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The Role of the Surgeon in Multidisciplinary Approach to Gastrointestinal Stromal Tumors

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1. Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms of the digestive tract with an estimated annual incidence of 10–20 cases per one million inhabitants (H. Joensuu et al;2002, B. Nilsson, et al; 2005). GISTs probably arise from precursor cells of the interstitial cells of Cajal. Their defining characteristic is a gain-of-function mutation in genes coding for the KIT tyrosine kinase receptor, which is considered the driving force of cell proliferation in this tumour(Y. Shinomura et al;2005) Gastrointestinal stromal tumors usually appear in patients above 50 years of age, whereas the maximum incidence is observed in the 5th and the 6th decade of life. The mean age at the diagnosis is 55–63 years(Tran T et al; 2005). It is very rare in children and affects males and females equally. GIST is mainly a disease of the GI tract, mesentery, and omentum. Most commonly, it originates in the stomach (60%), followed by the small intestine (30%), the colon and rectum (5%), and the oesophagus (5%) (Van Der Zwan SM, et al;2005). Fletcher et al. proposed a classification of aggressive behaviour for GISTs based on their maximum diameter and mitotic rate(C. D. M. Fletcher et al;2002). factors which were both shown to predict recurrence and survival(S. Singer et al;2002, R. P. DeMatteo et al;2000). GIST can present in many ways. Thirty percent are diagnosed incidentally on a pathological or autopsy resection specimen(B. Nilsson, et al; 2005). Small tumors may be asymptomatic and GISTs can grow to a large size before producing any symptoms. Most symptomatic patients present with tumours larger than 5 cm in maximal dimension. Symptoms at presentation may include abdominal pain, abdominal mass, nausea, vomiting, anorexia, and weight loss. The vast majority of metastatic GISTs are located intraabdominal, either in the liver, in the omentum, or in the peritoneal cavity(C. D. M. Fletcher et al;2002). Metastatic spread to lymph nodes and to other regions via lymphatics is very rare. Most of the patients with GIST are symptomatic and bleding due to mucosal ulceration is the most common symptom(Gold JS et al ; 2006). Mitotic count and tumor size have been shown to be very important. A large study examined 1765 tumors for prognostic markers(Miettinen et al; 2005). Tumours less than 10 cm with less than 5

mitoses per 50 high powered fields (HPFs) had only a 2%–3% risk of metastases. Conversely, the metastatic rate for tumors greater than 10 cm, with greater than 5 mitoses per 50 HPFs, was as high as 86%. Non-gastric primary tumor location and male gender may also be independent adverseprognostic factors(Rutkowski et al; 2007). Fletcher et al. proposed a classification of aggressive behaviour for GISTs based on their maximum diameter and mitotic rate(C. D. M. Fletcher et al;2002), factors which were both shown to predict recurrence and survival(S. Singer et al;2002, R. P. DeMatteo et al;2000). Surgery remains the standard initial management for all localized GIST. The tumor should be removed en bloc, with a clear margin. The pseudocapsule should be removed and not penetrated. Therefore, a wedge resection (stomach) or segmental resection (intestine) is required. If neighboring structures are involved, en-bloc resection should still be contemplated. It is mandatory that the resection achieves negative margins verified by intraoperative frozen section examination, since the presence of residual disease negatively influences survival(S. Singer et al;2002). The 5‐year survival rate after surgery amounts to 28–65%(Debol SM et al;2001 ,Blay JY et al;2005). It is not necessary to resect the regional lymph nodes during the operation, because gastrointestinal stromal tumors do not metastasize to the regional lymphatic system.

2. Surgery

Primary GIST may occur anywhere along the GI tract from the esophagus to the anus(Judson I et al; 2002). The most frequent site is the stomach (55%), followed by the duodenum and small intestine (30%), esophagus (5%), rectum (5%), colon(2%), and rare other locations.

