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Complete resection of an infrequent tumor in the lower third of esophagus by laparoscopy via abdominal

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Abstract

A gastrointestinal stromal tumor (GIST) is an infrequent tumor with a complex development of disease. This kind of tumor shares a unique characteristic: a KIT-activated mutation, which differentiates them from other mesenchymal malignancies. In half of cases, localization is in stomach, less frequent locations are: omentum, peritoneum, rectum and esophagus. Treatment mainly consist is surgical resection and target therapy. This article's main objective is to report a totally laparoscopic abdominal resection of a GIST tumor located in lower third of esophagus that was found during a laparoscopic procedure carried on for a different cause than found it. Medical record is: a 48 -years-old- male with previous story of gastro-esophageal reflux disease that underwent to elective laparoscopic fundoplication, during hiatus dissection, the presence of a 5 cm bilobulated-tumor in lower third of esophagus was observed. Excisional biopsy was taken and reported the probability of GIST. We could identify tumor was attached to esophagus's superficial planes so a complete dissection without breaking tumor's pseudo-capsule was achieved. Definitive histopathology report was: surgical specimen with free margins of disease and immunohistochemical staining confirmed the GIST diagnosis. Incidence of GIST in lower third of esophagus is a rare and infrequent condition; hence, there are not many reports of totally laparoscopic abdominal resection in tumors bigger than 2 cm; So that's the purpose of reporting this surgical achieve with satisfactory results. The first of its kind reported in a medical center in the State of Mexico.

Key words: Gastrointestinal stromal tumor in esophagus, laparoscopy.

Resumen

Los tumores del estroma gastrointestinal (TEG o GIST, por sus siglas en inglés) son neoplasias raras con una historia natural compleja. Comparten un rasgo casi uniforme: una mutación en el KIT activado, lo que los diferencia de otras tumoraciones mesenquimatosas. En la mitad de los casos son de localización gástrica. Las localizaciones menos frecuentes son: omento, peritoneo, recto y esófago. Su tratamiento es primordialmente la resección quirúrgica y la terapia dirigida. El objetivo de este artículo es reportar la resección total de un GIST en tercio inferior de esófago por laparoscopia vía abdominal, durante un procedimiento quirúrgico realizado por una causa distinta a la encontrada. Se trata de un paciente masculino de 48 años con diagnóstico de enfermedad por reflujo gastroesofágico. Se programó funduplicatura laparoscópica electiva, durante la disección del hiato se observó imagen sugestiva de tumoración bilobulada de 5 cm en tercio inferior de esófago, se tomó biopsia excisional que reportó probable GIST, se identificó que estaba adherido a planos superficiales, por lo que se logró una disección completa sin romper su pseudocápsula. El examen patológico definitivo reportó márgenes libres y el examen inmunohistoquímico confirmó el diagnóstico de GIST. La presencia de un GIST en tercio inferior de esófago tiene una incidencia tan baja, que no se encontraron reportes previos de una resección completa vía abdominal por cirugía de mínima invasión, por lo cual reportamos este logro quirúrgico con resultados satisfactorios. El primero en su clase reportado en un centro médico del Estado de México.

Palabras clave: Tumor del estroma gastrointestinal, esófago, laparoscopia.

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are a malignant-rare mesenchymal entity of the gastrointestinal tract (GIT) with clinical course and pathology's features that allow to recognize them from other non-epithelial malignant tumors since the end of the eighties decade and the beginning of the nineties. Nowadays it is well-known; they share commonly a mutation in a tyrosine kinase transmembrane-receptor (KIT) which is also intimate related to platelet derived grow factor receptor (PDGFR). This is a characteristic that

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has a great influence upon its classification, prognosis and treatment.^{1,2}

