

Preoperative endoscopy and pathology report of the specimen to be recommended in sleeve gastrectomy?

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Summary

Objective. Preoperative upper gastrointestinal endoscopy (UGIE) and postoperative histopathological examination (HPE) of resected specimens are still controversial issues in bariatric surgery.

Methods. A retrospective review of prospectively collected laparoscopic sleeve gastrectomies (SG) performed at our institution for morbid obesity was carried out. All patients underwent pre-operative UGIE with biopsy, post-operative HPE and conventional post-operative follow-up.

Results. From January 2019 through January 2021 we performed a total of 501 laparoscopic SG. A total of 12 (2.4%) neoplasms were found, 2 evident at preoperative UGIE, 4 detected during operation, and 6 at HPE. Eight of these 12 cases had some malignant potential and 5 would not have been detected without HPE of the specimen. The most significant unexpected case was a fundic gland type adenocarcinoma in a 64-year-old female with severe obesity.

Conclusion. On the basis of our clinical experience, we recommend both preoperative endoscopic assessment and postoperative HPE of the specimen to provide the best available treatment to these patients.

Key words: bariatric surgery, gastrectomy, gastric neoplasm, pathology

Introduction

Obesity is currently one of the major concerns of public health and healthcare systems due to its increasing prevalence, not only in Western countries but also in lower income countries, and its negative economic impacts in terms of related comorbidities such as type II diabetes mellitus, cardiovascular diseases, cancer and reduced life expectancy ¹.

According to the World Health Organization (WHO), the worldwide prevalence of overweight in adults was more than 39% in 2016, nearly three times more than in 1975. Among these, over 650 million were obese ². Currently, bariatric surgery represents the best available treatment for obesity in terms of weight loss, comorbidity resolution and improvement in life-expectancy ³.

Laparoscopic sleeve gastrectomy (SG) is one of the most performed bariatric procedures worldwide ^{4,5}. Moreover, laparoscopic SG represents the only surgical procedure that provides a specimen for histopathological examination (HPE).

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It is still controversial whether upper gastrointestinal endoscopy (UGIE) should be always taken into consideration for the routine diagnostic work-up prior to bariatric surgery. Nevertheless, according to published international guidelines, UGIE should be reserved for patients with symptoms. Obesity is associated with an increased risk of gastroesophageal reflux disease (GERD), erosive esophagitis, esophageal adenocarcinoma, and gastric cancer^{6,7}. Moreover, the stomach is one of the main targets of bariatric surgery. Any pathological findings at preoperative work-up or at HPE of the specimen after laparoscopic SG may prompt us to change the entire postoperative therapeutic strategy⁸. For these reasons, routine UGIE and HPE of the resected specimens are reasonably warranted.

We here report on incidental findings discovered in HPE of the specimens harvested from laparoscopic SG performed in the last two year at our academic center. In particular, we moved from the last case, an incidental adenocarcinoma of fundic gland type that was found at HPE of the excised stomach.

Materials and methods

A retrospective review of prospectively collected laparoscopic SG specimens performed at our institution from January 2019 until January 2021 for morbid obesity. All specimens were examined grossly and microscopically per clinical standard of care.

All preoperative UGIEs were assessed in terms of gross description and histopathological findings. Conventional post-operative follow-up (1, 3, 6, 12 months) was scheduled and recorded for all the cases, with a

particular attention to evaluate whether additional clinical actions were required.

Results

From January 2019 through January 2021, a total of 501 laparoscopic SG was performed. There were 12 (2.4%) incidental findings of neoplasms: 3 leiomyoma, 7 gastrointestinal stromal tumors (GIST), 1 schwannoma and 1 fundic gland type adenocarcinoma (GA-FG). Only 2 of 12 cases were evident at preoperative UGIE, while 4 more were detected during intervention. Most of the findings had some risk of malignancy (8 cases) and most would not have been suspected (5 cases) without HPE of the specimen (Tab. I).

