 11 - Nov. 7

pii: S2239253X22038750

Online Epub

Marianna Capuano, Giuseppe Palomba, Giuseppe Sorrentino, Raffaele Basile,
Alessia Chini, Rosa Maione, Francesco Maione, Giovanni Domenico De Palma,
Giovanni Aprea

Department of Clinical Medicine and Surgery, Federico II, University of Naples, Naples, Italy

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BACKGROUND: *Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. They are 1% of all gastrointestinal cancer and 60% of them affects the stomach. Up to 10% to 30% of GISTs are malignant. They occur in people over the age of 50 in both sexes. The most common symptoms of gastric GIST are bleeding, dyspepsia, vague abdominal pain or discomfort, and mass palpation. Some are asymptomatic and diagnosed incidentally. The first choice of treatment for primary localized gastric GISTs is surgery. The most suitable type of resection is not yet clear and it depends on size and location of tumor, especially for difficult localizations, such as subcardial, posterior wall and less curvature GISTs.*

METHODS: *We report a rare case of a patient with subcardial gastric GIST treated with laparoscopic atypical quadrangular resection guided by intraoperative endoscopy. Furthermore, we performed a review of the literature about this topic.*

RESULTS: *Despite the difficult localization an atypical resection of the gastric GIST was performed without breaking the lesion but preserving the lumen of the esofagogastric junction.*

CONCLUSIONS: *An atypical quadrangular resection for subcardial gastric GISTs, located along the posterior wall and lesser curvature, can be a safe and reliable alternative technique. However, we believe that it should be performed by an experienced surgeon and endoscopist to decrease the risk of mass's break and the narrowing of the cardial region's lumen. In our literature's knowledge there aren't cases treated with this technique.*

KEY WORDS: Gastric GIST, Gastrointestinal stromal tumors, Intraoperative endoscopy, Laparoscopic resection, Minimally invasive surgery

Introduction

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract ¹ Up to 10% to 30% of GISTs have a malignant clinical course ². GISTs can involve all the gastroin-

testinal tract: 60% of them affects the stomach 35% the small intestine, and less than 5% the rectum or the esophagus ³. In rare cases involve primary the omentum, mesentery or retroperitoneum ⁴.

Gastric GISTs generally occur in patients older than 50 years in both sexes. It can rarely be associated with hereditary syndromes such as neurofibromatosis 1 and von Hippel-Lindau disease ⁵. Clinical presentation varies from small benign tumors to massive lesions. The most common symptoms are bleeding, followed by dyspepsia, vague abdominal pain or discomfort, and mass palpation. Most patients are asymptomatic, and the diagnosis is incidental ⁶.

Pervenuto in Redazione Agosto 2022. Accettato per la pubblicazione Ottobre 2022

Correspondence to: Marianna Capuano, MD, Department of Clinical Medicine and Surgery, Federico II, University of Naples, Via Sergio Pansini 5, 80131 Naples, Italy. (e-mail: mariannacapuano1@libero.it)

First choice of treatment for primary localized gastric GISTs is surgery. Good quality of life is achieved after wedge or segmental organ resection with preservation of tissue and its functions^{7,8}. Laparoscopic resection of gastric GIST compared to the open surgery improved short term outcomes with similar long-term outcomes⁹. However, there are no absolute indications for the type of resection based on size and location of tumor. We report a rare case of a patient with an unfavorable position gastric GIST (subcardial, along the posterior wall of the lesser curvature of the stomach) treated with an atypical laparoscopic resection associated with intraoperative endoscopy.

In our literature's knowledge there aren't cases treated with this technique. Thus, this is the first case of this atypical resection. Furthermore, we performed a review of the literature about this topic.

Case Report

A 53-years-old man was referred to the Department of Gastroenterology for repeated episodes of severe epigastric pain. Initially he underwent an abdominal computed tomography (CT) in June 2021 that showed a large mass (59x35x39mm) occupying part of the lumen, the fundus and gastric body native from the muscular component of the lesser curvature (Fig. 1). Then a gastroscopy was performed in July which was not diagnostic for GIST but revealed only eroded papules in the antral and pre-piloric site, as from chronic gastritis, then confirmed by biopsy, associated with HP infection. In August an ultrasound (US) endoscopy with biopsy diagnosed subcardial gastric GIST along the lesser curvature about 5 cm in diameter.