GIST are very rare neoplasms with an incidence reported in European papers as low as 13 cases per 1 million per year,³ while in papers from The United States (US) 4 cases are reported per every million of citizens, so it is believed they represent 3,000 to 5,000 new cases per year in that nation.⁴ Although this reports, GIST are consider tumors that constitute less than 1% among all tumors in the GIT. They arise from connective-tissue-precursors-cells and Cajal's cells (these are considered TGI peacemakers) innervated by Auerbach's plexus.^{5,6}

As a general rule GIST may be classified based on its microscopically appearance as spindle cell (70% of cases), epitheloid (20%) and mixed.¹ Several markers for immunohistochemical staining have been proposed such as: KIT, CD34, ACAT2, S100, DES and keratin, which are necessary to establish diagnosis; classically it's given for a KIT-positive test that is present in 95% of cases.⁷

GIST is more common in older adults between the fourth and eighth decade of life with a middle age of 60 years-old by the time of diagnosis. The risk of presenting one is slightly high in black men.⁸ Although GIST may appear at any location of the GIT, they also may appear –although infrequent– in extra-gastrointestinal locations such as esophagus, mesentery, omentum or retroperitoneum. Most frequent locations are stomach (50%), small intestine (25%) and bowel (10%).⁸⁻¹⁰

The clinical scenario that permits to suspect GIST is constitutive of symptoms related with the accelerating growing of the abdominal tumor (early gastric plenitude, nausea, emesis, palpable tumor) bleeding (by an ulcerate wall due to intraluminal extension) or intestinal obstruction (by protrusion towards the serosa layer) tough is also possible to be diagnosed at the moment the patient has been taken to a surgery or an endoscopic procedure for a different cause.¹¹ Once the diagnosis has been established, up to 50% of patients with GIST present metastasis.¹⁰ These may be present in liver or at peritoneal surface, but it's uncommon to spread to lymphatic vessels.¹²

Due to GIST comprehend a wide range of tumors with different prognosis *The National Institutes of Health* (NIH) consensus workshop of 2001, was the first to propose a risk stratification schema with several categories that ranged from very low, low, medium and high risk; taken account on size (< 2 cm, 2-5 cm, 5-10 cm and > 10 cm) and mitotic index (< 5, 5-10 and > 10 mitosis per 50 fields of high power). Ever since, bad-prognosis for risk conditions had been identified such as: male gender, incomplete resection, extra-gastric location, elevated count of KI-67 and high tumor cellularity.¹¹

Complete surgical GIST resection is the treatment's corner stone and the most appropriated initial therapy to those patients with local disease, while in patients with

advanced disease or with difficult access to surgical margins, target therapy should be considered in an attempt to render the tumor unresectable to resectable. Chemotherapy and radiotherapy are ineffective against GIST and are only used to palliative proposes.¹³

Target therapy consists in administrating imatinib sub-salicylate (STI 571, Gleevec®) 400 to 800 mg per day for 12 months, at least. This is a high power KIT-inhibitor that when administrate has demonstrate –in prospective trails– a good response in 50% of patients with metastatic disease.¹⁴ It is also administrated –as previously noticed– in an attempt to render the great tumor to shrink and those located in troublesome sites to be resected.¹⁵ After a complete resection, recurrence is expected as high as 40% of cases in those patients whose target therapy is not administrated.¹⁰

In general terms GIST have better prognosis when they are at gastric location, their morphology is favorable and resection is complete.

CASE REPORT

48 years-old Male, with family history that included diabetes mellitus type 2 and lung cancer, allergic to penicillin. Medical record started six-years earlier with a clinical course characterized by persistent heartburn and regurgitation. Patient was send from his primary care clinic to the surgery department of the Institute's Medical Center and the diagnosis of gastroesophageal reflux disease (GERD) was confirmed. Physical exploration did not reveal relevant findings. As part of protocol of study for GERD, endoscopy was include, findings where: acute C-grade esophagitis (Los Angeles, scale. *Table 1*), hiatal hernia type I, Barret's esophagus, chronic gastritis and one gastric polyp was found; biopsy was taken. Histological report: confirmed benign polyp's features (hyperplasic). Manometry was indicated and reported, lower esophageal sphincter (LES) incompetent, with complete relaxation. Effective peristalsis in the esophageal body. Upper esophageal sphincter with

Table 1. Los Angeles classification (for esophagitis).

