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DOTTORATO DI RICERCA IN
Medicina Molecolare

CICLO XXXVII

Advances and surgical therapeutics in the management of immunoistochemical CD-117 positive subepithelial lesions of the gastrointestinal tract

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1. INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are parenchymal neoplasms of the gastro-intestinal tract and abdomen, originating in the muscular wall of the viscera, whose cells show phenotypic similarities to the interstitial cells of Cajal, which coordinate the peristaltic movement of the gastro-intestinal tract[1]. Immunohistochemistry of these tumors is positive for c-KIT (Figure 1) (90 percent of c-KIT mutations involve exon 11). A possible differential immunohistochemical diagnosis is with solitary fibrous stromal tumors that expresses positivity also for CD-34 and locate mainly in the pleural cavity [2-3], but the mesenteric localization has been described in the literature [4-5].

Although GIST are the most frequent mesenchymal tumors of the gastro-intestinal tract they correspond to only 01.-0.3 % of gastrointestinal neoplasm[6]: presentation is most common in the stomach (60-70%) and small intestine (20-30%). Esophageal, colon and rectal GIST are rarer, exceptionally they occur at the level of the omentum, mesentery and retroperitoneum[7] (Figure 2).

The identification and proper definition of GIST has become more important after introduction of targeted treatment with KIT tyrosine kinase inhibitor Imatinib mesylate, STI571, commercially known as Gleevec®/Glivec® for metastatic and unresectable GISTs [8].

The early results on isolated cases and clinical trials have shown tumor stabilization or regression in a great majority of metastatic and unresectable GISTs expanding the trials to large numbers of patients with malignant GISTs so management of GISTs has been transformed. Neoadjuvant therapy can be effectively used for the treatment of metastatic and recurrent GIST or when the surgery can't be radical at the first time.

In resectable GIST patients, the risk of recurrence after surgery alone and in those who received adjuvant imatinib therapy can be estimated based on tumor size and location, mitotic activity, and capsule rupture[9] using nomograms; statistical analysis showed better predictive ability than systems developed by National Institute of Health (NIH) (Figure 3).

Apart from microscopic GISTs (micro-GISTs), commonly found in the general population but having a very low probability of malignant transformation, no GIST should be considered completely benign.

The most common symptoms of GISTs are abdominal pain, palpable mass, intestinal obstruction, vomiting and nausea, anemia and gastrointestinal bleeding, and hemoperitoneum due to rupture of the neoplasm in the peritoneal cavity (Figure 5).

Most GISTs are documented incidentally (CT-scan Figure 6.1, endoscopy Figure 6.2) and present at diagnosis less than 5 cm in size.

Surgical resection is always the first treatment choice if the disease is radically removable but resectable GIST with significant morbidity should be evaluated with mutational testing (next generation sequencing [NGS]) and immunohistochemistry for neoadjuvant therapy according to NCCN guidelines. Surgery following Glivec therapy is the choice in metastatic, relapsed GISTs and in situations whereby site or size surgery might not be radical or might qualitatively compromise the patient's life. Incisional biopsy occurring either before or at the time of the operation should be strictly avoided.

All patients, especially borderline cases, should be evaluated and treated by a multidisciplinary team with expertise and experience in gastrointestinal stromal tumors (Table 1).

The surgical choice in resectable cases depends on the site and size: in gastric GISTs larger than 2 cm, surgery involves atypical segmental resection or traditional gastric resection in those tumors located in a pre-pyloric or cardial site. Segmental resection is indicated in GISTs of the jejunum-ileum, while a traditional resection is the choice in colorectal cancers. In sites such as the duodenum, lower rectum and esophagus, in the case of large tumors, neo-adjuvant therapy with Glivec may be indicated, alternatively an enucleation of the mass may be considered to avoid extremely demolitive surgery.

GISTs located in the stomach less than 2 cm in size can be kept under control by close follow-up, may possibly be excised endoscopically in compromised or elderly patients. Except for such cases, enucleation should always be avoided: the most important oncologic rule dictates gentle handling of the lesion by avoiding capsular effacement and rupture of the mass. Proper surgery is one of the

essential prognostic factors of the disease along with the number of mitoses, site and size[10-11-12-13-14].

Regarding endoscopic enucleation techniques , these can be used as both a diagnostic and therapeutic tool for non-symptomatic GISTs; as mentioned earlier about 15-30% of stromal tumors are diagnosed incidentally without any clinical manifestation [15-16-17]; because of the difficulty in predicting the malignant behavior of GISTs and the rarity of spread by the lymphatic drainage , the theoretical basis for an endoscopic approach to this pathology is justified assuming complete excision is observed and spread to the peritoneal cavity is avoided.

The most used treatments are endoscopic submucosal dissection (ESD) (Figures 6) and endoscopic submucosal tunneled dissection (ETSD). Endoscopic enucleation has a number of advantages including that of not having to demolish a gastric segment for removal of the neoplasm, shorter hospital stay, a procedure under conscious sedation, low cost, and fewer personnel compared with surgery. Although endoscopic submucosal dissection (ESD) is noted to achieve complete resection, this procedure is associated with a relatively high complications rate and a long procedure time.

Transanal minimally invasive surgery (TAMIS) is a technique that was originally devised as a hybrid between transanal endoscopic microsurgery (TEM) and single-site laparoscopy for resection of rectal lesions[18]. It was developed out of the need for a practical alternative to TEM that was both affordable and technically feasible without specialized equipment. It is categorized using a single-site port transanally in combination with ordinary laparoscopic instruments, a laparoscopic camera lens, and a standard laparoscopic CO2 insufflator for the purpose of performing endoluminal rectal surgery (Figure 6.1).

For very small gastric GIST <2 cm consider endoscopic ultrasound guided fine-needle aspiration biopsy (EUS-FNAB) or Endoscopic ultrasound-guided core needle biopsy (EUS-CNB).

It should be noted, however, that there are drawbacks: first, there are no data showing whether or not there is residual neoplasm when an R1 resection is performed, although several studies have shown that microscopically positive margins are not a risk factor for recurrence[19-20].

Second, because perforation is often accompanied by capsule infraction, it increases the possibility of neoplastic insemination of the peritoneal cavity with high risk of recurrence and poor prognosis. Izumi et al described for the first time, a technique combining endoscopy and laparoscopy has also been reported for the removal of a subepithelial lesion of the esophagus: in this technique, the submucosal tumor is pushed by a balloon mounted on an endoscope, and the thus protruded neoplasm is enucleated thoracoscopically[21-22].

2. MATERIALS AND METHOD

Our retrospective study analyzed the case history of a series of 52 patients referred to the Units of Surgery, AUSL Piacenza, with histological diagnosis of gastrointestinal cancer, treated with surgical resection from January 2005 to December 2015.

Site, size, mitotic index (high power field-HPF), adequacy of surgical maneuver, any other risk factors such as ulceration or necrosis were considered in the analysis.

These data consequently allowed the grade of aggressiveness of the disease to be stratified into low, medium and high risk (Figures 7).

Medium- and high-risk patients have a higher risk of recurrence, metastasis, and mortality. For this reason, it was necessary to send the patient to the oncologist and establish an appropriate follow-up program and an adequate Glivec therapy.

The outcome assessment was done considering the incidence of disease recurrence and mortality. Kaplan Meier statistical analysis was used to evaluate factors related to disease-free survival.

3. RESULTS

From January 2005 and December 2015, 52 patients underwent resective surgery for primitive neoplasm identifiable as GIST of the gastrointestinal tract. Of these 29 patients (56%) were men and 23 were women (44%).

The primary site was found to be the stomach in 33 patients (63%), ileum in 15 patients (29%), rectum in 3 patients (6%), other site (retroperitoneum) in 1 patient (2%).

The size was found to be less than 2 cm in 6 patients (11%), >2 and < 5 cm in 29 patients (56%), > 5 cm in 17 patients (33%) (Table 4).

The number of mitoses was >1 /hpf in 12 patients (23%), >1 and < 5/hpf in 29 patients (5%), > 5/hpf in 11 patients (21%).

Based on these results, our patients were distributed into three groups: 25 patients at a low risk (48%), 16 patients at medium risk (31%), 11 patients at high risk (21%).

All patients were treated with surgery as the first treatment choice according to NCCN guidelines[12].

Operations were performed in elective setting in 45 cases (87%), in urgent setting in 7 cases (13%).

Patients undergoing emergent surgery were operated for severe bleeding in 3 cases (2 gastric bleeding and ileal bleeding), for occlusion and pain in 3 cases (GIST located in the ileum), and for perforation resulting in capsule breach (ileal GIST).

Surgical adequacy was achieved in 88% of cases, or 46 patients. The six patients in whom suboptimal surgery is described include three patients operated in urgent setting for active bleeding, one infraction of the neoplasm capsule in a perforated bowel, two patients with margins less than one millimeter in loco-regional excisions (GIST of the rectum).

Follow-up lasted from 6 to 96 months.

The disease-free survival is 43 months (average). The median overall survival is 60 months.

Survival according to size <5 cm was 100% at 5 years, between 5 and 10 cm was 75% at 5 years, <10 cm was 80% at 3 years and 70% at 5 years.

Survival according to site was in the 33 gastric-site patients 82% at 5 years, in the 15 ileal-site patients 75% at 5 years, in the 3 patients with rectal disease the survival was 100% at 5 years but two patients out of three developed recurrence of a locoregional and liver disease, respectively.

Survival based on the number of mitoses if less than 5 is 75% at three years and 50% at 5 years; if the number of mitoses is >25 the mortality at 5 years is 100%.