The patient was then sent to our Department of Surgery for treatment. After a multidisciplinary evaluation (oncologist, anesthetist, endoscopist and surgeon), a laparoscopic approach was selected for the resection of the gas-

tric GIST. In November 2021 the patient underwent surgery. Four trocars were placed: the first 12mm trocar for the camera on the left side of the navel at 2 cm and up to 3 cm. The second 5mm sub-xiphoid trocar to lift the liver. The third 12mm trocar on the left side and the fourth 5mm trocar on the right side both on the level of the emiclavicular lines.

The initial laparoscopic vision was unable to identify the mass except for a slight imprint on the anterior wall of the stomach in the subcardial region that extended along the lesser curvature (Fig. 2).



Fig. 2: laparoscopic vision identifying a slight imprint on the anterior wall of the stomach in the subcardial region that extended along the lesser curvature.



Fig. 3: intraoperative gastroscopy showing an ulcerated mass with endophytic growth on the posterior wall of the stomach, under the cardia, along the lesser curvature.



Fig. 1: CT showing a mass occupying part of the lumen, the fundus and gastric body (59x35x39mm) native from the muscular component of the lesser curvature.

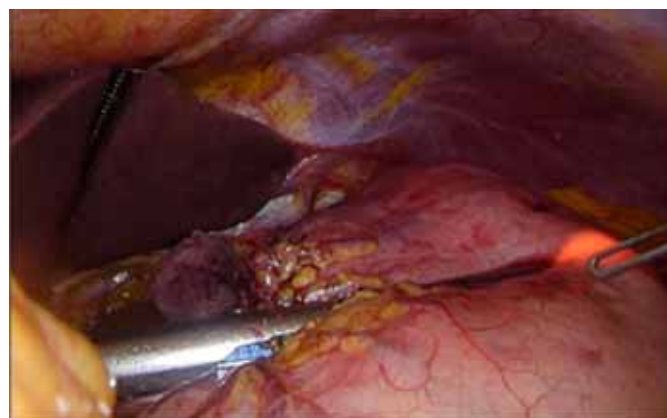


Fig. 4: the first suture performed on the caudal margin of the lesion.

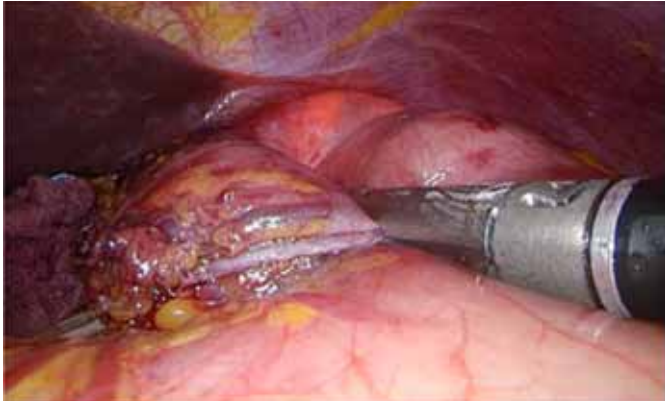


Fig. 5: the second suture performed on the lateral margin of the lesion.



Fig. 8: final appearance of the stomach.



Fig. 6: mobilization of the stomach recovering the range of motion for the last suture.

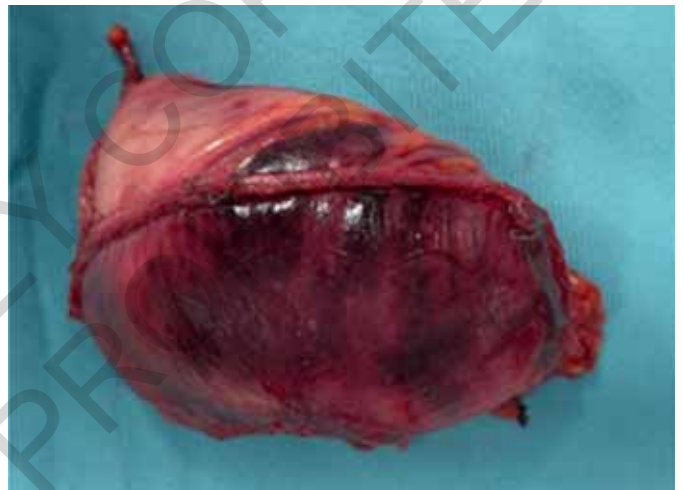


Fig. 9: surgical piece.