MACROSCOPIC FINDINGS

The two lesions discovered at preoperative UGIE were a leiomyoma and a schwannoma, both described as a submucosal bulge covered by regular mucosa in the body of the stomach, along the greater curvature. No biopsy was performed on those lesions. At gross HPE the leiomyoma was described as a 1.3 cm submucosal nodular lesion with clear margins and fasciculate aspect; the schwannoma was described as a 2.2 cm dyschromic intramural neoplasm.

Intraoperative findings turned out to be 3 GISTs and 1 leiomyoma at HPE, and consisted in observation of a subserosal bulge with no irregularity of serosa in each case. At gross HPE all lesions were described as subserosal or submucosal whitish nodules.

The 6 neoplasms found only at HPE were 1 leiomyoma, 4 GIST and 1 GA-FG. At gross inspection of the

Table I. Pathological findings in laparoscopic sleeve gastrectomy specimens.

Tumor parameters						Miettinen risk assessment system for GIST (2006)	
	Pre-op UGIE findings	Intra-op findings	Post-op HPE findings	Size (cm)	Mitotic count (per 5 mm ²)	Risk group	Rates of metastases or tumor related death
1	Leiomyoma	-	-	1,3	0		
2	-	-	GIST	0,6	0	1	0%, none
3	-	-	Leiomyoma	0,4	0		
4	-	-	GIST	0,5	0	1	0%, none
5	-	GIST	-	0,8	1	1	0%, none
6	-	Leiomyoma	-	0,4	0		
7	-	-	GIST	0,9	0	1	0%, none
8	-	GIST	-	1	0	1	0%, none
9	-	-	GIST	0,4	< 5	1	0%, none
10	-	GIST	-	0,7	< 5	1	0%, none
11	Schwannoma	-	-	2,2	0		
12	-	-	FG-GA	0.3	0		

Pre-op UGIE: preoperative upper gastrointestinal endoscopy; Intra-op: intraoperative; Post-op HPE: postoperative histopathological examination; GIST: gastrointestinal stromal tumor; FG-GA: fundic gland type adenocarcinoma.

specimens 3 GIST were described as well-circumscribed parietal whitish nodules; in the other 3 cases no macroscopic lesions were found.

All lesions, with the exception for the two discovered at preoperative UGIE, were smaller than 1 cm. All lesions resulted completely excised with clear margins (R0). No irregularity in mucosa or serosa was observed.

MICROSCOPIC FINDINGS

The gastric schwannoma appeared as a biphasic spindle cell neoplasm with thickened and hyalinized blood vessels and absence of atypia or mitosis. Tumor cells were positive for S100 and CD56, but negative for muscular markers, CD117 and DOG1.

Leiomyomas had a bland spindle cell morphology with eosinophilic cytoplasm and minimal atypia. No mitotic figure was found. All the three leiomyomas originated from the muscularis propria. Tumor cells were positive for smooth muscle actin (SMA) and desmin, but negative for CD117, DOG1 and S100.

All the GISTs included in our case series had a spindle cell morphology. No epithelioid GIST was found. There was no or only isolated slight atypia. Mitotic rate was < 5 mitosis per 5 mm^2 for each case. Tumor cells were positive for CD117 and DOG1, but negative for SMA and S100.

FUNDIC GLAND TYPE ADENOCARCINOMA (GA-FG)

The last unexpected case of a GA-FG is briefly described here.

A 64-year-old female was referred to our Bariatric Surgery Unit for severe obesity associated with impaired glucose tolerance (IGT) on oral hypoglycemic medications, dyslipidemia and severe osteo-arthritis. Her weight was 125 kg, her body mass index (BMI) 54.1 kg/m^2 , with a long history of obesity, previous multiple medical supervised weight-loss attempts with weight cycling. The patient did not report heartburn/pyrosis or nausea and physical examination was unremarkable. Bile reflux was evident at preoperative UGIE,