Grade	Description
A	One or more mucosa disruption, with a length equal or less to 5 mm that do not extend between the upper limit of two mucosa folds
B	One or more mucosa disruption, with a length superior to 5 mm that do not extend between the upper limit of two mucosa folds
C	One or more mucosa disruption, which do extend beyond the upper limit of two mucosa folds. But affects less than 75% of esophagus circumference
D	One or more mucosa disruption that affects at least 75% of esophagus circumference

Source: Lundell 1999

adequate synchrony. Preoperative laboratory work-up was in-between normal parameters. Therefore patient was taken to an elective laparoscopic fundoplication.

During the surgical procedure, after gastric short-vessels were cut with an harmonic scalpel and while dissecting esophageal hiatus cutting freno-esophageal membrane, an extra-esophageal bi-lobulate tumor was observed, with a brain-like aspect measuring 5 x 4 cm (*Figure 1*). When carefully manipulated with dissector clamp, it felt firmly attached to the anterior surface of the lower third of esophagus. Laparoscopy was re-asses looking intentionally

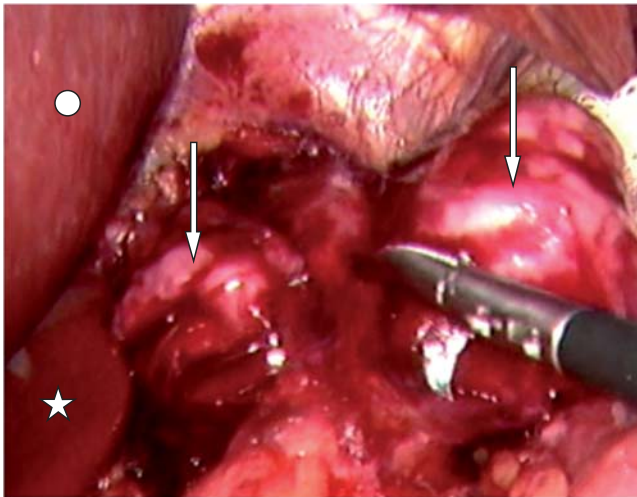


Figure 1. Two-lobe tumor is shown at esophagus lower third (arrows). Dissector clamp points to the anterior face of esophagus. Liver visceral surface is shown (circle) and Spiegel's lobe (star).

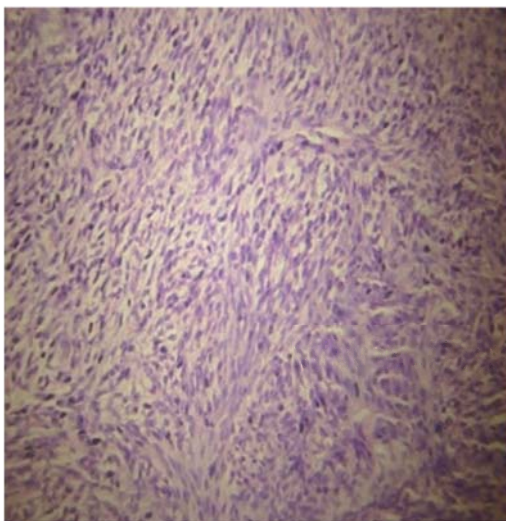


Figure 2A. Vision at 10x. Hematoxylin-eosin stain shows diffuse grown patter with length cells, with blunt borders, separated by collagen. In the middle spin zones are identified.

for tumor implants in liver and peritoneal cavity; and once again it was confirmed negative. A carefully dissection of one tumor's lobe was conducted, we achieve to dissected it from its attachment and excision biopsy was obtained extracting the specimen with a collecting endoscopic bag (Endocathc t™) trough a 10 mm port. Trans-operative histology report was: Low-grade malignity GIST (*Figures 2A and 2B*). Nevertheless confirming the report with immunohistochemical staining with CD 117 or KIT, was yet, necessary to obtain.