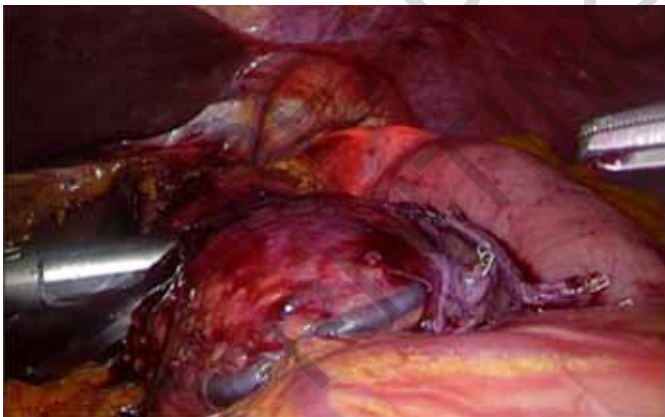


Fig. 7: the last suture performed on the cranial margin of the mass.



Fig. 10: surgical piece engraved.

Thus, we performed an intraoperative gastroscopy that showed an unexpected mass on the posterior wall of the stomach, under the cardia, along the lesser curvature (Fig. 3). The lesion was visualized endoscopically thanks to laparoscopic ab-extrinsic compression on the posterior wall of the stomach. Intraluminal tumor growth may be due to the time between preoperative and intraoper-

ative gastroscopy. The mass has a size of 5 cm in diameter with endophytic growth and central ulcer. It had a mixed intramural and intraluminal development. Thanks to the combined laparoscopic and endoscopic vision

through the combination of two monitors, the operating surgeon was able to understand the upper, lower and lateral margins of the lesion.

A quadrangular excision was performed using a linear stapler on three sides: the first suture was performed on the caudal margin of the lesion (Fig. 4), the second on the medial margin upward (Fig. 5). The first two sutures allowed a greater mobilization of the stomach recovering the range of motion for the last suture (Fig. 6). This was performed on the proximal margin of the mass with the endoscope positioned to preserve the lumen of the esophagogastric junction (Fig. 7).

Under endoscopic vision we were able to verify the stapler branches and the sutures performing them on healthy tissue (Fig. 8) and removing the tumor entirely (Figs. 9, 10).

Discussion

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract¹⁰. They are 1% of all gastrointestinal cancer and the annual incidence is 10-20/ million and occurs mainly in the stomach (60%), in the jejunum or ileum (30%) and colon – rectum (15%)^{10,11}.

Gastric GIST surgery is very heterogeneous and this depends on size and location of the tumor¹². It is not yet well understood which is the most suitable surgical technique in the various cases, especially for difficult localizations, such as subcardial, posterior wall and lesser curvature.

A traditional narrative literature search was performed using PubMed, Scopus, Medline and Cochrane. We used several search terms such as “GIST, gastrointestinal stromal tumors, gastric GIST, gastric stromal tumor” in different combinations to improve the retrieval of articles. It is believed that GISTs origin from the interstitial cells of Cajal (ICC) considered the pacemaker cells of the gastrointestinal tract wall that allow autonomous movement¹³. In most cases (75-80%) they are caused by a gain of function mutations of the protooncogene *c-kit*, that encodes the receptor tyrosine kinase KIT, while in a minority of cases (5-10%) by gain-of-function mutations in platelet-derived growth factor receptor- α (PDGFRA) gene⁵. Some GISTs are considered wild-type because they don't have mutations in either the KIT gene or the PDGR- α gene. They are divided into succinate dehydrogenase (SDH)-deficient and non-SDH-deficient groups. The first generally involved cases of young women with Carney-Stratakis syndrome and occur in the gastric antrum, while the second are found in pediatric cases or patients with Neurofibromatosis I and occur in the small intestine¹⁴.

