Incidental detection of gastrointestinal stromal tumors during laparoscopic sleeve gastrectomy. What to do?

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Hasan Erdem*, Mehmet Gençtürk**, Seyfi Emir**, Abdullah Şişik***, Selim Sözen****

**Department of General Surgery, Istanbul Obesity Surgery (IOC), Kurtköy Ersoy Hospital, Istanbul, Turkey*
***Department of General Surgery, Reyap Hospital, Tekirdağ, Turkey.*
****Department of General Surgery, University of Health Sciences, Ümraniye Education and Research Hospital, Istanbul, Turkey*
*****Department of General Surgery, Sözen Surgery Clinic, Kurtköy Ersoy Hospital, Istanbul, Turkey*

Incidental detection of gastrointestinal stromal tumors during laparoscopic sleeve gastrectomy; what to do?

INTRODUCTION: *We evaluated and characterized the incidental GISTs during laparoscopic sleeve gastrectomy in our clinic.*
METHODS: *All GISTs identified during laparoscopic sleeve gastrectomy between January 2015 and December 2017 were evaluated. Typical demographic, clinicopathologic, treatment, location, resection margins, immunohistochemistry (CD 34, CD 117, ASMA, desmin and S100) and criteria for oncological aggressiveness (tumor size, number of mitoses, presence or absence of tumor necrosis) data were recorded.*
RESULTS: *Within the 800 bariatric surgeries at our institution, 7 GISTs were identified (0.87%). The median age of the patients was 32 years (age range: 24-42 years). The mean BMI was found to be 40.66 kg/m^2 (range: 35-44 kg/m^2). All GIST cases were found in the stomach samples. All tumors were not larger than 20 mm. All tumors were found close to the greater curvature of the stomach; in five cases, tumors were located in a single focus, while in 1 case, it was located both in the corpus and fundus. CD117 and CD34 were found to be positive in the pathological examination of all parts. In addition, desmin, smooth muscle actin (SMA) and S-100 were also positively stained. No complications or mortality were observed in this series.*
CONCLUSION: *Tumor resection with a negative surgical margin may be considered complete oncologic treatment in case of presence of very low or low risk classification of postoperative GIST recurrence. After GIST resection, all patients should remain under long-term postoperative care.*

KEY WORDS: Bariatric surgery, Incidental gastrointestinal stromal tumors, Obesity, Sleeve gastrectomy

Introduction

Gastrointestinal stromal tumors (GISTs) are seen in the gastrointestinal system; most frequently in the stomach (50-60%), small intestine (30-35%), colon (5%) and less frequently in the esophagus (1%) [1]. Interstitial cells of Cajal (ICCs) are considered as precursor cells of GISTs involved in the regulation of intestinal peristalsis. These are considered pacemaker cells of the gastrointestinal tract [2]. Characteristically, most GIST cases (>95%) are positive for KIT protein staining (CD117).
Approximately 80-90% of GISTs carry a mutation in the c-KIT gene (80%) that encodes type III receptor tyrosine kinases or in the platelet-derived growth factor receptor alpha (PDGFRa) gene [3]. Malignant behaviors are determined according to the mitotic activity level, tumor size and, in some classifications, location. In most cases, GIST is likely to be asymptomatic. Asymptomatic GIST is often found incidentally during radiographic, endoscopic, or surgical evaluation[4].
Obesity is an important public health and socioeconomic burden that is increasingly common worldwide [5]. Morbid

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Correspondence to: Mehmet Geneturk, MD, Istanbul Obesity Surgery (IOC), Kurtköy Ersoy Hospital, Istanbul, Turkey (e-mail: drgencturk@hotmail.com)

obesity (body mass index, BMI >40 kg/m^2) is often associated with an increased risk of developing neoplasms as well as metabolic complications such as type 2 diabetes, hypertension, and dyslipidemia [6-8]. Thus, morbid obesity is considered to reduce life expectancy and quality of life. In the absence of effective noninvasive therapies, bariatric surgery is currently the most effective treatment for morbid obesity, causing sustained long-term weight loss and has been proven to be effective in preventing and reversing the associated comorbidities [9,10].