Due to few resistance that tumor presented, when dissecting it from the esophagus muscle layer, we decide to complete tumor enucleation in the follow way: loose adherences were dissected with a laparoscopic dissector clamp, avoiding hemorrhage in an attempt to expose completely the esophagus muscle plane; when achieved, it helped to expose and isolate the tumor's muscle pedicle. The pedicle itself was dissected and cut using an endo-GIA 60 stapler (*Figure 3*), so a stapler line over the

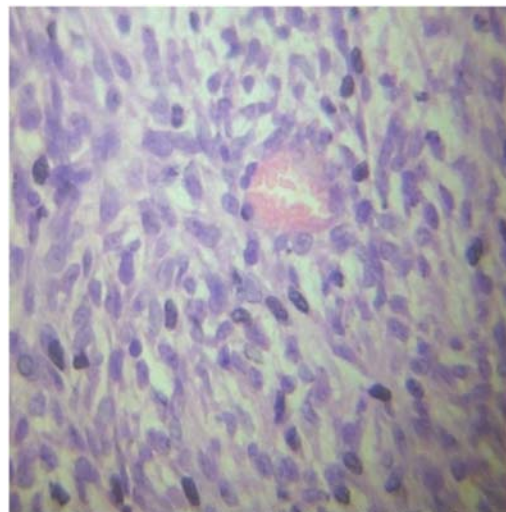


Figure 2B. Vision at 40x. Hematoxylin-eosin stain shows spindle-cell enclosure, with homogeneity in forms and sizes.



Figure 3. Tumor's pedicle is cut-off with an endo-GIA 60 stapler.

esophagus muscle plane was observed. Simultaneously; a trans-operative upper endoscopy was performed, with the intention of assessing and ruling out esophagus perforation when tumor manipulation over the dissecting site. Once tumor was enucleated, with no macroscopic evidence of tumor residual parts and since tumor pseudocapsule was intact, the entire specimen was inducted to a collecting endoscopic bag, and extracted through a 10 mm port. Upper endoscopy assessment did not show up irruption to the esophageal mucosa, thereby once tumor was enucleated, we decide to complete the original procedure: nissen laparoscopic fundoplication (*Figures 4A and 4B*). Wrapping gastric fundus with three (000-polyester) suture stitches over the dissection site. Procedure was concluded without further complications.

After the surgery, and due to findings at the operative room; as a part of GIST study protocol; a chest-abdominal computed tomography (CT) scan was performed in order to rule out Carney's triad, which is confirmed by pulmonary chondroma, functioning extra-adrenal paragangliomas and GIST. But none of the first two could be demonstrated after the scan was done.

At postoperative period, due to esophagus manipulation, antibiotic cover was indicated as well as pain control drugs, intravenous solutions and fasting for 72 hours as a precaution measure to avoid distention of the stapler line over the esophagus. When this period of observation passed, an esophagogram with oral water-soluble contrast dyer was performed to assess integrity of esophagus wall;