GISTs can present in several ways. Patients with gastrointestinal stromal tumors may complain of abdominal swelling or pain, loss of appetite and early satiety.

These tumors can cause anemia due to intraluminal bleeding with melena or hematemesis or even intraperitoneal hemorrhages¹⁵. The most common symptom of gastric GIST is bleeding, followed by dyspepsia, vague abdominal pain or discomfort, and mass palpation⁶. Symptomatic gastric GISTs typically are larger than 2 cm¹⁶. Some are asymptomatic and diagnosed incidentally with tests performed for other reasons¹⁷. In our case the patient complains of epigastric pain as only symptom.

GISTs are often detected as sub-epithelial lesions (SELs) during endoscopic examinations, they appear as smooth lumps covered by normal mucosa. Irregular edges and/or ulcerations are considered malignant features¹⁸. CT can detect primary or recurrent GISTs and provides information on size, growth pattern, relationship to the gastrointestinal wall and surrounding organs, and detects distant metastases¹⁹. The Endoscopic UltraSonography (EUS) allows to identify the GIST as a hypoechoic mass and to differentiate with other lesions such as cysts (anechoic), lipomas (hyperechoic), varices or external masses, evaluating lesion's size and type and the layer of the wall from which originates¹⁸. Endoscopic UltraSonography Fine Needle Aspiration (EUS-FNA) is the most reliable and useful tool in the histological diagnosis of submucosal tumor (SMT), although it can be influenced by location, size and heterogeneity of the tumor^{18,20}. Our patient underwent first to a CT scan examination which raised the suspicion for GIST however the gastroscopy was negative. EUS with biopsy was decisive for the diagnosis and localization of the tumor. For localized primary tumor (without evidence of direct or metastatic spreading) total resection with free margin is the therapeutic goal to reduce the risk of recurrence²¹. However, there aren't clear evidence of worse prognosis with microscopic residues during resection²². To keep a good quality of life the wedge or segmental resection with organ's structure and function preservation is recommended^{7,23}.

Systematic reviews and meta-analyses present in the literature show that laparoscopic approach for the surgical treatment of gastric GIST is safe and effective²⁴. Laparoscopic resection has major advantages in terms of perioperative outcomes, such as shorter duration, lower blood loss, decreased time to oral intake, shorter length of stay, decreased morbidity and lower recurrence²⁵.

A Propensity Score-Matching Analysis about Short- and Long-Term Outcomes of Laparoscopic Versus Open Resection for Gastric GIST published in 2016 which considered wedge resection, proximal gastrectomy, distal gastrectomy, and total gastrectomy for localized gastric GIST, demonstrated that laparoscopic resection (LR) for gastric GIST resulted in improved short-term outcomes and similar long-term outcomes compared with open surgery (OR)⁹. LR results in superior short-term post-operative outcomes without compromising oncological safety and long-term oncological outcomes compared

with OR, as tumor free resection margins and recurrence rate^{26,27}. The laparoscopic approach should be preferred for the treatment of gastric GISTs, unless advanced GIST I diagnosed^{28,29}.

The current version of NCCN, ESMO and EURACAN guidelines considered mitotic rate, tumor size and site the three main prognostic factors³⁰. Very low-risk and low-risk diseases can be treated with surgery alone. Tumor break during surgical resection is also recognized as an independent risk factor and the most important technical point is to avoid it during removal^{29,30}.

Gastric GISTs can be classified according to their location. Favorable locations for surgical resection are gastric fundus, anterior wall and greater curvature while unfavorable locations are gastroesophageal junction, lesser curvature, posterior wall, antrum and pylorus³¹. In our case it was a GIST with an unfavorable position localized under the cardia, along the posterior wall of the lesser curvature of the stomach.

According to location and size there are several laparoscopic wedge resection (LWR) techniques for gastric GIST such as: laparoscopic exogastric wedge resection (LEWR), laparoscopic transgastric tumor-everting resection (LTER), intragastric tumor wedge resection. LWR is the preferred choice for most GISTs, although partial gastrectomy or total gastrectomy may be necessary in some cases³².