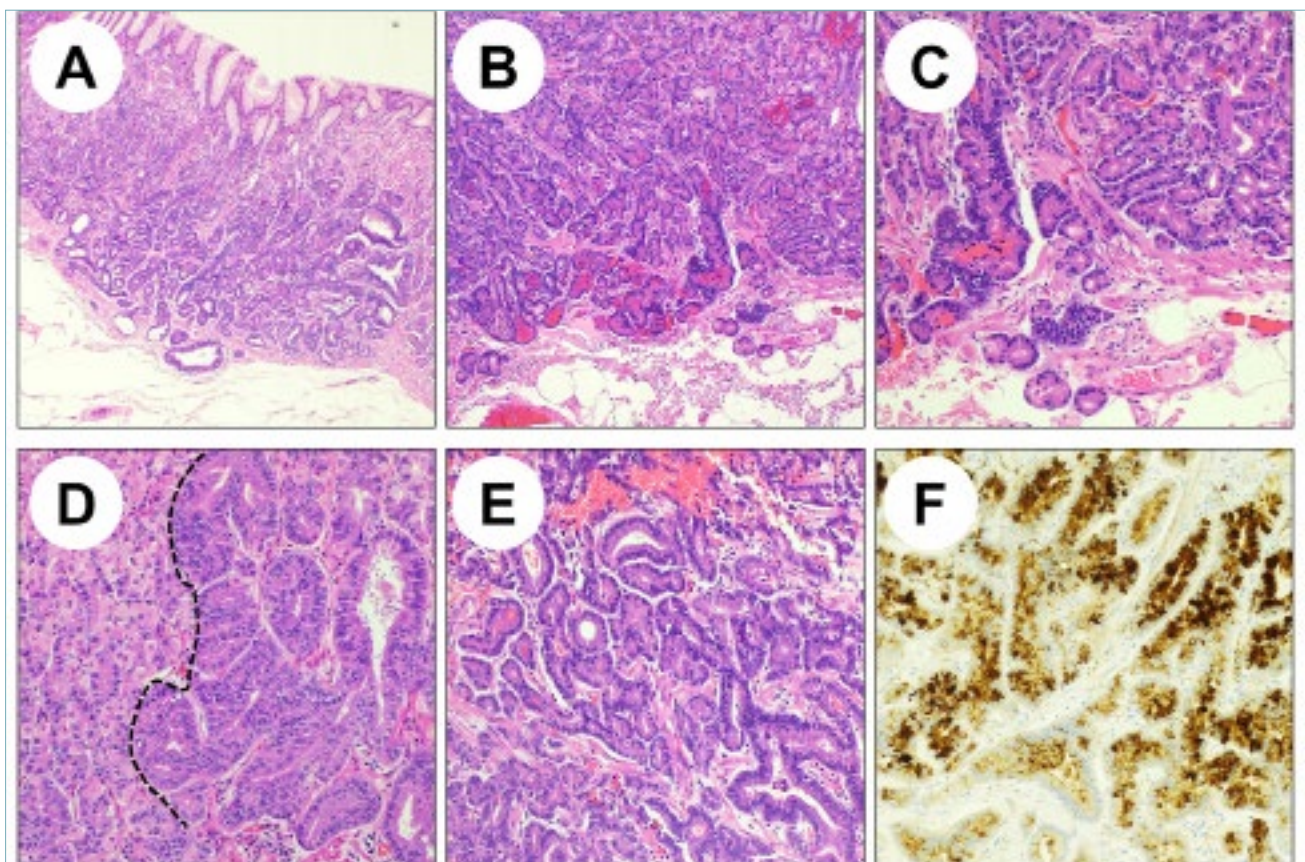


Figure 1. Representative features of the presented case. (A) Microscopic appearance of the lesion, which occurred within the oxyntic mucosa. (B, C) The neoplasm, mainly intramucosal, focally invaded the submucosa ($< 1 \text{ mm}$ of invasion). (D) Relationship of the lesion (right) with the surrounding mucosa. (E) Microscopically, the lesion was characterized by a glandular proliferation of monotonous columnar cells. (F) Positive Pepsinogen-I immunohistochemical expression in neoplastic glands.

non-atrophic gastritis of the antrum and oxyntic-antral transitional area were found at histological evaluation. *Helicobacter pylori* microorganisms were not detected. Laparoscopic SG was modeled on 40 Fr bougie with multiple firings of 60 mm endostapler reloads. Nothing remarkable was found at the inspection of the abdominal cavity during laparoscopy. The excised specimen was sent for pathological examination. Post-operative course was uneventful and the patient was discharged on POD-2 on a customary soft diet.