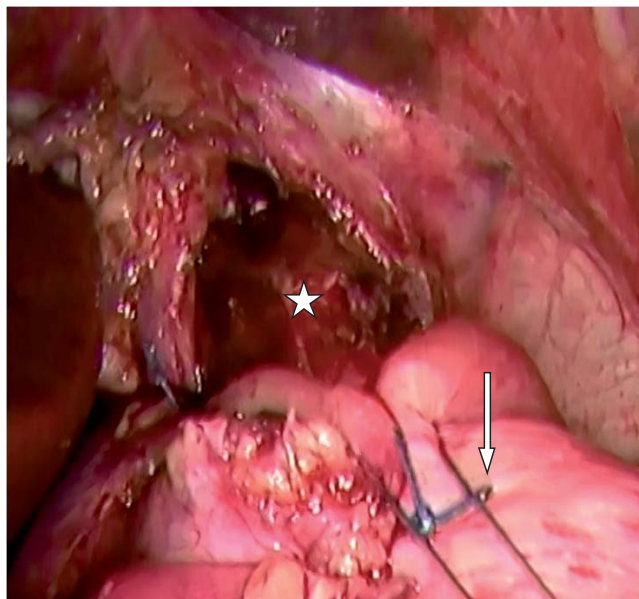


Figure 4A. Fundoplication is made over tumor resection site. Esophagus anterior wall, where GIST emerged, is shown (star). The arrow shows suture material approaching gastric fundus wrap.

we observed adequate pass of contrast dyer, with no delay or leak underneath diaphragm (*Figure 5*). At this stage, liquid diet was indicated, progressing to soft diet with good intake by the patient until the discharge day, seven days after the surgery.

The pathology specimen was sent to an immunohistochemistry stain that reported: intensive positivity in neoplastic cells, CD34 positive for a low-grade malignancy GIST, with mitotic index of 2 for 50 high power fields (HPF). During microscopic revision there was not necrosis or cellular atypia. Surgical borders did not show up tumor rests. Ever since GIST diagnosis was confirmed; target therapy was indicated with imatinib sulfate at doses of 800 mg per day, for 12 months. Currently, the patient has return to his daily activities.

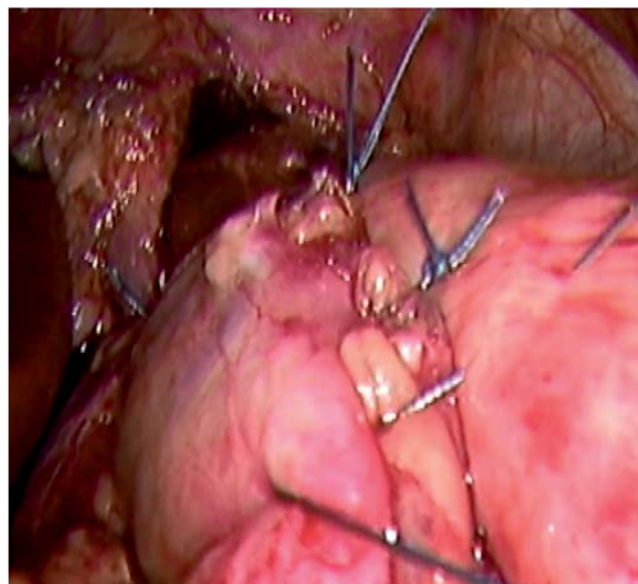


Figure 4B. Three polyester-suture knots complete classic Nissen fundoplication.

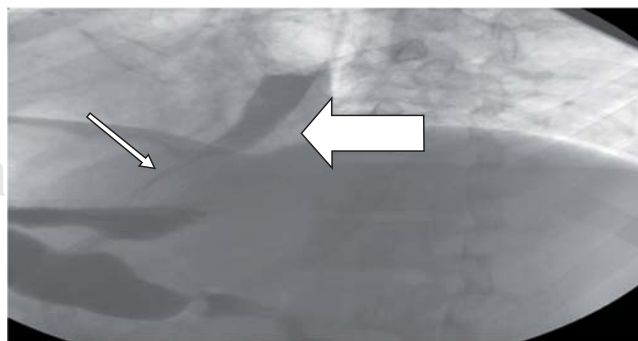


Figure 5. Esophagogram with oral contrast dyer observed along esophagus at lower third (bold arrow) passing towards the stomach (thin arrow). No delay or leak was observed.

DISCUSSION

The surgical scenario we present it's the clinical history of a GIST that was incidentally found in one of the most unusual sites of location, during an elective anti-reflux surgery.