Laparoscopic sleeve gastrectomy (LSG) has been accepted as the primary bariatric procedure for the treatment of obesity in recent years [11]. This operation type showed good outcomes in terms of weight loss and resolution of comorbidities and has been associated with lower morbidity and mortality rates compared to other techniques [12-15].

The increasing obesity epidemic has increased the number of bariatric surgical procedures performed worldwide and more unexpected pathologies to be discovered later. In parallel, obese patients present with benign tumors, premalignant conditions, and even malignant lesions before, during or after the bariatric procedure [16].

GIST, which is thought to have an incidence of approximately 1/100,000 for all individuals, has a much higher incidence (0.3-1.2%) in patients undergoing bariatric surgery [17-20].

The aim of this study was to analyze the incidence of GIST in patients undergoing bariatric surgery and to investigate whether simultaneous resection can be oncologically radical and safe. Second, we aimed to compare our findings with previously published reports.

Patients and Methods

In this retrospective study, the medical records of patients who underwent sleeve gastrectomy between January 2015 and December 2017 were reviewed. All patients who presented incidental GIST during LSG for obesity were included. Demography, anthropometry and pathology findings were analyzed. Features such as location, resection margins, immunohistochemistry (CD 34, CD 117, ASMA, desmin and S100), criteria for oncological aggressiveness (tumor size, number of mitoses, presence or absence of tumor necrosis) [21] and evolution were also investigated. All operations were performed by the same bariatric surgeon team. It was decided whether to continue the bariatric operation in case of any abnormal macroscopic finding during the operation samples.

Results

Of the six patients included in the study, four (66.6%) were female, and two (33.3%) were male. The patients did not report any complaints that may be caused by the tumor. The median age of the patients was 32 years (age range: 24-42 years). The mean BMI was found to be 40.66 kg/m^2 (range: 35-44 kg/m^2) (Table I). The operative time was 50±11.8 minutes (range: 50-65 minutes). The mean hospital stay was 3 days. There were no serious complications or perioperative mortality. All GIST cases were found in the stomach, were not larger than 20 mm, and were found close to the greater curvature of the stomach; in five cases, tumors were located in a single focus, while in 1 case, it was located both in the corpus and fundus (Figs. 1,2). Five tumors were in the corpus, and two were in the fundus of the stomach. Additional immunohistochemical examinations were performed in all cases, and the results are shown in Table II together with the mitotic count. All tumors were excised with negative margins greater than 10 mm. No cases of local metastasis to lymphatic nodes were found.

CD117 and CD34 were found to be positive in the pathological examination of all parts. In addition, desmin, smooth muscle actin (SMA) and S-100 were also positively stained. No complications or mortality

TABLE I - *Demographic data and characteristics of tumors.*

Case	Size (mm)	Localization	Age (years)	Gender	BMI
1	10 × 5	Corpus	29	Female	38
2	10 × 1	Corpus	42	Female	44
3	6 × 4	Corpus	38	Female	40
4	12 × 6	Fundus	27	Male	42
5	11 × 8	Corpus	32	Male	39
6	14 × 2	Corpus	24	Female	41
	18 × 4	Fundus			

BMI: Body mass index.

TABLE II - *Features of immunohistochemical tumors.*

Case	CD117	CD34	SMA	Desmin	S100	PGFRa	Ki67	HPF	Surgery margin	Malignancy risk
1	+	+	+	+	+	-		50	R0	Very-low risk
2	+	+	+	+	+	-	+	1/50	R0	Very-low risk
3	+	+	+	+	+	-		0/50	R0	Very-low risk
4	+	+	+	+	+	-	+	3/50	R0	Very-low risk
5	+	+	+	+	+	-		0/50	R0	Very-low risk
6	+	+	+	+	+	-		1/50	R0	Very-low risk
7	-	-	+	-	-	+	+	3/50	R0	Low risk