Totally, considering all risk factors together the 2-year and 5-year survival in LOW-RISK patients and 95% and 80% respectively, with 100% disease-free patients, in INTERMEDIATE-RISK patients and 100% and 70% respectively, and in HIGH-RISK patients 70% and 50% with 45% disease -free.

In conclusion 6 of 52 (12%) patients developed GIST synchronously to another gastrointestinal tract cancer (one in the pancreas, two of colon rectum, three in the stomach). All synchronous GISTs were at low overall risk and had immunohistochemical positivity for CD117 and CD34.

4. DISCUSSION AND CONCLUSION

According to international guidelines identifying the risk and degree of aggressiveness of the disease and using Fletcher's classification, patients were stratified into low, medium and high risk. The determinants for this definition were the site, size and number of mitoses.

Specifically, low-grade tumors are those with a size of less than 5 cm and mitotic count of less than 5/50 HPF; intermediate-grade tumors are those between 5 and 10 cm in size with an index less than 5 or tumors with a diameter of less than 5 cm, mitotic index greater than 5/50 HPF but less than 10/50 HPF (Figure 7).

Finally, all lesions with size greater than 10 cm, regardless of mitotic count index or size < 5 cm and mitotic index > 5 HPF, are to be considered at the high grade of malignancy.

The gastric localization is associated with a better prognosis. The site, although much rarer, of the colon and rectum, to a worse prognosis.

The other characteristics considered were the degree of necrosis and ulceration, found in six patients, all of whom had medium- and high-risk lesions due to high numbers of mitoses.

Female gender was not associated with any increased risk factors, contrary to other studies reported in the literature[23-24].

For primary gastric tumors, the surgery of choice has been anatomic resection or wedge resection, depending on site and size; in small bowel tumors, ileal and segmental resection has always been the standard. GIST of the rectum have been treated with standard rectal resection, except in one case where advanced age (>80 years old) and size (< 1 cm) have permitted an endoscopic resection (Figure 4.1).

Lymphadenectomy is not considered oncologically necessary. In none of our patients were described lymphatic dissemination on histopathological examination.

Laparoscopic was used in 12 cases (23%), (8 gastric resections, 4 ileal resections, all lesions were less than 5 cm in size).

All cases considered at high and medium risk were sent for Gleevec therapy.

Surgery can be considered adequate in 95% of cases, considering resection margins and lack of capsule breach as clinical parameters.

The major risk factor for surgery-related disease recurrence remains capsule breach and bleeding of the lesion intraoperatively. Tumor rupture increases the risk of bleeding and contamination; Thus, emergency surgery or improper manipulation can dramatically change the patient's prognosis.

In our specific case series, 13% of patients underwent emergency surgery. Obvious effacement of the capsule was described in only one case. Even in emergency setting, adequate resection of all disease was performed, avoiding manipulation of the mass and proceeding with adequate lavage of the peritoneal cavity.

Microinvasion of margins does not appear to be significant for the risk of recurrence. However, the gold standard is complete excision of the lesion with a negative margin. In our specific case, the margin was < 1 mm millimeter, but without margin microinvasion, it is not necessarily an indication for reintervention.

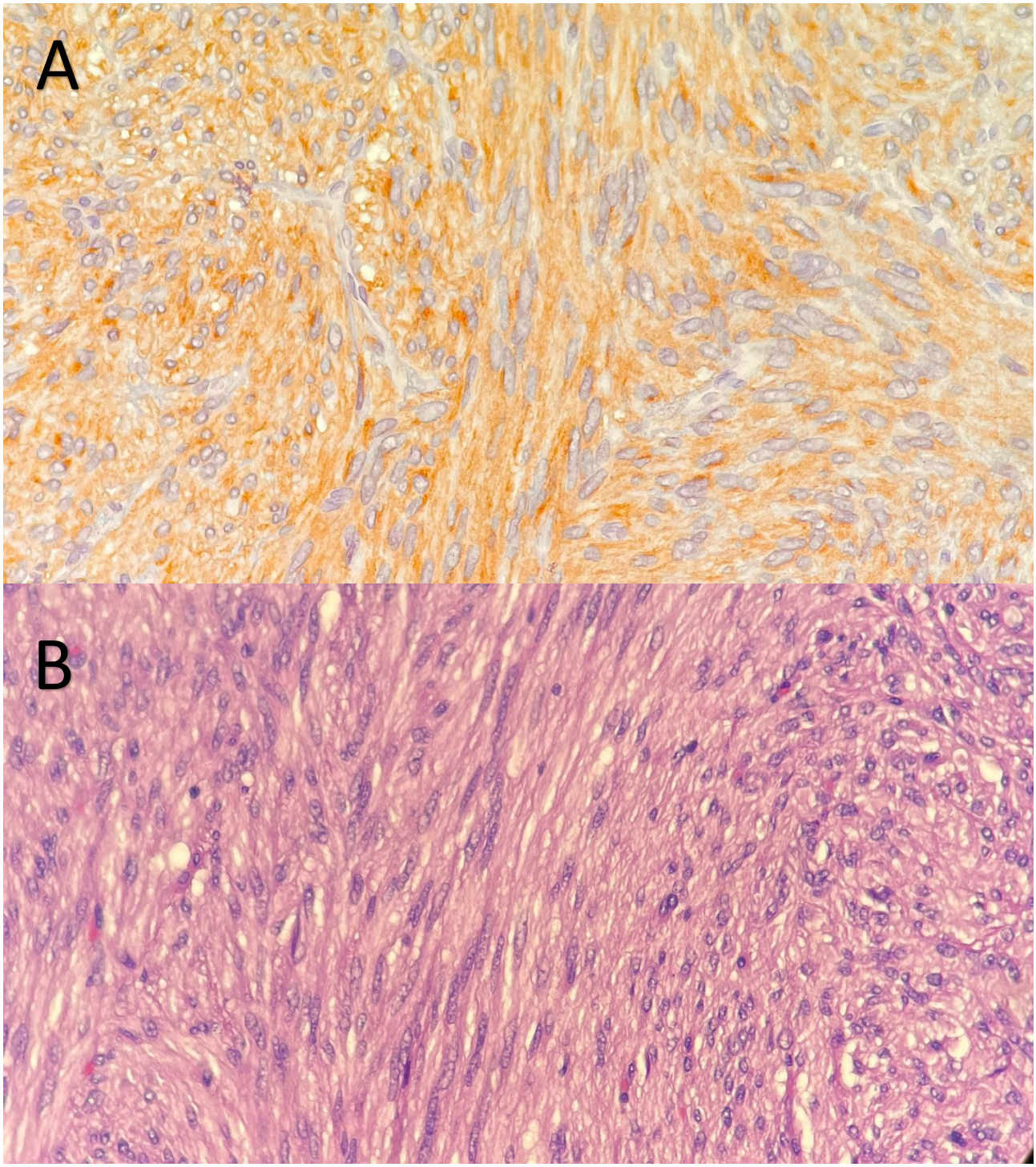
As mentioned before there is no evidence that the patient with complete macroscopic resection of disease but R1 margin should undergo re-excision. Moreover, a reintervention is justified only by acceptable redo surgery-related morbidity.

In both cases (inadequacy of margins, emergency surgery), the oncologist must consider the need for adjuvant treatment with Glivec because the site, size, and number of mitoses are of less significance than the adequacy of the surgical procedure in defining high risk.

The results of our series were expressed using Kaplan-Meier curves. The risk of disease recurrence and survival were studied in relation to the individual risk factor and by evaluating the distribution of patients defined as low, medium, and high risk (Table 2) according to Fletcher classification that considers site, number of mitoses, and size of disease.

Overall survival is significantly dependent on tumor size: patients with tumors smaller than 5 cm are all alive and disease-free in the period analyzed, patients with tumor size between 5 and 10 cm or larger than 10 cm have a significantly increased recurrence rate and lower survival (Figure 8).
Regarding the site of disease of the 33 patients with GIST with gastric localization, 18% died at 5 years of the 15 patients with ileal disease 75% are alive at 5 years, 70% at 10 years of the three patients with rectal disease, two patients are alive but with liver metastasis on Glivec therapy, one patient presented local recurrence at 18 months (Figures 9).
Mitosis index appears to be the most significant prognostic factor with a marked reduction in survival in patients with mitosis number > 5 (75% at three years, 50% at five years), with a mortality of 100% at three years if mitotic index is > 25 % (Figure 10).
Patients classified as low risk according to Fletcher had a 2- and 5-year survival of 95% and 80%; all patients were disease-free, and death occurred due to age or other comorbidities.
The intermediate-risk group had a survival rate at two and five years of 100% and 70% respectively, and disease-free survival was 100% at the same.
High-risk group had a survival rate at 2 and 5 years of 70% and 50% respectively and disease-free survival was 45%. This confirms that tumors with low and intermediate risk had a significantly better prognosis and recurrence-free survival ($p= 0.0007$ χ squared test) (figure 11-12).
These data are consistent with the current literature, in which an increased risk of developing gastrointestinal tract tumors seems to be associated with presence of GIST.