The tumor presented dimensions such peculiar that despite it measured 5 cm-length on its major axis, those dimensions did not cause clinical symptoms that suggest obstruction at the lower third of esophagus such as: dysphagia, heartburn or early satiety when eating. There were not wasting syndrome that during physical examination would permit us suspect on a tumor: perhaps a practical reminder that in the modern medicine, there is no place to early pathognomonic symptoms to any disease.

As concerns GIST located at the lower third of esophagus, current data is fickle. In a 17-esophagic GISTs cohort, reported by Miettinen and co-workers in 2000; an overall incidence of 5% was considered.¹⁶ While in a multicentric pathologic study conducted by Álvaro-Cabrero and co-workers in Mexico City; after a review of 275 GISTs, only 2% of them were located in esophagus.¹⁷ Nevertheless, according to data base of the surveillance epidemiology and end results its incidence is around 1%.⁸ Differences between reports may be understood as the result of few evidence available to set a principle regarding the therapeutic conduct that GIST –in such location– require.

Two papers published in recent years –although they both had a small cohort– may set an example of how polemic, the treatment of a GIST in the lower third of esophagus may be:

The first: Blum and co-worker's report¹⁸ after a broad literature review, they (found only 7 reported cases of esophageal GIST in The United States between 1999 and 2007 and) suggest esophagectomy over tumor enucleation; after a 33-months follow-up in 4 patients in whom performed tumor enucleation in esophagus and one esophagectomy included, that locally recurred. The study postulate the fine-needle aspiration biopsy guided by endoscopic ultrasound (EUS-FNA) for suspicious lesions located at the esophageal sub mucosa; and to submit the aspirated material to immunohistochemistry stain as part of work-up, previous to treatment (resection). They also suggest that administration of target therapy before surgery may improve results when attempting tumor resection.

The second: Lee and co-worker's report¹⁹ that on the contrary to Blum's group opinion, they recommend tumor enucleation by video-thoracoscopy in well-limited tumors, with macroscopic-benign characteristics and size less than 5 cm. For tumors bigger than 5 cm, this group recommendation is esophagectomy. Another substantial difference between studies is the judicious employ of positron-emitted tomography (PET) as a differential diagnosis method between a GIST and leiomyoma.

Now and then, both studies differ in diagnostic and therapeutic recommendations but they coincide with respect to local tumor enucleation that can be attempting in tumors less than 2 cm, limited to esophagus wall in patients with surgical high-risk (by co-morbidities) and when tumor is not located near to gastro-esophageal union (GEU) or LES; relegate esophagectomy for what Blum's group would call «great tumors»;¹⁸ the same as Lee's group would consider to those tumors bigger than 5 cm.¹⁹

As concerns to this standard measure of tumor size, one of the ultimate recommendations is included in the National Comprehensive Cancer Network guide (NCCN) of 2007 for treatment of GIST-patients,¹³ that as one of many differences with NCCN guide of 2004, it recommends laparoscopic approach in tumors of 5 cm or less, while in tumors bigger than 5 cm, the hand-assisted laparoscopic technique (that constitutes an hybrid concept of surgery that maintains laparoscopy advantages –more accurate-detail vision– with the re-gain of touching sense by introduction of one hand to a special device into the insufflated abdominal cavity) is considered the best choice, to treat GIST, since they are more fragile, posses more vascularity, have major necrotic component and with a higher possibility of being attached to adjacent structures.

Another essential point of convergence between studies we discuss, respect to GIST treatment is collected in an enlightening review report by Fernández and coworkers²⁰ that enlists objectives of surgical technique principles that must be respected when treating these kind of tumors; with no matter if open or laparoscopy approach is selected. These principles are basics for GIST adequate resection. Given its nature based on observation and principles of surgery, they could be replicated at any hospital that counts itself among those with basic resources at the operating room and with pathology department, but also in those hospitals that not only count with the basics facilities, but with a laparoscopic equipment too. Those same principles were respected when operating our patient and are displayed in *table 2*.