TABLE III - *Literature review of incidental GIST in bariatric surgery*

Study	Incidence	Type of the operation	Localization of the tumor (Stomach)	Size (cm)	Mitotic index	Surgery margin	Features of the patients Mean age (Years)	Gender (M/F)
Waledziak et al. (2017)	1.2% (16/1252)	RYGB/LSG	(16/16) 100%	0.3–2	<5/50 HPF	R0	55.5	10/6
Viscido et al. (2017)	0.5% (5/915)	LSG	(5/5) 100%	0.5–1.5	<5/50 HPF	R0	59.6	1/4
Chiappetta et al. (2015)	0.31% (8/2603)	RYGB/LSG	(8/8) 100%	0.5–1.3	<5/50 HPF	R0	54	4/4
Crouthamel et al. (2015)	0.8% (12/1415)	LSG	(12/12) 100%	0.3–2.9	<5/50 HPF	R0	55	3/9
Yuval et al. (2014)	0.6% (5/827)	LSG	(5/5) 100%	0.32–1.3	<5/50 HPF	R0	55.4	4/1
Sanchez et al. (2005)	0.8% (4/517)	LSG	(4/4) 100%	0.4–1	<5/50 HPF	R0	52.7	3/1
Lyros et al.	1.27% (9/707)	RYGB/LSG	(7/9) 85%	0.2–3.7	<5/50 HPF	R0	55.6	2/7
Erdem et al.	0.87%(7/800)	LSG	(6/6) 100%	0.6- 2	<5/50 HPF	R0	32	2/4
Total	0.73% (66/9036)	RYGB/LSG	(63/65) 96.6%	0.2–3.7	<5/50 HPF	R0	52.4	29/36

M/F: Male/Female, BMI: Body mass index.

Fig. 1: Two stromal tumors in the laparoscopic sleeve gastrectomy material. (Case number 6) (From Clinic Bariatric, Istanbul archive).

Fig. 2: Other stromal tumor focus in case no.6 (Clinic Bariatric, Istanbul archive).

were observed in this series. All patients were evaluated by an oncologist after surgery. None of them required postoperative adjuvant treatment.

Discussion

Gastrointestinal stromal tumors (GISTs) are the most common soft tissue sarcoma of the gastrointestinal tract that usually occurs in adults over 40 years old. It is equally observed in women and men 22. Only a few studies reported a slightly higher incidence of males [23]. Gastrointestinal stromal tumors (GISTs) represent a spectrum of diseases with a variety of clinical behaviors and varying degrees of aggressiveness depending on the location, size and mitosis rate of the primary tumor [24]. ICCs are considered as precursor cells of GISTs involved in the regulation of intestinal peristalsis. These are considered pacemaker cells of the gastrointestinal tract [2,25]. Since ICCs are mostly found in the corpus and fundus of the stomach, they are also the most common sites of gastric GISTs [26].

c-KIT/CD117 is usually stained positive immunohistochemically in 95% of the cases, CD-34 in 40-50%, SMA in 20-30% and S100 desmin in approximately 10%. Ki67 is required as an indicator of cell proliferation to make a definitive diagnosis of GIST [27]. Cajal cells contain the c-KIT gene protein that regulates intracellular events. The mutation in the c-KIT proto-oncogene is involved in the pathogenesis of GISTs. In some GISTs, instead of the c-KIT, mutation is detected in another tyrosine kinase protooncogene, PGFRa gene. In addition, no mutation can be detected in some GIST cases. The immune marker of c-KIT is CD117 [28,29].

GISTs are considered to have malignancy potential. Malignant potentials are categorized as very low risk, low risk, medium risk and high risk [30]. The most important factors determining the prognosis are tumor diameter (maximum tumor diameter in cm) and mitotic index (mitosis count/50 High Power Field of Magnification, HPF). Other poor prognosis factors are anoploidy, presence of metastasis at diagnosis, non-resectable tumors, advanced age, and male gender [31,32]. A practical staging system for GIST after surgical resection is recommended by Bucher et al. [33]. This consists of five minor (Tumor size ≥5 cm, mitotic index ≥5 mitosis, presence of necrosis, spread to surrounding tissue, Ki-67 (MIBI) index >10%) and two major (presence of lymph node invasion or metastasis) criteria. Tumor with less than four