5. FIGURES



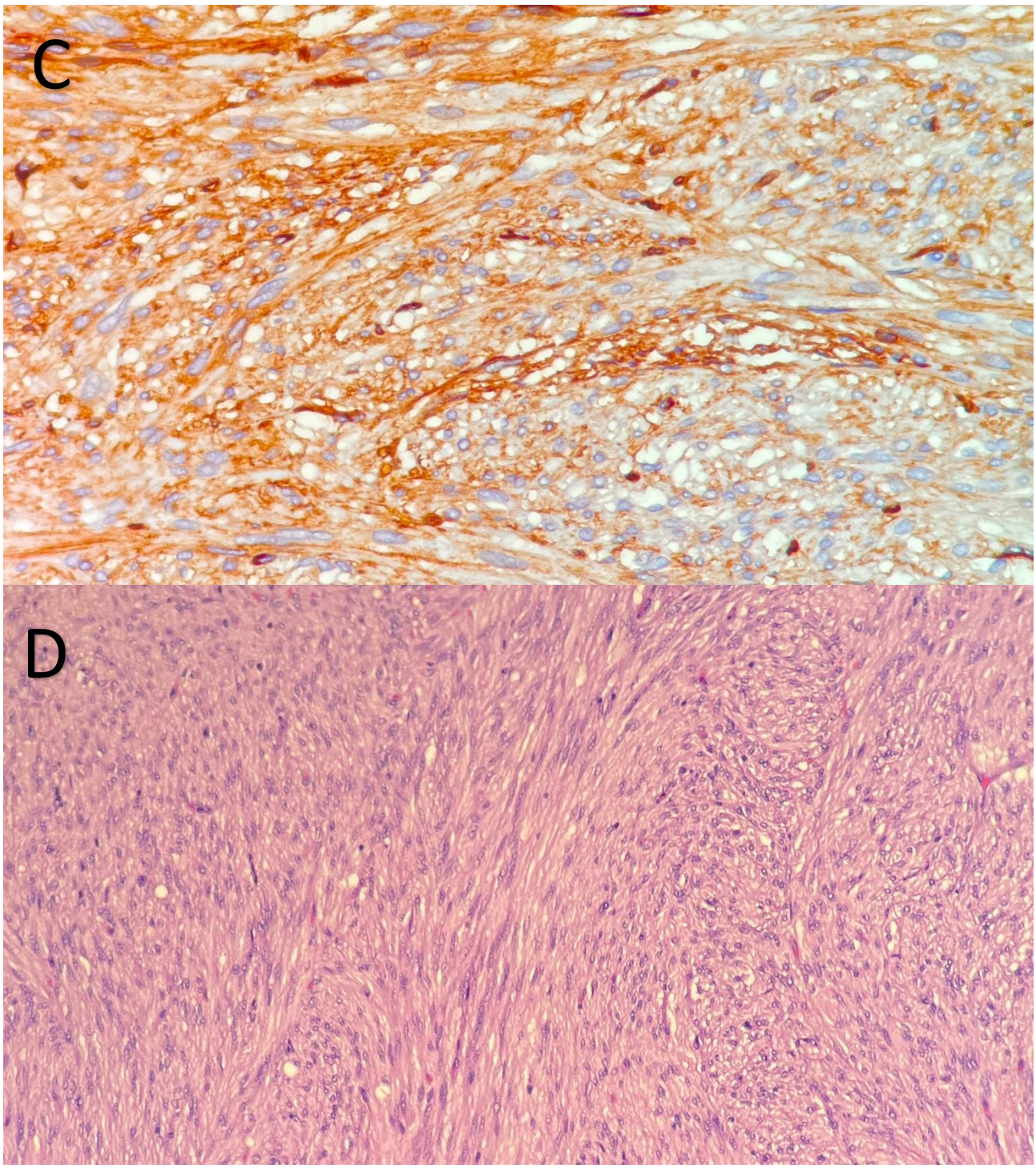


Figure 1. A: Immunohistopathological sample of gastric GIST shows CD 117 positivity, magnification 40 X

B: Hematoxylin-eosin staining of GIST cell proliferation, magnification 40X

C: CD 34-positive GIST cells

D: Atypical spindle cell proliferation, organized in bundles, sometimes, storiform separated by abundant hyaline fibrous matrix, CD 34 positive immunophenotype.

(Courtesy of Dr. Rodolfo Monaco, Unit of Pathology, AUSL Piacenza)