Pathology report of the specimen revealed a neoplasm of oxyntic cell origin (3 mm of diameter), located in the body-fundic area, characterized by cellular monomorphism, absent mitotic activity and with focal and minimal infiltration of the submucosa (Fig. 1). No lymphovascular invasion was observed. Tumor cells were positive for pepsinogen-I and MUC6 at immunohistochemistry, whereas negative for MUC1, MUC2 and MUC5AC. The lesion resulted completely excised with clear margins (R0). This finding had neither been detected on previous endoscopy nor at gross inspection of the surgical specimen.

Discussion

Bariatric surgery proven to be safe and effective in the treatment of obesity, eliciting durable weight loss⁹⁻¹¹, promoting comorbidities improvement/resolution^{4,12,13} and significantly improving life-expectancy and quality of life¹⁴⁻¹⁹.

The stomach is one of the main target organs of bariatric surgery, as it is involved in most surgical interventions. Before any bariatric procedures patients usually undergo thorough preoperative medical assessment in order to reduce operative risks, but there is still conflicting evidence whether or not UGIE with biopsy is essential in the routine preoperative work-up, especially in patients not complaining significant gastrointestinal (GI) symptoms. Current guidelines suggest that selective endoscopy might be more appropriate in patients with symptoms²⁰ in order to rule out different conditions such as esophageal webs, ulcers, esophagitis, hiatal hernia, tumors, etc.^{21,22}. We routinely prefer to perform UGIE with biopsy prior to surgery because symptoms are not clearly associated with histological findings²³ and vice versa, although in most of our case nothing was apparently evident.

Laparoscopic SG is one of the most commonly performed bariatric procedures²⁴. It involves the removal of the vast majority of the greater curvature of the stomach, quite a large specimen for Pathologists. As for other elective surgery specimens, those obtained

after sleeve gastrectomy are expected to be normal, except for unexpected incidental findings²⁵.

Although several studies^{26,27} suggest HPE of laparoscopic SG specimens may not be routinely needed, more reports have shown several incidental findings, including benign and malignant lesions.

GISTs are the most common mesenchymal neoplasms in the GI tract. GI mesenchymal tumors also include leiomyomas, leiomyosarcomas and schwannomas²⁸. A recent meta-analysis²⁹ reported an incidence of incidental GISTs of 0.45% undergoing bariatric surgery. Single-center case series³⁰⁻³² reported an incidence ranging from 0.5% to 1.97%. Incidental leiomyomas and schwannomas in sleeve gastrectomies have been described in the literature as rare findings (< 0.2%)³²⁻³⁴.

GI mesenchymal tumors are similar in clinical features, gross and histological appearance; but they differ in prognosis^{28,35-37}. 10-30% of GISTs are reported to be malignant^{28,35,38}. Malignant risk of GISTs can be determined based on mitotic count, tumor size and anatomic location of the lesion. According to clinical malignant risk, GISTs are stratified into no, very low, low, moderate, or high risk³⁹. Micro-GISTs (i.e., GISTs smaller than 1 cm) are not an uncommon finding in gastric specimens (in particular in the proximal part of the stomach) and often have spontaneous regression with hyalinization and calcification. In our case series, the GISTs had a low mitotic count (< 5 mitosis per 5 mm²) and a small size (< 1 cm). Thus, according to the Miettinen risk assessment system³⁹, the risk of progression to malignancy was virtually absent⁴⁰ (Tab. I). Leiomyomas and schwannomas do not have malignant potential and are associated with excellent prognosis^{36,37,40}.