Anterior wall and greater curvature GISTs protruding into the abdominal cavity are easily resectable with a linear stapler. Single-incision laparoscopic surgery (SILS) may be considered the most appropriate type of laparoscopic surgery for GISTs located mainly on the anterior wall³³. High and posterior wall tumors, instead, remain difficult to resect through mobilization of the greater curvature and eversion of the posterior wall, so LTER approach is preferred³⁴. LTER starts with a gastrotomy of the anterior wall, the tumor is found and everted through the gastrotomy, the lesion is then resected by stapling and finally the anterior aspect of the stomach is sutured³⁵. Intraluminal growth type tumors less than 4 cm in size, especially when located near the cardia, were candidates for Endoscopic Full-thickness resection (EFTR) or Laparoscopy and endoscopy cooperative surgery (LECS)³⁶. Small gastric GISTs less than 5cm with intraluminal or intramural growth and without ulceration can be treated with a Laparoscopy and Endoscopy Cooperative Surgery (LECS) techniques: these lesions are easily visible and the resection area is demarcated under endoscopic observation. Endoscopic circumferential mucosal incision under direct visualization used to isolate and resect the lesion in a full-thickness fashion by subsequent endoscopic or laparoscopic seromuscular incision. Then the gastric margins of resection closed by laparoscopic linear staplers or laparoscopic suturing techniques³⁷. LECS has similar outcomes to conventional LWR with the advantage to reduce the resected area of the gastric wall³².

Some authors reported that laparoscopic segmental gastrectomy with residual gastric end-to-end anastomosis may be a feasible function-preserving gastrectomy for treatment of GISTs that grow in the middle third of the stomach and on the lesser stomach curvature³⁸.

A combined endoscopic/laparoscopic intraluminal enucleation technique has also been described: a laparoscope is introduced into the gastric cavity and the gastric iuxta-cardial lesion is grasped and tractioned by an endoscopic polipectomy snare introduced per mouth. Through an other laparoscopic trocar, the lesion is removed with a complete submucosal resection. The specimen is then pulled away from the mouth after its introduction into a plastic bag and the gastric holes are closed with monofilament non-absorbable sutures.

Zheng GL et al.³⁹, showed a new technique called con-formal resection (CR) for open surgery of esophagogastric junction (EGJ)-GIST involving Z-line. This approach realizes a precise excision according to the shape of the GIST, preserving the Z-line. Then these authors perform a manual interrupted full thickness suture⁴⁹.

In our case a laparoscopic approach selected for the resection of the gastric GIST. The preoperative instrumental examinations suggested a GIST with intramural growth, partially occupying the lumen but not directly visible on gastroscopy. Under laparoscopic vision, the lesion was initially difficult to identify as it was located on the posterior wall of the stomach. Only a coarse raised imprint was visible on the anterior gastric wall. We performed an intraoperative gastroscopy and used a combined laparoscopic and endoscopic approach for direct intra and extraluminal vision.

This allowed the identification of an ulcerated intramural and unexpectedly also intraluminal growth mass approximately 5 cm in diameter on the posterior wall, below the cardiac region in the lesser curvature. Thanks to laparoscopic ab-extrinsic compression on the posterior wall on the stomach, the mass was visualized endoscopically. We performed an atypical resection which allowed the resection of the lesion despite the difficult localization. We used a linear stapler for a quadrangular excision: the first two sutures on caudal and medial margins of the lesion allowed a greater mobilization of the gastric region to perform the last suture on the cranial margin.

Under endoscopic guidance, we removed the part of the stomach that contained the entire lesion without breaking it and at the same time we preserved the lumen of the esophagogastric junction leaving the passage between the esophagus and stomach free and smooth.

Despite the difference between the preoperative investigations and the real intraoperative vision of the GIST, the difficult localization of the tumor and the use of a non-standardized technique, the intervention was without complications and lasted 90 minutes.

This approach was possible thanks to the presence in the same department of integrated activity of operating theaters with endoscopic rooms. In our department the col-

laboration between surgeons and endoscopists for digestive tract's diseases is common and we are used to working together.