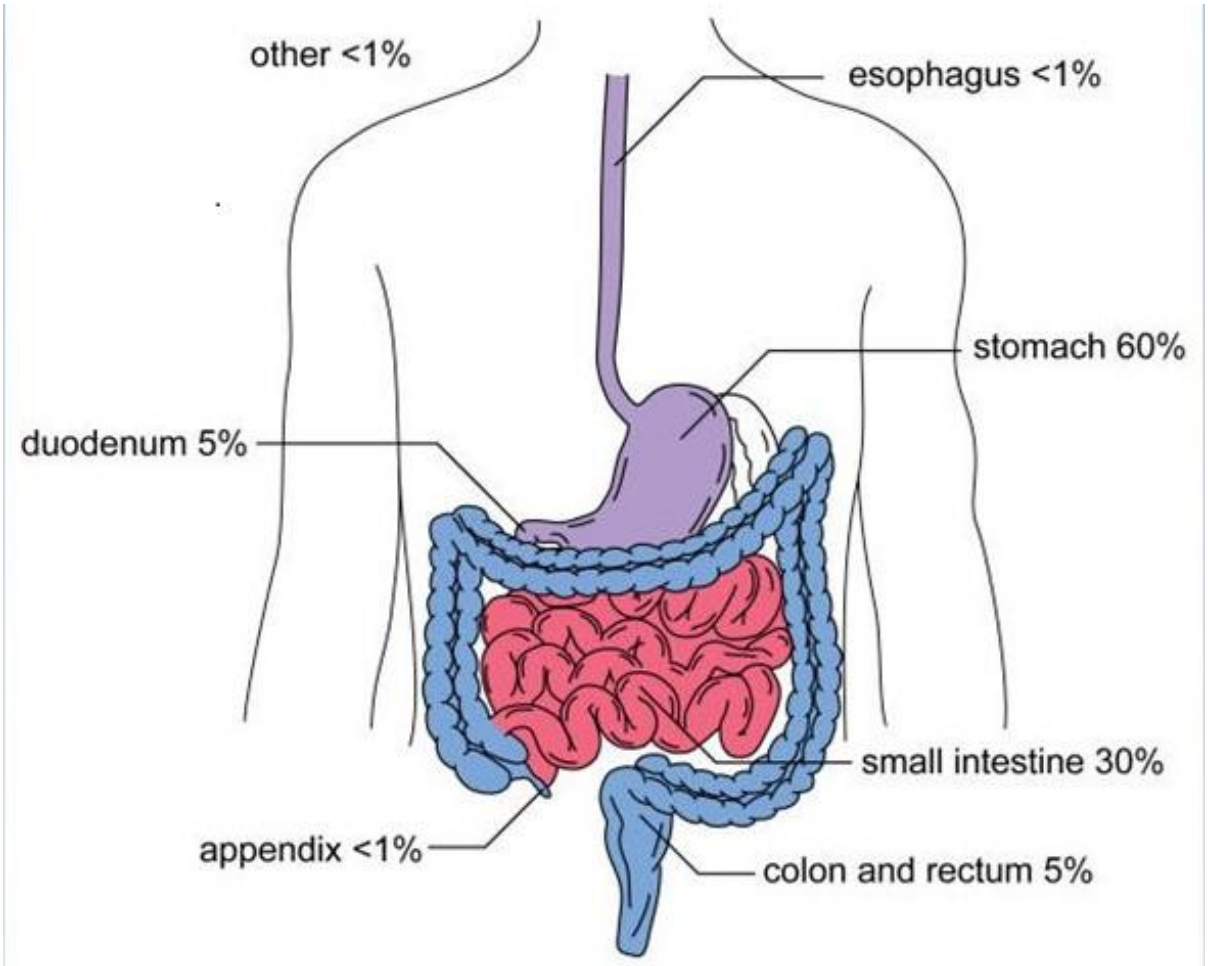


Figure 2. Site of presentation of GISTs

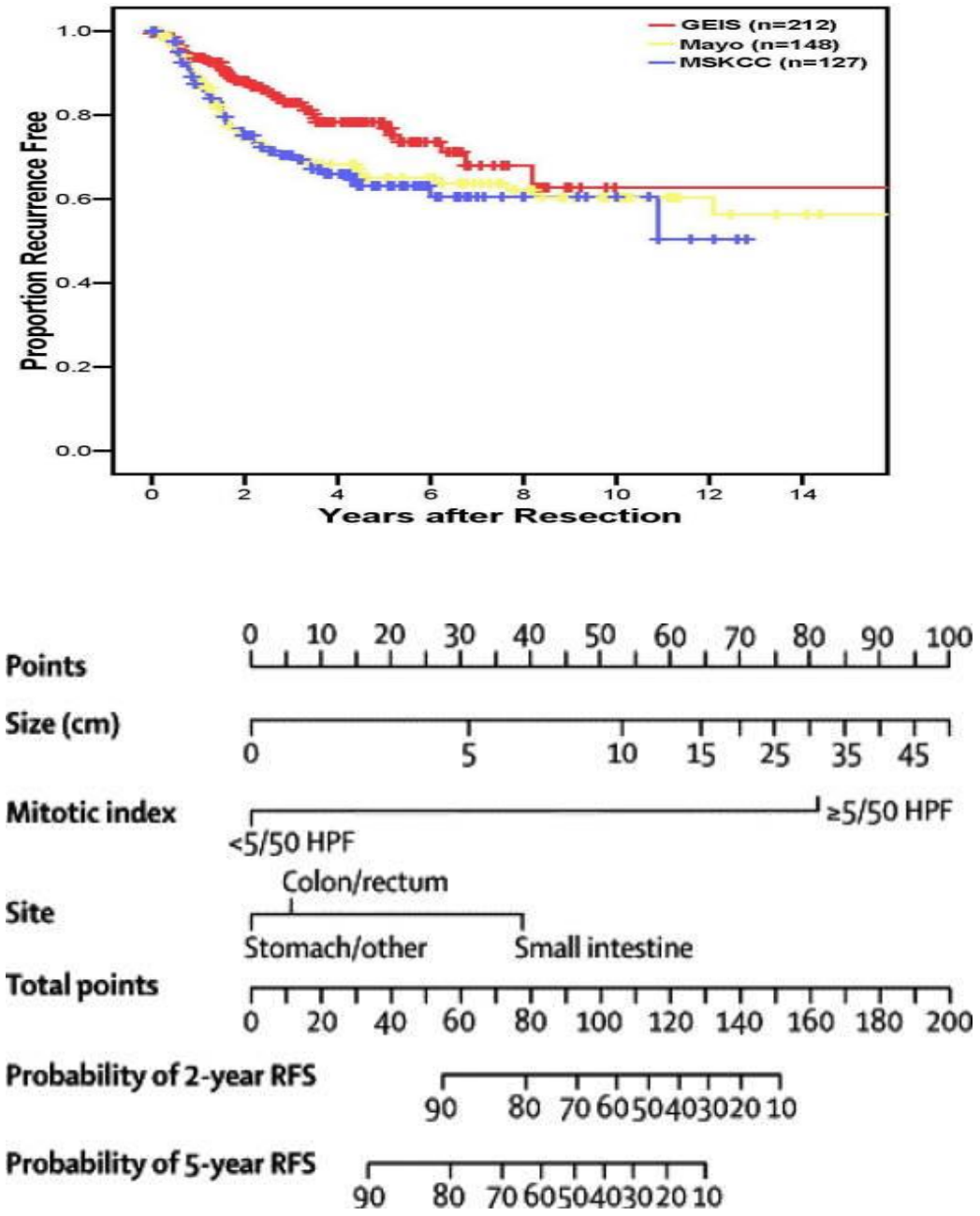


Figure 3. From Gold JS et al. Development and Validation of a Prognostic Nomogram for Recurrence-Free Survival after Complete Surgical Resection of Localized, Primary Gastrointestinal Stromal Tumor (GIST): A Retrospective Analysis. *Lancet Oncol.* 2009; 10: 1042-1052.

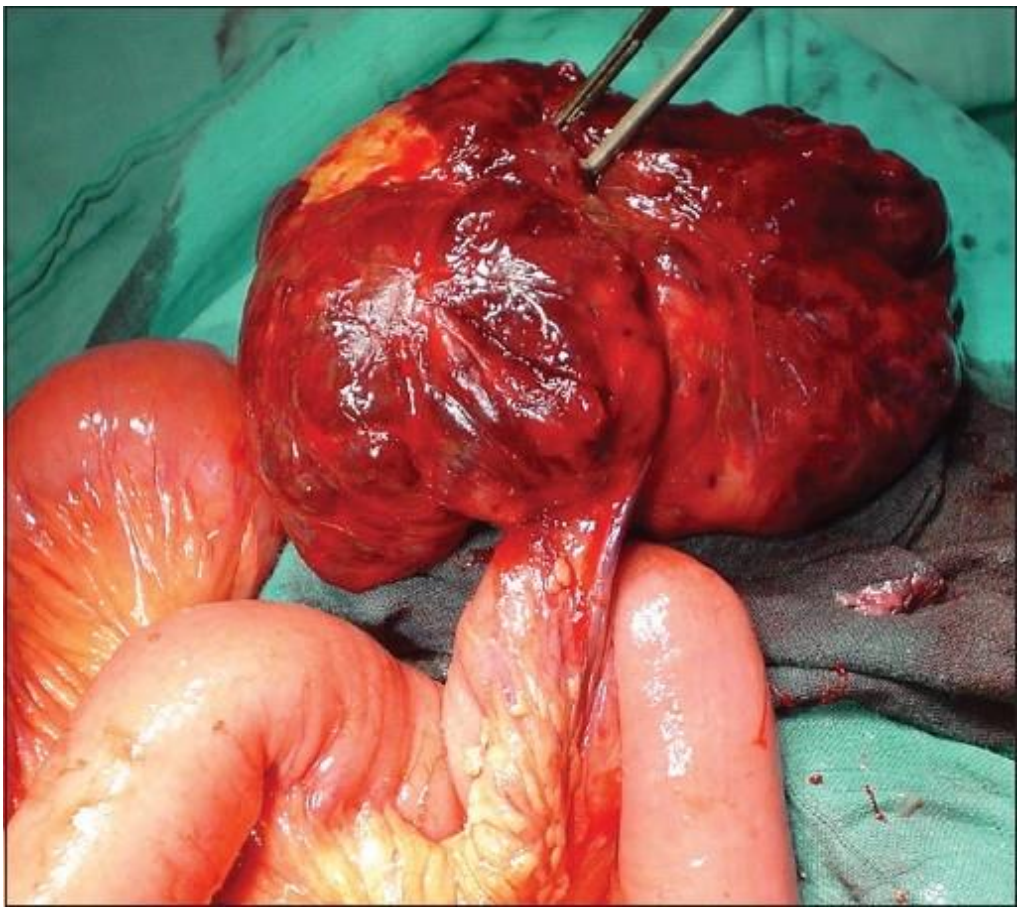


Figure 4. Hemorrhagic shock caused by a GIST localized in the ileum. (From Karim Ibn Majdoub Hassan. Gastrointestinal stromal tumors and shock. *J Emerg Trauma Shock*. 2009; 2(3): 199–202).

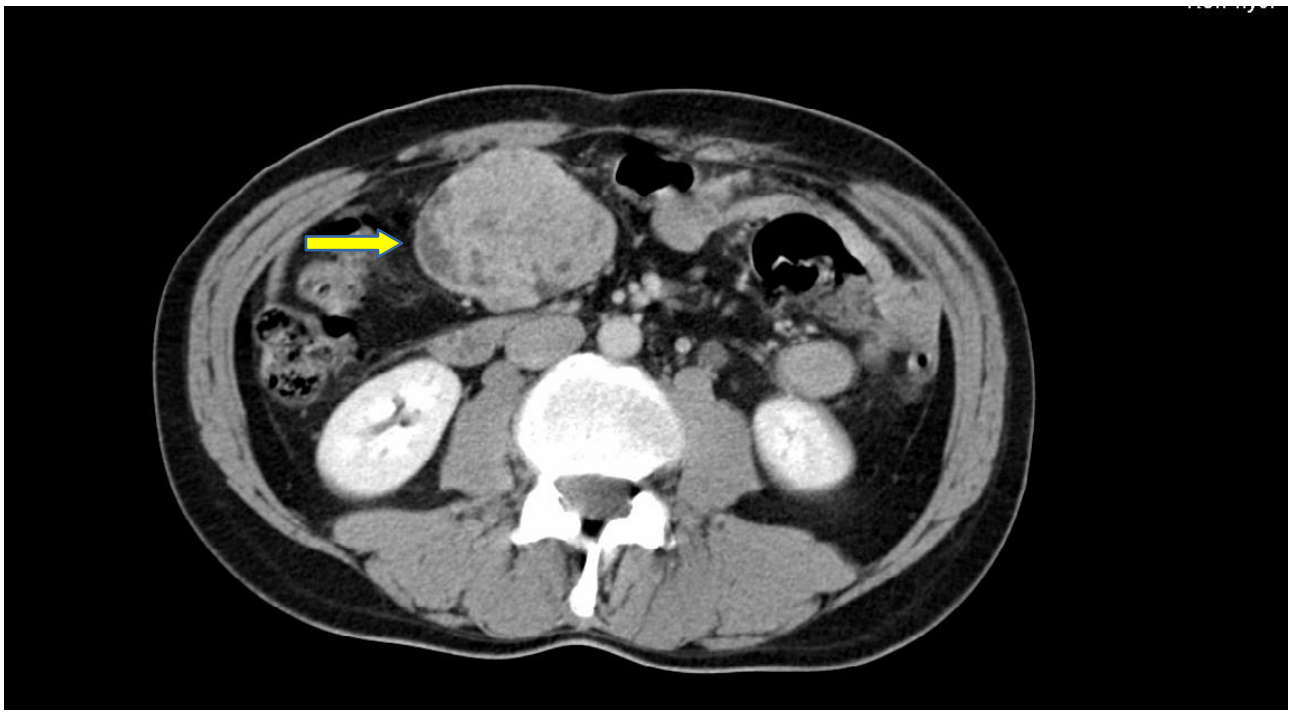


Figure 5.1 Incidental finding of gastric mass (arrow) discovered during ultrasound examination in a patient with Gilbert's disease.
Further examination with CT scan documented a lesion of the posterior wall of the stomach, measuring approximately 7 for 6 cm, without evidence of infiltration of the surrounding organs (Courtesy of Radiology Unit, Department of Radiodiagnostics, AUSL Piacenza).