As most of the diagnostic modalities cannot always provide enough information to differentiate between these tumor types, ultimately the definitive diagnosis of GIST, leiomyoma and gastric schwannomas are based on microscopic morphologic findings and immunohistochemical profile, which can only be performed on the formalin-fixed paraffin-embedded specimen. In fact, gastric GISTs, leiomyomas and schwannomas often share a bland spindle cell morphology and immunohistochemistry is crucial to differentiate between these tumor types^{35,40,41}.

In our experience, during the last 2 years 2.4% of specimens showed unexpected histopathological findings and two-thirds of them had some malignant potential. These cases, if recognized, could benefit from further observation or even treatment, suggesting that HPE of the specimens should be recommended. Luckily, all non-benign lesions we found had no risk of progression to malignancy. Furthermore, size

of the lesions can explain why part of these were not previously detected at initial UGIE.

It is still questionable whether this low incidence and low risk of malignancy warrants both preoperative UGIE with biopsy and HPE of the specimen in all the patients. However, in our opinion this can be a valuable and affordable strategy not to overlook undetected malignancies.

Our last incidental finding was a GA-FG. This tumor was firstly reported in 2007 by Tsukumoto et al.⁴² as a new subtype of gastric adenocarcinoma and in 2019 inserted in the WHO's list of digestive system tumors⁴³. It is considered a rare neoplasm, the exact incidence still unknown. Only 111 cases were reported in the English language literature up to 2018⁴⁴. Most cases of GA-FG have been described in East Asia, with anecdotal reports from Europe and North America. The natural history of this neoplasm is still unclear and there is a lack of awareness of GA-FG even among experts.

GA-FG is an epithelial neoplasm with oxyntic gland differentiation. Tumors can be classified according to their typical or atypical histologic and cellular features, mucosal or submucosal invasion or the presence of lymphovascular invasion. According to a recent paper by Ushiko et al.⁴⁵, the presence of an initial infiltration of the submucosa, a mild degree of atypia and the absence of angiolymphatic invasion places this lesion in group B oxyntic gland neoplasm of the stomach, defining the tumor as "adenocarcinoma of fundic gland type".

These tumors appear to have a benign clinical course^{46,47}, but those with submucosal invasion, atypical cell differentiation and lymphovascular spread are closely associated with a more aggressive behavior. As in current literature they are usually under-reported and available data are not sufficient to define predictors of their malignant potential, for this case we preferred to adopt a watch-and-see policy with contrast-enhanced CT scan for staging and yearly UGIE follow-up. Moreover, we decided to extend this strategy to the other unexpected findings on the specimen harvested, whenever a malignant potential was reported.

Laparoscopic SG has been increasingly performed worldwide in the last decade²⁴. In this view, the definition of a common line of action, prior to and after the operation is warranted, given the potential increasing number of unexpected malignancies retrieved and overlooked if the specimens are not processed for histopathology. Larger series and longer follow-up are needed to confirm our initial results.

Conclusions

Preoperative UGIE with biopsy in combination with HPE of the specimens may have an important role for the optimal management of patients who are candidates for laparoscopic SG. Based on our clinical experience, we recommend fully deploying this strategy as the best available treatment. The results of our study point out the important role of the pathologist in the differential diagnosis of incidental preoperative and intraoperative findings and in discovering previously small undetected lesions with accurate macroscopic examination.

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All members met the authorship criteria.

Conflicts of Interest

No existing or potential conflicts of interest of a financial, personal or any other nature related to the present work.

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Authors' Contributions

The authors confirm contribution to the paper as follows: study conception and design: Remo Alessandris, Mirto Foletto, Matteo Fassan; data collection: Federico Moroso, Valentina Angerilli, Linda Callegari; analysis and interpretation of results: Remo Alessandris, Federico Moroso, Mauro Michelotto, Valentina Angerilli, Linda Callegari; draft manuscript preparation: Remo Alessandris, Federico Moroso, Valentina Angerilli; review for important intellectual content: Mirto Foletto, Matteo Fassan. All authors reviewed the results and approved the final version of the manuscript.

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