Therefore, for this case the choice to perform an atypical resection through the simultaneous use of laparoscopy and endoscopy was possible with a certain degree of safety and confidence. In our literature's knowledge there aren't cases treated with this technique. Thus, this is the first case of this atypical resection.

The patient underwent a gastrografin esophagus-stomach x-ray check on the 4th postoperative day which showed no spillage, started eating on the 5th postoperative day and discharged on the 6th postoperative day. There were no postoperative complications. After one month the patient reported only a slight sensation of gastric swelling, which resolved over time changing eating habits, eating slowly trying not to swallow air.

The risk of recurrence of surgically treated primary GISTs can be assessed according to Fletcher's criteria which define four prognostic categories: very low, low, intermediate and high risk. They are based on tumor size (≤ 2 , $>2-5$, $>5-10$, and >10 cm) and mitotic activity (<5 vs. $>5/50$ HPFs). A size of 5 cm was fixed as the cut-off value to define low and nonlow risk tumors [41]. Tumor rupture has a high risk for metastasis ⁴².

Unlike Fletcher's criteria, Miettinen's criteria consider the anatomic location and include the risk group of "benign tumors" with no risk of malignancy [41]. Gastric GISTs ≤ 10 cm and ≤ 5 mitoses for 50 HPFs have low risk for metastasis, whereas those with >5 for 50 HPFs and >5 cm in diameter have high risk for metastasis ⁴⁴. The risk of recurrence at the 10th year after surgical treatment of a GIST can be calculated using the maximum diameter of the tumor, the number of mitoses, the tumor site, and the presence or absence of tumor capsule rupture and this is useful for decision-making about adjuvant therapy ⁴².

The modified Fletcher classification (Joensuu classification) is also widely used: gastric GISTs ≤ 5 cm and ≤ 5 mitoses per 50 HPFs have low risk for metastasis, gastric GISTs ≤ 5 cm and >5 mitoses or <10 cm and ≤ 5 mitoses per 50 HPFs have intermediate risk for metastasis, gastric GIST ≥ 10 cm or >10 mitoses for 50HPF or >5 cm and >5 mitoses for 50HPF or with tumor rupture have high risk for metastasis ⁴².

Finally, MSKCC Nomogram, considering tumor size, site and mitotic rate, is useful for stratifying GISTs risk of recurrence and planning the therapeutic strategy ⁴³. Patients who have a substantial risk for recurrence should be treated with at least 3 years of imatinib, an inhibitor of KIT and PDGFRA. The optimal duration remains unknown. GISTs with PDGFRA D842V mutation or lacking a mutation in KIT or PDGFRA are unlikely to benefit from adjuvant imatinib ³⁹. Imatinib is the standard treatment for locally advanced inoperable and metastatic disease. Imatinib is also the standard treatment for patients with metastatic disease who had all

lesions removed surgically, although surgery is not recommended as a primary approach in the metastatic setting ⁴⁶.

The optimal follow-up program is not known but risk assessment is useful in choosing the routine with abdominal CT scan or MRI follow-up policy. High-risk patients generally have a relapse within 1-3 years from the end of adjuvant therapy ⁴⁷. Low-risk patients may have a relapse later ⁴⁶.

Elderly patients need a closer follow-up for a higher risk of recurrence ⁴⁷. A reasonable strategy may be to image the abdomen at 6- to 12-month intervals for the first 10 years after surgery. More frequent imaging at 3- or 4-month intervals may be considered for 2 years after stopping adjuvant imatinib ⁴⁵.

In our case the histological diagnosis confirmed the presence of GIST with very low risk according to the Miettinen classification of 2006 (4x4cm of size, mitotic activity of 1mitosis / 5mm²). The patient underwent oncological control with abdominal CT 6 months after the operation which showed no recurrence of the disease.

Conclusions

Laparoscopic atypical quadrangular resection for subcardial gastric GISTs, located along the posterior wall and the lesser curvature, can be considered a safe, feasible and reproducible technique. This approach could be an alternative surgical choice to total or partial gastrectomy for these tumors.

However, it requires integrated surgical theaters with endoscopic activity and it should be performed by experienced surgeon and endoscopist to decrease the risk of mass's break and the narrowing of the cardial region's lumen.