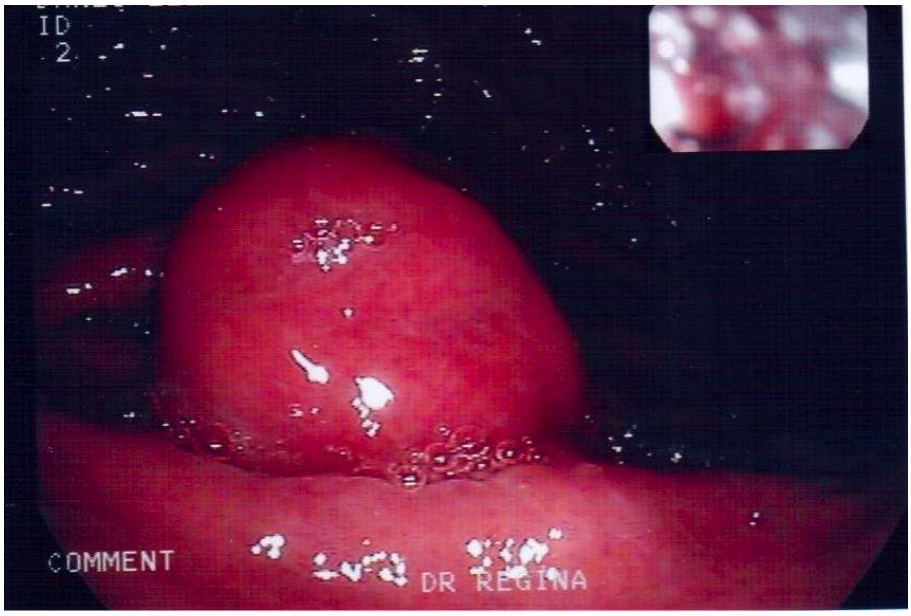


Figure 5.2 Incidental endoscopic finding of gastric sub-epithelial lesion (Courtesy of Dr. G. Regina, Emergency Surgery Unit, Department of Surgery, AUSL Piacenza)

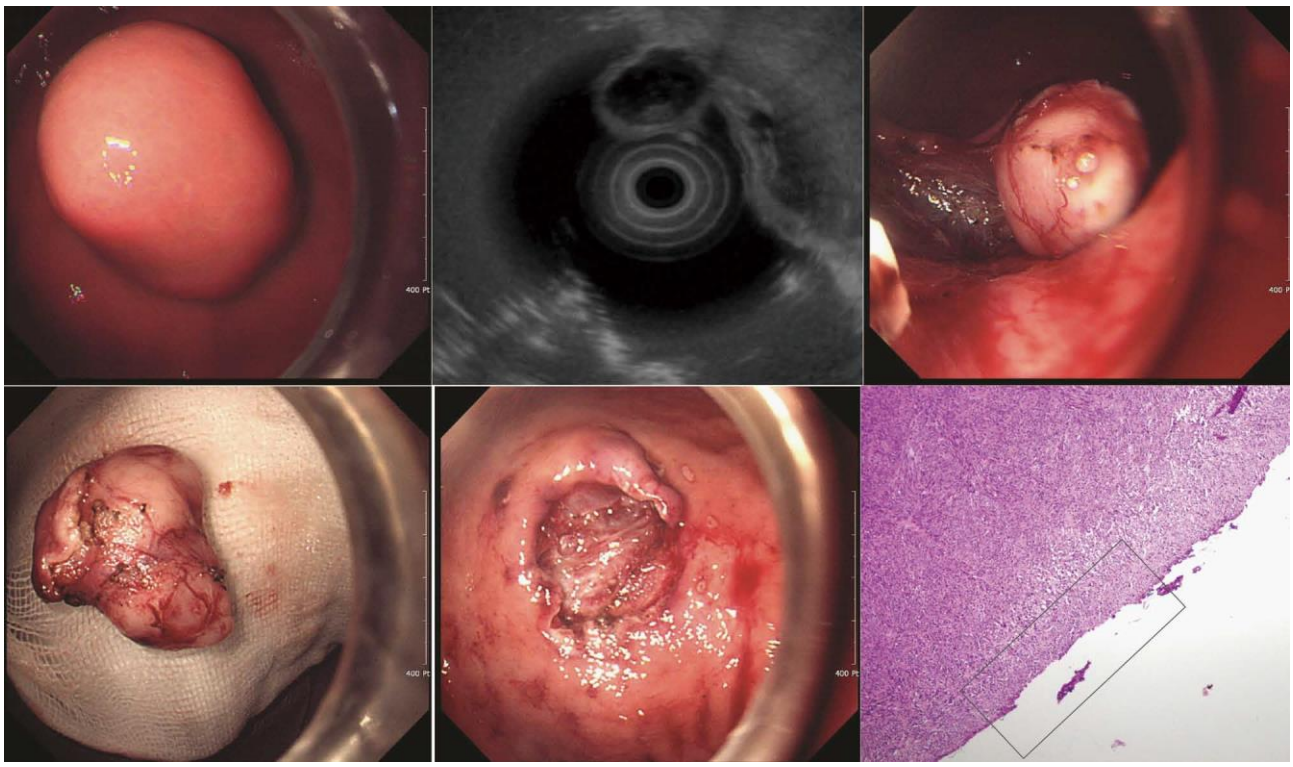


Figure 6. From Kyung Oh Kim. Endoscopic treatment for gastrointestinal stromal tumor: Advantages and hurdles. *World J Gastrointest Endosc*. 2015: 16; 7(3): 192-205

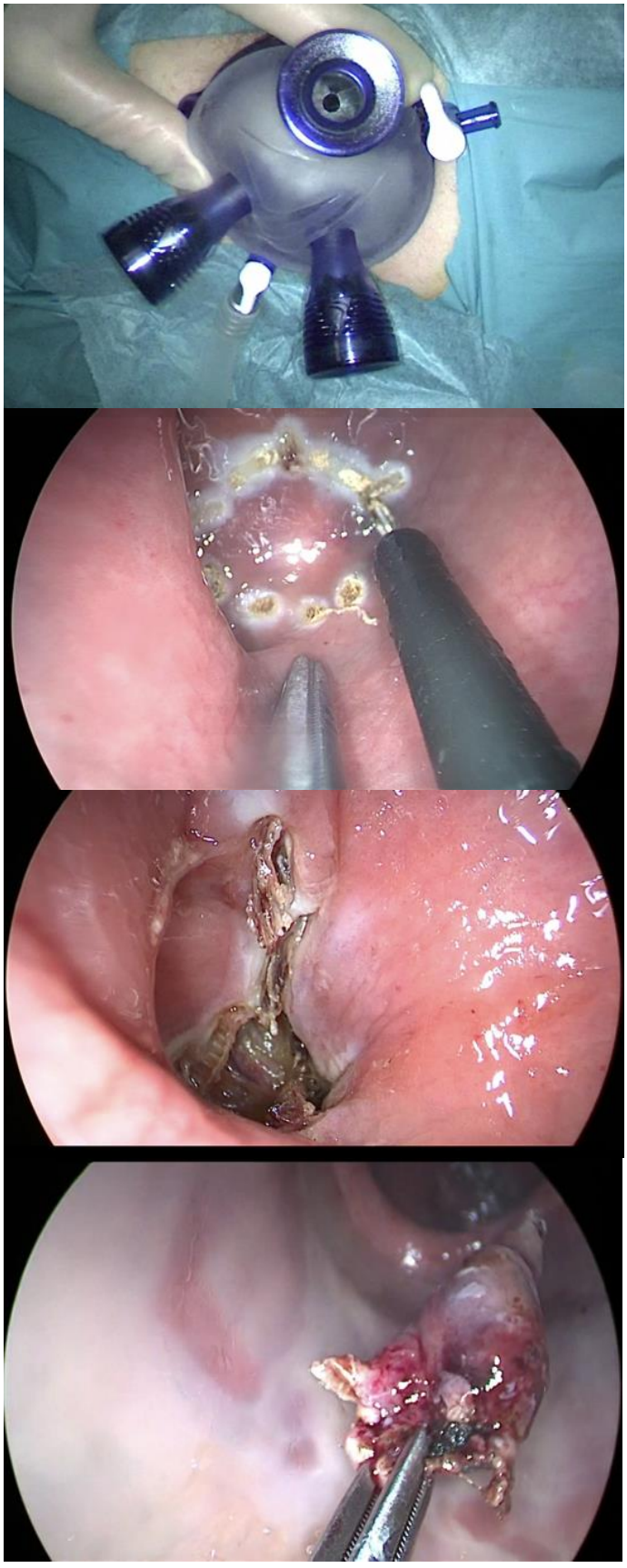


Figure 6.1. Endoscopic surgical enucleation of rectal lesion using a single port access by inducing pneumorectum.

Malignancy risk	Size (Cm)	Mitotic (50 hmf)
Very low	<2	<5
Low	2-5	<5
Intermediate	<5	6-10
	5-10	<5
High	>5	>5
	>10	Any index
	Any size	>10

Note: 50 hmf = 50 high magnification fields (400x)
Source: Fletcher et al., 2002.

Figure 7. Classification of Fletcher.

Table 3 Modified NIH risk of recurrence (21)

Risk	Tumor size (cm)	Mitotic count (HPF)	Tumor site
Very low risk	<2	<5/50	Any
Low risk	2.1–5	<5/50	Any
Intermediate risk	<5	6–10/50	Gastric
	5.1–10	<5/50	Gastric
High risk	Any	Any	Perforated tumor
	>5	>5/50	Any
	>10	Any	Any
	Any	>10/50	Any
	2.1–5	>5/50	Non-gastric
	5.1–10	<5/50	Non-gastric

HPF, high power field.