2.1 Treatment of the non-metastatic disease approach to the primary lesion (stomach)

The radical surgical treatment is the most effective treatment option for GIST. The 5‐year survival rate after surgery amounts to 28–65%(R. P. DeMatteo et al;2000). It is not necessary to resect the regional lymph nodes during the operation, because gastrointestinal stromal tumors do not metastasize to the regional lymphatic system. Lymphatic metastasis rarely occurs (0–3.4%) in patients with GIST(Tashiro T et al; 2005). It is mandatory that the resection achieves negative margins verified by intraoperative frozen section examination, since the presence of residual disease negatively influences survival(S. Singer et al;2002). More recently, there has been a move to laparoscopic surgery, particularly for gastric GIST. One series of 50 consecutive patients showed this approach was associated with low morbidity and short hospitalization. All resections had clear margins and the long term disease free survival was 92%(Novitsky YW et al;2006). Current recommendation is that laparoscopy should be restricted to the treatment of small lesions (up to 5 cm) due to the possibility of tumor rupture as a result of the manipulation of larger lesions(Guitierrez JC et al;2007). Current NCCN guidelines do not contain a clear statement on whether surgery for GIST should be performed laparoscopically or through open surgery but recommend that surgery should produce minimal surgical morbidity(National Comprehensive Cancer Network (NCCN);2008). Recently, a new technique of endoscopic full-thickness resection using a flexible stapler was described. This approach seems particularly useful in tumours of the posterior distal part of the stomach(G. Kaehler et al;2006).

2.2 Treatment of the non-metastatic disease approach to the primary lesion (small intestine, duodenum and esophageal GISTs)

GISTs of the small intestine with histopathologic features including mitotic counts >5/50 HPF, high cellularity, absence of a predominant organoid growth pattern, absence of skeinoid fibers, presence of severe nuclear pleomorphism, presence of mucosal infilatration, and tumor cell necrosis have been significantly associated with an adverse outcome in the literature (Tworedk JA et al; 1997, Chang MS et al;1998). The treatment of choice is the complete resection of the tumour.(Figure 2) With regard to local invasion and tumor perforation, a tumor that has invaded a contiguous organ is considered to be advanced and associated with poor outcome(Shiu MH et al;1982, Ng EH et al;1992). Local invasion and tumor perforation were associated with poor DFS; although all gross disease was removed, these conditions were similar to those that occur with incomplete resections. Unlike therapy of mucosa and submocasa derived duodenum tumor, pancreas or duodenum resection is not required in therapy of duodenal stromal tumor which is tumorectomy. Unique treatment option of duodenal GIST is not Pancreatico-duodenectomy. Pancreas preserving segmental duodenum resection may be useful, comfortable and safe especially for the third

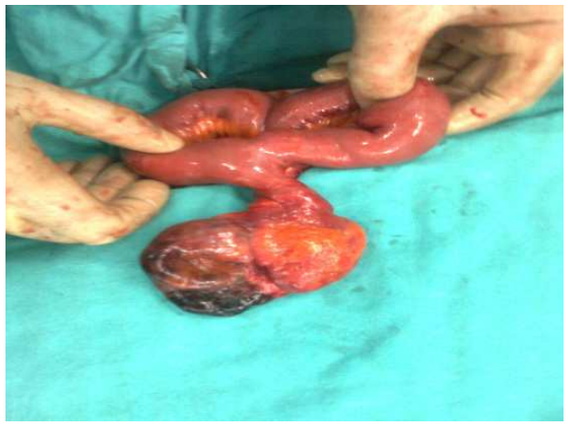

Fig. 1. Intraoperative picture showing tumour and Meckel's diverticulum.
(Archived by SELİM SÖZEN)

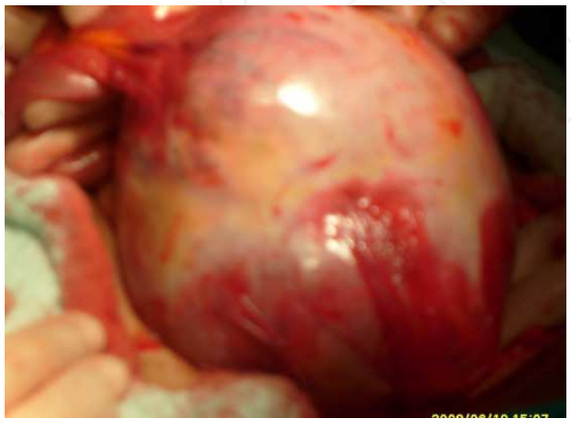

Fig. 2. The well-circumscribed lesion of the ileum before its removal.
(Archived by SELİM SÖZEN)

part GIST of duodenum. Esophageal tumors are usually small and asymptomatic, larger lesions present with dysphagia, and sometimes they may be found accidentally, as an abnormal mediastinal shadow on chest X-ray. Relevant literature reports only a few cases of these kinds of tumors, some treated with esophageal resection and others treated with enucleation (Spinelli GP et al;2008).