minor criteria is classified as low-grade GIST, and four or five minor criteria or one major criterion means high grade. Adjuvant imatinib therapy is recommended for high-grade GIST patients [33].Small GISTs (less than 2 cm in diameter) are usually asymptomatic and are detected during examinations for other unrelated diseases. In fact, endoscopic gastric cancer screening and bariatric surgery are able to find smaller lesions lacking symptoms and that would have gone otherwise unnoticed [34]. In contrast, GISTs larger than 2 cm are usually associated with clinical signs and symptoms such as nausea, vomiting, abdominal pain, obstruction, abdominal mass, anemia, and melena [35,36]. Common symptoms occurring in GISTs are bleeding, both insidious chronic and acute life threatening, dyspepsia or discomfort, nausea and even palpable mass [34]. Small GISTs<1 cm in diameter are defined as micro-GIST [37].

Multiple GISTs are very rare. Multiple GISTs can be divided into four subtypes: (i) familial multiple GISTs with germline mutations of KIT or PDGFRa genes, (ii) NF-1-associated multiple GISTs without c-KIT or PDGFRa mutations, (iii) multiple GISTs associated with the Carney triad and without c-KIT and PDGFR mutations, and (iv) sporadic multiple GISTs [38]. These tumors do not show more aggressive behavior than other GISTs. They can be sporadic, familial, or a component of the Carney triad. Although sporadic multiple GIST is generally seen in elderly patients, it can also be seen in the pediatric age group. It is mostly located in the stomach. They are incidentally detected at autopsy or during surgery. Familial multiple GISTs are tumors with an autosomal dominant inheritance, affecting one or more family members and associated with KIT gene mutations. Appearing as a component of the Carney triad, multiple GISTs are generally seen in women, and accompanying tumors such as extra-adrenal paraganglioma and pulmonary chondroma have been reported [39,40]. GISTs are relatively common in NF-1 patients, with a prevalence estimated to range from 5% to 30% [41].

Approximately 90% of NF-1-associated GISTs are found in the small intestine, and only 5.4% are located in the stomach [42].

Agaimy et al. [43] detected multiple GIST clustering in the proximal stomach, close tumor affinity and different KIT mutations in various lesions in the same patient. Thus, multiple primary GISTs can be formed with different sizes, locations, morphology and risk categories [44]. As reported in the literature, the majority (approximately 79%) of multifocal and closely related GIST cases referring to the c-KIT-positive and CD34-positive phenotypes are initiated with different types of somatic KIT exon 9 and 11 mutations [43-46].

Multiple sporadic GISTs outside of familial and syndromic settings are rarely defined [43,44,47-48]. In the study of Li et al. [49], nine men and seven women with a median age of 66 were diagnosed with multiple sporadic GIST.

The incidence of GIST is higher in obese patients [19]. Symptoms are non-specific, making diagnosis difficult. Most GISTs in bariatric surgery patients are incidentally found intraoperatively and usually have low grade malignancy [19,50]. The increased incidence of GIST in patients with obesity may be based on a strong relationship at the molecular level between the presence of this specific tumor and obesity [4]. Recently, the molecular pathogenesis of GIST has been linked to grehlin, a well-known hormone that stimulates food intake and is known to play a role in obesity etiology [51]. Interestingly, both GIST and ghrelin producing cells are found mainly in the gastric fundus. GIST was found to express grehlin and grehlin receptors, suggesting a grehlin autocrine/paracrine ring in GIST tissues [52].

In the literature, it has been reported that the incidence of GIST is higher in obese patients who underwent bariatric surgery (0.6-0.8%) than the general population (0.0006-0.0016%) [19,26]. These incidence rates are even higher in obese patients older than 50 years [19,32]. Men and women are equally affected, however, there is a slight male dominance [17,53]. In the study of Stiles et al. [54] GIST size showed an overall inverse association with BMI, while obese patients seemed to have a smaller and more surgically manageable GIST. It has also been reported that patients with low BMI (<30 kg/m^2) frequently undergo multi-visceral resection for removal of the GIST compared to more obese patients (BMI>30 kg/m^2) [54]. Such an inverse relationship between obesity and favorable outcomes has previously been demonstrated for other malignancies [55-57]. Mendes et al. [58] noted that GISTs found in bariatric populations were smaller than those excluded from symptomatic general surgery patients, that bariatric patients were on mean much younger than the mean GIST patient, and that their body mass index was significantly higher. However, this is simply because patients undergoing elective bariatric surgery are younger and are not studied for a symptomatic lesion [59].