Figure 7.1 From Trisha M. Parab. Gastrointestinal stromal tumors: a comprehensive review. *Journal of Gastrointestinal Oncology.* 2019; 10 (1)

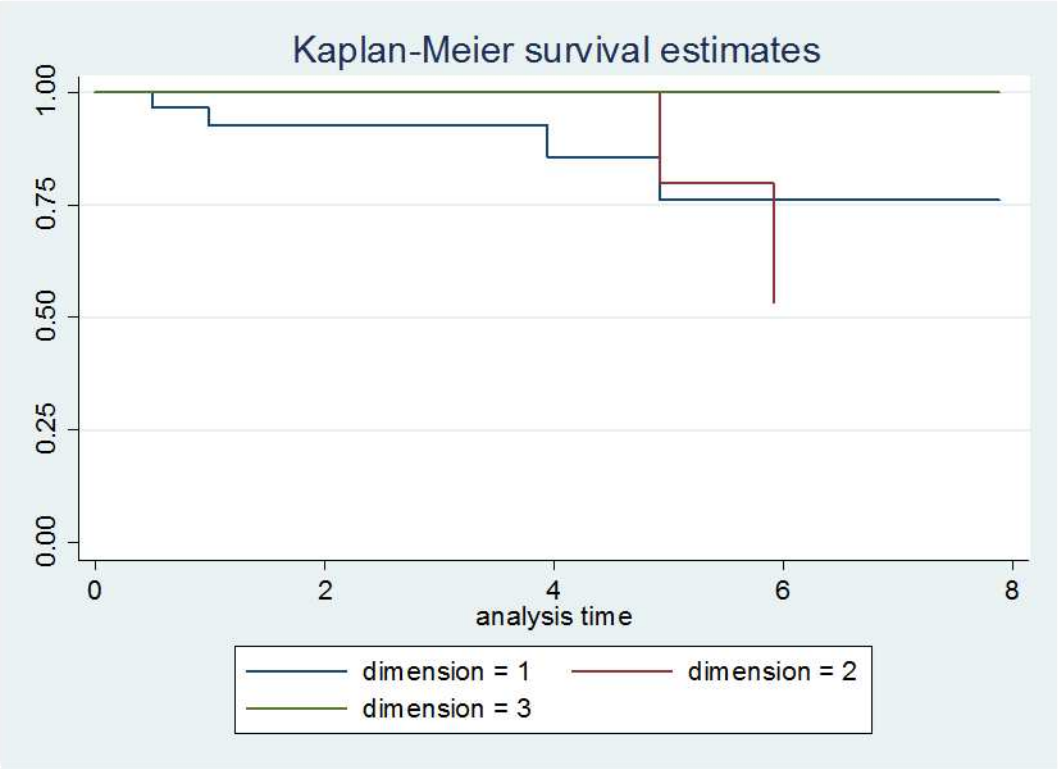


Figure 8. Survival related to lesion size.

1= < 5 cm

2= 5< and <10 cm

3= > 10 cm

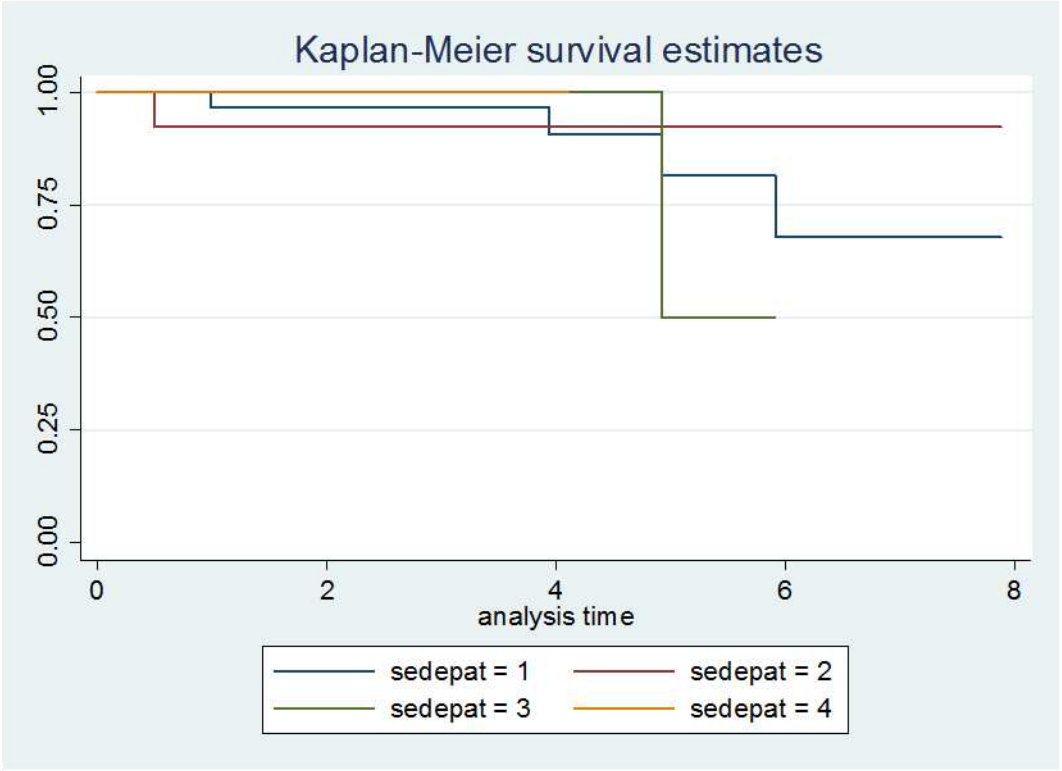


Figure 9. Survival estimates depending on the GIST localization.
1= stomach; 2= ileum, 3= rectum; 4= other sites

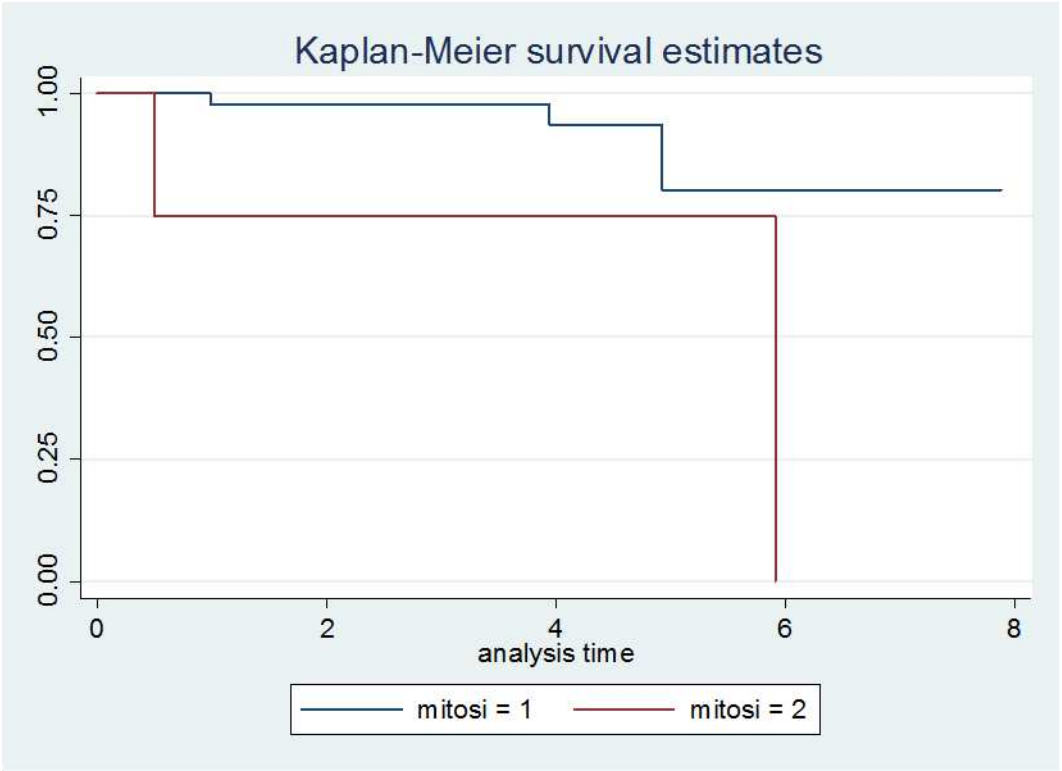


Figure 10. Mitosis number is a significant prognostic factor in reduced survival.
Mitotic index =1 > 5 HPF, 2> 25 HPF

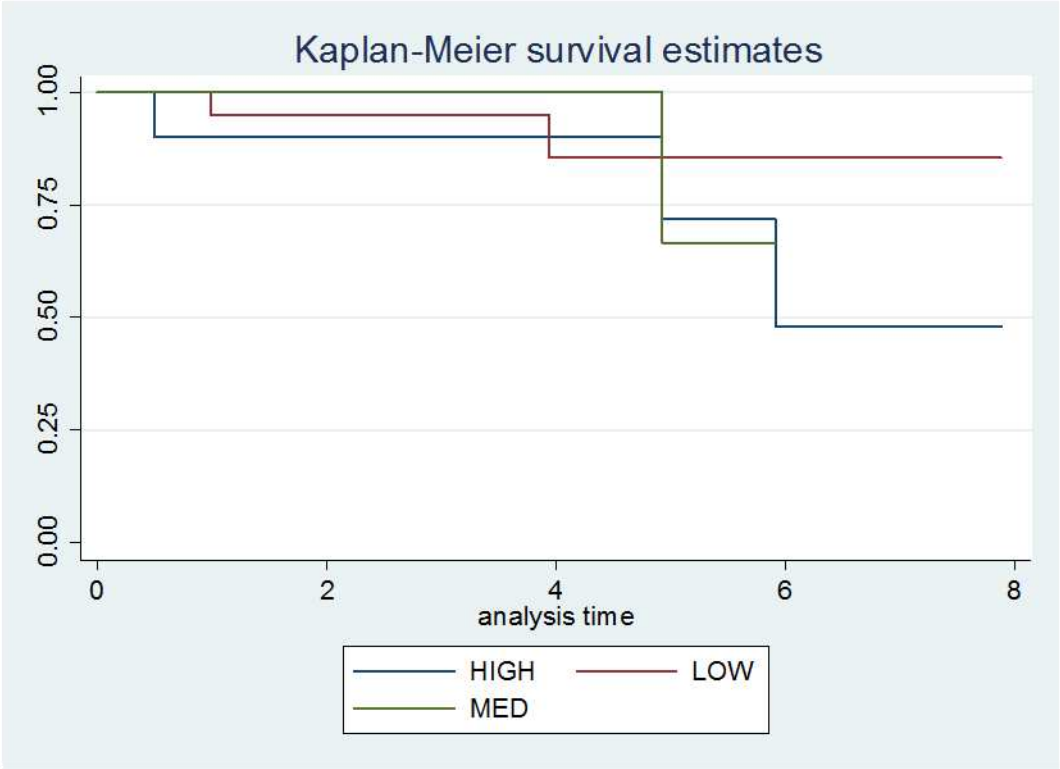


Figure 11. Depending on risk factors, HIGH-RISK patients had a 5-year survival of 50%.