About the limit of laparoscopy and the need of conversion to an open procedure, there are several factors involved; one of most important is that surgery must be conducted in long-experienced centers in laparoscopy approach. Other factors reported are: tumor located at GEU, heavy adhesences, great tumor size, local invasion to adjacent organs and tumor perforation before surgery.²⁰

In none of the studies previously mention, resection «In bloc» of tumors located at lower third of esophagus is recommended and due to the few publications that refers to this kind of tumor at this specific location, enucleation by laparoscopy is not yet a recommended option, or perhaps to experienced-surgical groups only.¹⁹ Hence we found valid the intension of this report, since we had found GIST at this rare location we choose for that surgical choice: the enucleation. Not before consideration of two main factors: 1) tumor size

Table 2. Oncologic surgical principles for primary GIST.

Surgical approach	Resection principles
Laparotomy	<ul style="list-style-type: none"> • Complete abdominal assesment • Extensive resections if necessary • Resection in bloc of adjacent organs if necessary • Wide margins are unnecessary • Linfadenectomy is not indicated • Pseudocapsule intact • Complete macroscopic resection with negative margins (R0) • Re-laparotomy must be considered if microscopic margins are not disease free (R1)
Laparoscopy	<ul style="list-style-type: none"> • Same technical principles as laparotomy • Limited appliance due to tumor size • Acceptable if permits a R0 resection • Specimen extraction in endoscopic collector bag device • Great tumors (T > 5 cm) only for experienced groups
Endoscopy	<ul style="list-style-type: none"> • For follow up use in gastric GIST < 1 cm • Supporting of laparoscopy • Endoscopic resection is contraindicated

Source: Fernández 2010

was 5 cm and 2) it was over the GEU. These facts maybe were sufficient –facing the lack of validated evidences in this matter– to abort surgery, differing surgical procedure and ordering EUS-FNA or PET in the out-patient to confirm diagnosis. In the same period of time ordering immunohistochemistry stain for the biopsy we took during surgery and then wait for results. After diagnosis confirmation and with the risk that implies a second surgical time we would attempt tumor's resection. But perhaps with an open approach since the recommendation for this tumor location justifies the technique.

With so many variants to consider and because in the modern surgery absolute indications are less frequent but

surgical criteria must be taken account in order to opt for a choice; we choose to follow the NCCN 2007 lineaments for tumor sizes and the universal surgical principles for tumor's handling in the transoperative period (*Table 2*); Hence we attempted laparoscopic enucleation via abdominal and after we did so; we completed the original procedure (fundoplication) by wrapping gastric fundus over the tumor's resection site, covering primary stapler line in order to provide an additional safety mechanical barrier to esophagus.

Other factors must be considered in case patient would had presented any esophageal motility disorder. In this scenario where the probability of making a complete rather than a partial fundoplication is quite low, the mechanical barrier should be provide with another anatomic resource such as: serosa or epiplon's patch. Nevertheless this kind of patients would represent a great challenge even to the experienced surgeon.

In the postoperative follow and due to the absence of sing and symptoms of esophageal perforation assessed by esophagogram with oral contrast dyer, oral intake was started. Once patient was discharged, target therapy was given and after 12 months of surgery, patient is incorporate to a normal life.

CONCLUSION

Although GISTs are infrequent esophageal tumors, they must be taken account on surgeon's mind when an incidental tumor is found in the operating room at this site. Laparoscopic abdominal enucleation can be achieved on GIST locate at lower third of esophagus with a 5 cm-diameter or less; without adopting for another radical option such as esophagectomy, as long as oncologic principles of resection are followed. It is necessary to rule out Carney's triad once GIST diagnosis is established. Hence it is important to be familiar with the surgical treatment as well as with target therapy for esophageal GIST.

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