Riassunto

I tumori stromali gastrointestinali (GIST) sono i tumori mesenchimali più comuni del tratto gastrointestinale, il 60% dei GIST interessa lo stomaco.

La prima scelta di trattamento per i GIST gastrici primari localizzati è la chirurgia. La resezione laparoscopica del GIST gastrico rispetto alla chirurgia a cielo aperto ha migliorato i risultati a breve termine con risultati simili a lungo termine. Tuttavia, non ci sono indicazioni assolute sul tipo di resezione in base alle dimensioni e alla posizione del tumore. Riportiamo un raro caso di un paziente di 53 anni con un GIST gastrico localizzato in una posizione sfavorevole (sottocardiale, lungo la parete posteriore della piccola curvatura dello stomaco) trattato con resezione laparoscopica atipica supportata da un'endoscopia intraoperatoria. La TC addominale nel giugno 2021 mostrava una grossa massa (59x35x39 mm) che occupava parte del lume, il fondo e il corpo gastri-

co a partenza dalla componente muscolare della piccola curvatura. La gastroscopia, tuttavia non era diagnostica per GIST ma rilevava solo papule erose in sede antrale e prepilorica, come da gastrite cronica.

Ad agosto un'acoendoscopia (US) con biopsia ha diagnosticato un GIST gastrico sottocardiale lungo la piccola curva di circa 5 cm di diametro. Dopo una valutazione multidisciplinare il paziente è stato sottoposto ad intervento chirurgico di resezione laparoscopica del GIST gastrico. La visione laparoscopica iniziale non è stata in grado di identificare la massa tranne che per una leggera impronta sulla parete anteriore dello stomaco nella regione sottocardiale, che si estendeva lungo la piccola curva. Pertanto, è stata eseguita una gastroscopia intraoperatoria che ha mostrato inaspettatamente una massa di circa 5cm ulcerata, sulla parete posteriore dello stomaco, sotto il cardias, lungo la piccola curva.

La lesione è stata visualizzata endoscopicamente grazie alla compressione ab-estrinseco laparoscopica sulla parete posteriore dello stomaco e la crescita intraluminale probabilmente era dovuta al tempo intercorso tra la gastroscopia preoperatoria e quella intraoperatoria.

Grazie alla visione laparoscopica ed endoscopica combinata mediante l'utilizzo di due monitor, il chirurgo è stato in grado di comprendere i margini superiore, inferiore e laterale della lesione. È stata eseguita una resezione atipica che ha consentito l'asportazione della lesione nonostante la difficile localizzazione.

È stata realizzata un'asportazione quadrangolare utilizzando una suturatrice lineare su tre lati: la prima sutura sul margine caudale della lesione, la seconda sul margine laterale verso l'alto. Le prime due suture hanno consentito una maggiore mobilizzazione dello stomaco recuperando il range di movimento per l'ultima sutura, che è stata eseguita sul margine prossimale della massa con l'endoscopio posizionato in modo tale da preservare il lume della giunzione esofago gastrica.

La visione endoscopica ha permesso di rimuovere la parte di stomaco che conteneva l'intera lesione senza romperla e contemporaneamente di preservare il lume della giunzione esofago gastrica lasciando libero il passaggio tra esofago e stomaco. Nonostante la differenza tra le indagini preoperatorie e la reale visione intraoperatoria del GIST, la difficile localizzazione del tumore e l'utilizzo di una tecnica non standardizzata, l'intervento non ha avuto complicanze ed è durato 120 minuti.

La resezione quadrangolare atipica laparoscopica per GIST gastrici sottocardiali, situata lungo la parete posteriore e la piccola curvatura, può essere considerata una tecnica sicura, fattibile e riproducibile.

Questo approccio potrebbe essere considerato una scelta chirurgica alternativa alla gastrectomia totale o parziale per questo tipo di tumori. Tuttavia, esso richiede sale operatorie integrate con attività endoscopica e dovrebbe essere eseguita da chirurgo ed endoscopista esperti per ridurre il rischio di rottura della massa e il restringimento del lume della regione cardiaca. In base alle nos-

tre conoscenze non ci sono in letteratura casi trattati con questa tecnica. Pertanto, questo ne rappresenta il primo caso.

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