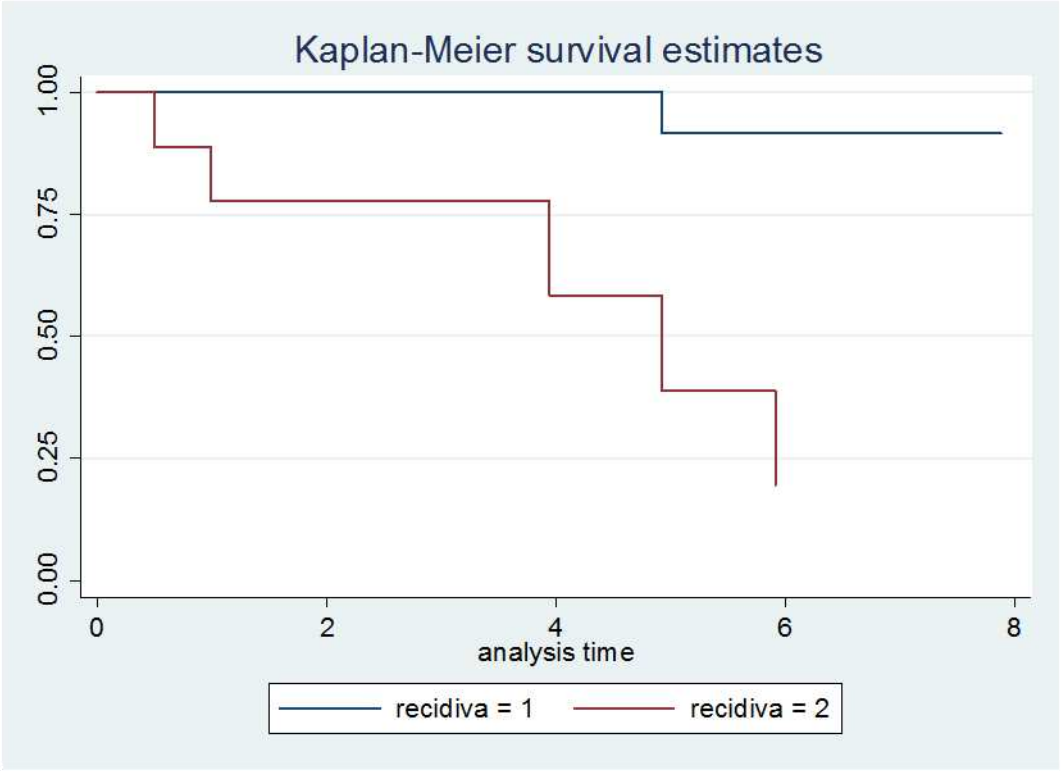


Figure 12. Survival estimated on recurrence. 1= no recurrence; 2= recurrence.

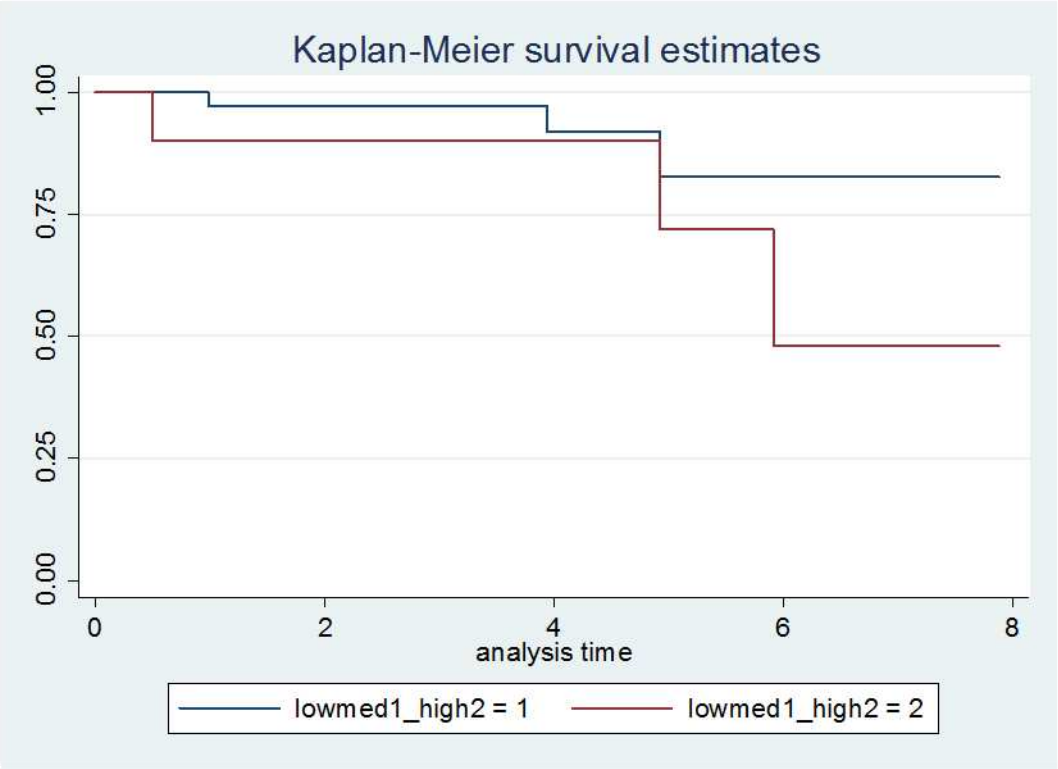


Figure 13. Low- and medium-risk GISTs (=1) have a significantly better prognosis and statistically significant recurrence-free survival (p= 0.0007)

Risk category	Tumor size (cm)	Mitotic index (per 50 HPF)	Primary tumor site
Very low risk	< 2.0	≤ 5	Any
Low risk	2.1–5.0	≤ 5	Any
Intermediate risk	2.1–5.0	> 5	Gastric
	< 5.0	6–10	Any
	5.1–10.0	≤ 5	Gastric
High risk	Any	Any	Tumor rupture
	> 10	Any	Any
	Any	> 10	Any
	> 5.0	> 5	Any
	2.1–5.0	> 5	Nongastric
	5.1–10.0	≤ 5	Nongastric

Table 1. Proposed modification of NIH consensus classification for selecting patients with GIST for adjuvant therapy.

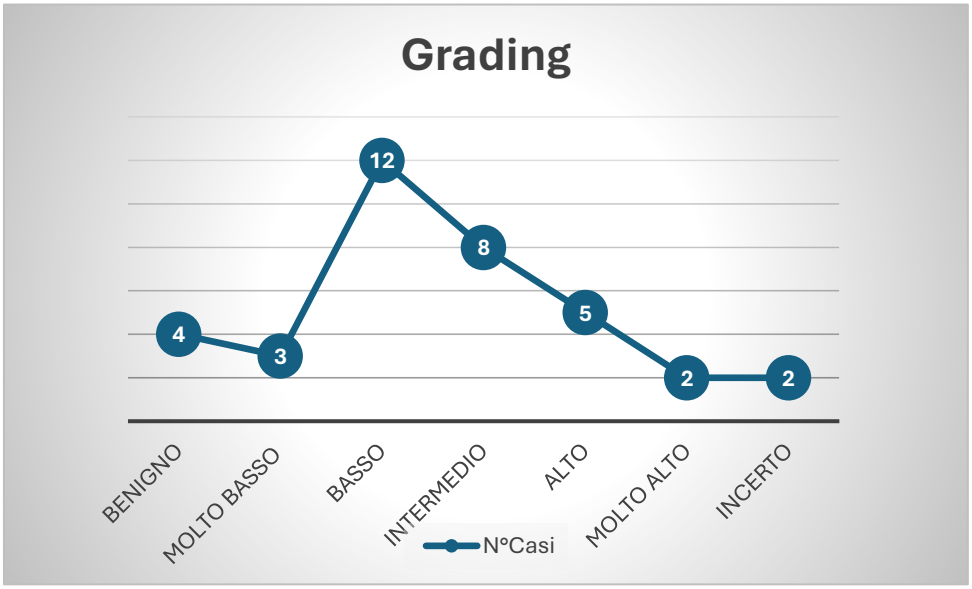


Table 2. Number of cases based on grading of GISTs

Tumor parameter			NIH criteria	Modified NIH criteria	
Mitotic count	Tumor size	Tumor rupture*		Gastric	Non-gastric
≤5/50 HPF	≤2 cm	No	Very low	Very low	Very low
	>2, ≤5 cm	No	Low	Low	Low
	>5, ≤10 cm	No	Intermediate	Intermediate	High
	>10 cm	No	High	High	High
6–10/50 HPF	≤2 cm	No	Intermediate	Intermediate	Intermediate
	>2, ≤5 cm	No	Intermediate	Intermediate	High
	>5, ≤10 cm	No	High	High	High
	>10 cm	No	High	High	High
>10/50 HPF	Any	No	High	High	High
Any*	Any*	Yes*	-*	High*	High*