Many studies have reported incidental GIST findings in obese patients undergoing laparoscopic sleeve gastrectomy. Chiappetta et al. [19] found GIST in 0.31% (8/2603) of the patients during Roux and Y Gastric bypass (RYGB) and SG. Yuval et al. [17] reported GIST in 0.6% (5/827) during SG. Sanchez et al. [60] detected GIST in 0.8% (4/517) during RYGB. Crouthamel et al. [61] found GIST in 0.8% GIST (12/1415) during SG, of which only one of them was greater than 20 mm.

Recent reports have shown an incidence of incidental GIST as 0.5% (5/915) in patients who underwent SG alone (50). In 1252 patients who underwent RYGB or SG, 16 GIST was found to have a 1.2% incidental GIST [62]. A study based on a single institution case series shows the highest incidence (1.27%) in GIST cases associated with bariatric surgery so far [4].

Endoscopy, endoscopic ultrasonography, abdominal tomography, magnetic resonance methods are used in

the diagnosis of GIST. However, any radiological or endoscopic examination method alone is not sufficient to diagnose GIST. Biopsy is essential for definitive diagnosis of GIST. Preoperative fine needle aspiration biopsy from surgically removable masses is not recommended due to the disruption of the capsule integrity of the tumor and the risk of tumor cell implantation [63].

Routine programs are used for ultrasonography and upper digestive system endoscopy before laparoscopic sleeve gastrectomy in many centers. GISTs are likely to be asymptomatic. GISTs are exophytic tumors, so they are not usually detected during endoscopy. They are unlikely to be detected during ultrasonographic examination [64]. It is difficult to diagnose GIST by endoscopy since it does not show mucosal involvement. Preoperative endoscopic examination can detect tumors larger than 2 cm, but misses smaller ones unless they are not submucosal [65].

The laparoscopic approach has also been shown to be safe and feasible for gastric GISTs [66]. However, in the latest guidelines of the European Society for Medical Oncology, the National Comprehensive Cancer Network (NCCN) and the Asian GIST guidelines, this option is valid only for the anterior wall of the gastric corpus, fundus, and antrum along the greater curvature [67]. Among the unfavorable locations are the cardia and prepyloric region, where the difficulty in exposing the tumor is high as well as small curvature tumors are common, and where the risk of stenosis of the lumen after surgery is high [68].

According to the NCCN and European Society of Medical Oncology (ESMO) guidelines, laparoscopic wedge resection is a feasible and safe approach, and full tumor excision is mandatory for GISTs >2 cm in size [69]. The management of the small incidental GIST smaller than 2 cm is a matter of debate. According to the latest ESMO guidelines, if GIST is diagnosed, endoscopic ultrasound surveillance should be performed for nodules smaller than 2 cm, and emergency excision should not be considered [69]. However, incidental small nodules discovered intraoperatively constitute a different situation, and their excision should be done unless there is great morbidity. This concept becomes more important if we consider that even small GISTs (less than 1 cm) with low risk features show the potential for recurrence and metastasis [70].

As reported in all patients, an incidental GIST can be safely removed laparoscopically during bariatric surgery with negative microscopic resection margins. Without changing the bariatric strategy, an adequate tumor removal can be achieved oncologically. If the procedure is performed properly, the risk of peritoneal contamination can be ruled out (no manipulation of the nodule, use of extraction bags). If sleeve gastrectomy is performed, the tumor can be resected with the specimen, if possible [4].

GIST has unpredictable behaviors, and long-term follow-up is required for all patients regardless of benign or malignant characteristics according to standard guidelines. The most appropriate follow-up program for the small and low-risk GIST encountered with weight loss in bariatric patients is unknown. The frequency of follow-up should depend on the risk assessed unanimously by the multidisciplinary team involved in the treatment [71]. Ultimately, a multidisciplinary team consisting of a surgical oncologist and medical oncologist must be involved in the evaluation and care of the patients to address the issues of the management of these low-incidence lesions [58].