Table 3. NIH (National Institute of Health) consensus conference modified criteria for estimation of malignant potential of GIST (HPF: high power field)

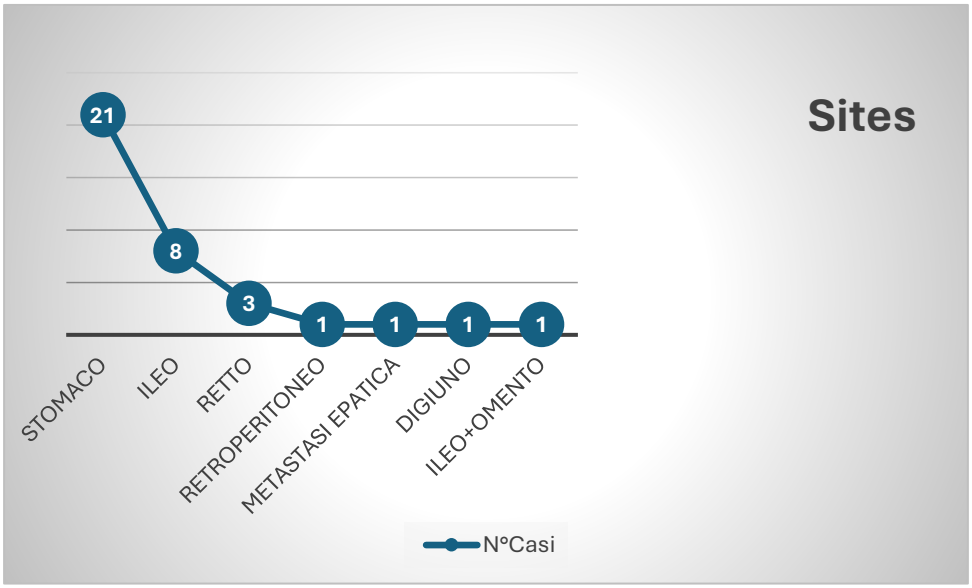


Table 4. The principal site of GISTs presentation in our analysis was the stomach as described in literature.

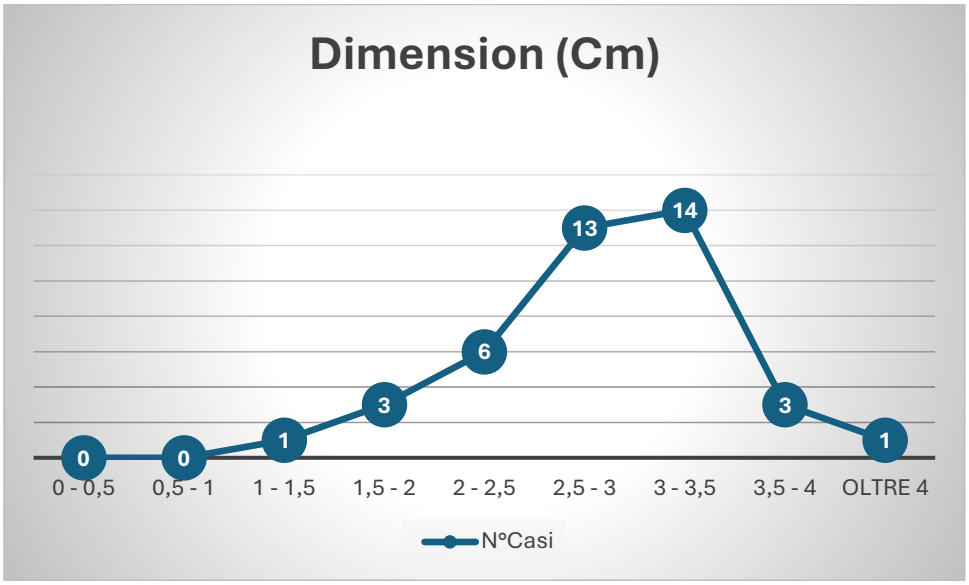


Table 5. GISTs sizes ranged mostly from 2.5 and 3.5 cm

6. REFERENCES

1. Kindblom LG, Remotti HE, Aldenborg F, Meis-kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol.* 1998, 152: 1259-1269.
2. Yi B, Bewtra C, Yussef K, Silva E. Giant pelvic solitary fibrous tumors obstructing intestinal and urinary tract: a case report and literature review. *Am Surg 2007*; 73 (5): 478-80
3. Moritsugu Tanaka, Hirozumi Sawai, Yuji Okada, Minoru Yamamoto, Hitoshi Funahashi, Tetsushi Hayakawa, Hiromitsu Takeyama, Tadao Manabe. Malignant solitary fibrous tumor originating from the peritoneum and review of the literature. *Med Sci Monit 2006*; 12(10): CS95-98
4. Shanbhogue AK, Prasad SR, Takahashi N, Vi- kram R, Zaheer A, Sandrasegaran K. Somatic and visceral solitary fibrous tumors in the abdomen and pelvis: cross-sectional imaging spectrum. *Radiographics* 2011; 31: 393-408.
5. Filosso PL, Asioli S, Ruffini E, Rovea P, Macri’ L, Sapino A, Bretti S, Lyberis P, Oliaro A. Radical resection of a giant, invasive and symptomatic malignant solitary fibrous tumour (SFT) of the pleura. *Lung Cancer.* 2009; 64: 117-20.
6. Joensuu H. Gastrointestinal stromal tumor (GIST). *Ann Oncol.* 2006; 17: 280-286
7. Miettinen M, Lasota J. Gastrointestinal stromal tumors definition, clinical, histological, immunoistochemical, molecular genetic features and differential diagnosis. *Virchows Arch.* 2001; 438: 1-12.
8. Miettinen M, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunoistochemical and molecular genetic study of 1765 cases with long-term follow up. Am J Surg Pathol. 2005; 29: 52-68.
9. Joensuu H, Vehtari A, Riihimaki J. Risk of recurrence of gastrointestinal stromal tumor after surgery: an analysis of pooled population-based cohorts. *The Lancet Onc*. 2012; 13: 265-274.

10. Demetri GD, Von Mehren M, Blanke CD et al. Efficacy and safety of imatinib mesylate in advanced gastro-intestinal stromal tumors. *N Engl J Med.* 2002; 347: 472-480.
11. Verweij J, Casali PG, Zalcberg J et al. Progression-free survival in gastrointestinal stromal tumors with high-dose imatinib: randomised trial. Lancet. 2004; 364: 1127-1134.
12. NCCN Clinical practice guidelines. Gastrointestinal stromal tumors. Ver 2.2024
13. Casali PG et al. ESMO guidelines. Ann Oncol. 2022; 33: 20-33.
14. Goth BK et al. Impact of the introduction of laparoscopic wedge resection as a surgical option for suspected small/medium-sized gastrointestinal stromal tumors of the stomach on perioperative and oncologic outcomes. *World J Surg.* 2010; 34:1847-1852.
15. Rutkowski P, Symonides M, Zdzienicki M, Siedlecki JA. Developments in targeted therapy of advanced gastrointestinal stromal tumors. *Recent Pat Anticancer Drug Discov.* 2008; 3: 88-89.
16. Hirota S, Isozaki K, Moriyama Y et al. Gain-of-function mutations of c-kit in human gastrointestinal tumors. *Science*. 1998; 279: 577-580.
17. Corless CL, McGreevey L, haley A et al. KIT mutations are common in incidental gastrointestinal stromal tumors 1 centimeter or less in seize. *Am J Pathol.* 2002; 160: 1567-1572.
18. So H, Yoo SH, Han S, Kim GU, Seo M, Hwang SW, Yang DH, Byeon JS Efficacy of precut endoscopic mucosal resection for treatment of rectal neuroendocrine tumors.. *Clin Endosc* (2017); 12: 2234-2243
19. De Matteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg. 2000; 231: 51-58.
20. Rivera RE, Eagon JC, Soper NJ, Klingensmith ME, Brunt LM. Experience with laparoscopic resection of gastrointestinal stromal tumours. *Ann Surg.* 2006; 243:738-745.

21. Izumi Y, Inoue H, Endo M. Combined endoluminal-intracavitary thoracoscopic enucleation of leiomyoma of the esophagus. A new method. Surg Endosc. 1996; 10:457-458.

22. Inoue H, Ikeda H, Hosoya T, Yoshida A, Onimaru M, Suzuki M, Kudo SE. Endoscopic mucosal resection, endoscopic submucosal resection, and beyond: full-layer resection for gastric cancer with non-exposure technique (CLEAN-NET). *Surg Oncol Clin N Am*. 2012; 21: 129-140.

23. Bucher et al. An audit of surgical management of gastrointestinal stromal tumor (GIST). *Eur J Surg Oncology*. 2006; 32: 310-314.

24. Amitabhad, Wilson R. Surgical therapy for gastrointestinal stromal tumor of the upper gastrointestinal tract. *J Gastrointest Surgery*. 20089; 13: 1220-1225.

25. Atallah S, Albert M, Larach S. Transanal minimally invasive surgery: a giant leap forward. Surg Endosc. (2010); 24: 2200‐2205