Some issues such as incidentally detected by surgical resection, GISTs smaller than 2 cm, guidelines for long-term follow-up are somewhat controversial in bariatric patients [19,60,72]. According to NCCN guidelines, lesions reported here will be classified as a low risk of progression [73], and endoscopic follow-up with 6- or 12-month intervals is recommended [74]. However, follow-up guidelines cannot address the risk of the anatomical barrier that occurs during RYGB [75]. In addition, there is no evidence to indicate what the post-surgical imaging time interval will be or whether computed tomography is useful in determining recurrence [19,28,60]. Preoperative imaging is ineffective, especially in detecting small lesions [28,76]. Ultimately, there is no consensus on a standard protocol for the follow-up of these "minimal risk" lesions [76]. Most of the incidentally detected GISTs detected during bariatric surgery are small and of low malignant potential [17,60,61,77,78]. The findings of the stromal tumor and BMI study conducted by Stiles et al. [54] suggest that a larger proportion of tumors in the obese population are smaller than those found in the non-obese population. A 3-year adjuvant therapy with imatinib is recommended for high-risk GISTs [79].

Post-resection follow-up should be based on standard guidelines in the general population, which consists a computed tomography scan every 3 to 6 months for 5 years, and then once a year [80,81]. If systemic spread is detected, imatinib should be added. However, these recommendations are also relevant for all GIST patients, regardless of their BMI. Undoubtedly, modified anatomy should be considered during follow-up and clinical evaluation in bariatric patients. Thus, in such situations, a more frequent surveillance program could be beneficial for these patients [4]. For small solid tumors, complete surgical resection can usually be curative. Larger metastatic lesions treated with targeted therapy (imantinib) with surgical resection have shown improved results as 50-60% for 5-year survival and as 80% for 2-year survival in metastatic GIST cases [72,74].

In this retrospective single-center study, we calculated the unexpected GIST incidence as 0.87 (7/800) encountered during bariatric surgery in morbidly obese patients (Table III). Incidental GISTs were detected intraoperatively and were resected simultaneously during bariatric operation in all patients. In the case of incidental findings of GIST during bariatric surgery, tumor resection

with a negative surgical margin may be considered complete oncologic treatment in case of presence of very low or low risk classification of postoperative GIST recurrence. After GIST resection, all patients should remain under long-term postoperative care.

Riassunto

Abbiamo valutato e caratterizzato i GIST accidentali nella nostra popolazione chirurgica bariatrica controllando tutti i GIST identificati durante la sleeve-gastrectomia laparoscopica tra gennaio 2015 e dicembre 2017. Sono stati registrati dati demografici, clinico-patologici, di trattamento, di localizzazione, dei margini di resezione, l'immunoistochimica (CD 34, CD 117, ASMA, desmina e S100) e i criteri di aggressività oncologica (dimensione del tumore, numero di mitosi, presenza o assenza di necrosi tumorale).
Risultati: All'interno degli 800 interventi chirurgici bariatrici presso il nostro istituto, sono stati identificati 7 GIST (0,87%). L'età mediana dei pazienti era di 32 anni (fascia di età: 24-42 anni). L'IMC medio è risultato essere di 40,66 kg/m^2 (intervallo: 35-44 kg/m^2).
Tutti i casi di GIST sono stati trovati nei campioni di stomaco. Tutti i tumori non erano più grandi di 20 mm, e tutti localizzati in adiacenza della grande curvatura dello stomaco; in cinque casi, i tumori erano localizzati in un unico focolaio, mentre in 1 caso era localizzato sia nel corpo che nel fondo. CD117 e CD34 sono risultati positivi all'esame patologico di tutte le parti. Inoltre, anche la desmina, l'actina del muscolo liscio (SMA) e l'S-100 erano colorati positivamente. Non sono state osservate complicazioni o mortalità in questa serie.
Conclusione: la resezione del tumore con un margine chirurgico negativo può essere considerata un trattamento oncologico completo in caso di presenza di classificazione a rischio molto basso o basso di recidiva di GIST postoperatoria. Dopo la resezione GIST, tutti i pazienti devono rimanere sotto cure postoperatorie a lungo termine.

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