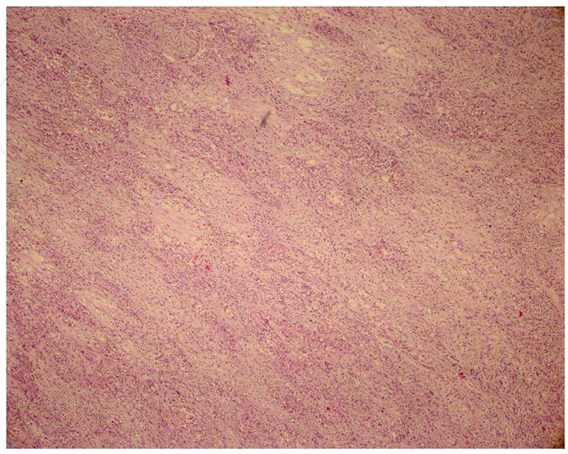

Fig. 3. Histopathology slide after Immunostaining for C-Kit; Tumour cells show positivity after C-Kit staining, which suggests GIST. (Archived by SELİM SÖZEN)

3. Small intestine

The clinical presentation is variable and depends on tumor size and anatomic site. Their submucosal location can produce local obstructive symptoms, particularly when arising in the oesophagus or the small intestine. Vague upper abdominal pain, fullness, GI bleeding, palpable mass are other modes of presentation whereas sometimes they are found incidentally during barium studies, endoscopy or abdominal scans performed for other reasons(Roberto Logrono et al;2004). According to some authors, visceral obstruction is a rare occurrence even in the presence of extensive peritoneal metastatic disease(Burkill GJC et al;2003). Although the diagnostic procedure includes several examinations, such as barium examination of the gastrointestinal track, computer tomography and angiography(Fang SH et al;2004) , none of them can establish the correct diagnosis with 100% certainty. The preoperative percutaneous fine needle aspiration of the tumor for diagnostic purpose is not indicated because of the danger for potential intraperitoneal migration or tumor rupture (Fang SH et al;2004). Recently, several studies pointed out the significance of endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of GIST with a reported accuracy of 89% (Eloubeidi MA, et al;2004). On the other hand, positron-emission tomography (PET) with 18F-fluoro-2-deoxy-D-glucose is a very useful tool for the postoperative follow-up of patients receiving imatinib(Gelibter A et al;2004). The treatment of choice for GISTs is the surgical excision of the tumor. All tumors must be completely resected (R0 resection), where possible, including the tissues that are infiltrated, while systemic lymph node dissection is not recommended by many authors(Chen TW et al; 2005, Aparicio T et al;2004). Complete surgical resection is connected with 48-65% five-year survival. Partial resection must only be performed in case of large tumors, for palliative purposes or for the control of symptoms or complications such as compression of other

organs, hemorrhage, or pain(Connolly EM et al;2003). The clinical presentations of GISTs of small bowel are variable and depend on the tumor size and anatomic site. In the review of Miettinen and Lasota(Miettinen M et al;2006) the most common presentation of GIST is reported as GI bleeding. The tumors smaller than 2 cm in size are generally asymptomatic and larger tumors may present with upper abdominal pain, palpable intra abdominal mass, vomiting, weight loss, and perforation or rupture. Computed tomography or magnetic resonance investigation is useful in tumors larger than 2 centimeters(Lupescu IG et al;2007, Spivach A et al;1999, Abbas M et al;2008). Endoscopic examinations fail in the diagnosis of GISTs originated from the small intestine. The long term survival is 50% at best. These tumors are believed to be potentially malignant lesions with an average rate of 20–25% of gastric and 40–50% of small intestinal localization. Metastases commonly develop in the abdominal cavity and liver; rarely, in bones, soft tissues, and skin (Abbas M et al;2008,Bucher P et al;2006, Miettinen M et al;2006). Prognostic factors for GISTs are the age, anatomic location, mitotic rate, and tumor size(Bucher P et al;2006, Efremidou EI et al;2006). Chemotherapy and radiotherapy do not increase the survival time. Radiotherapy is indicated in intraperitoneal hemorrhage and maintaining analgesia in unresectable tumors. Imatinib, a selective inhibitor of tyrosinekinases, is a hope promising drug, which is the first effective treatment for non-resectable or metastatic GISTs. Furthermore, imatinib is indicated in intraperitoneal perforated or ruptured GIST due to the possibility of peritoneal soiling (Efremidou EI et al;2006, Karagülle E et al;2008).

4. Duodenum

Duodenal GIST usually present with vague abdominal pain(50%–70%) or they bleed into the lumen(20%–50%)(Sturgeon C et al;2003, DeMatteo RP et al;2000). Second part of the duodenum seems to be the common site of duodenal GIST and most of them will require pancreatoduodenectomy for complete resection(Winfield et al;2006). Completely resected GIST has a five year survival of 30%–80%(Casper ES; 2000). Incompletely resected tumors have a high recurrence rate(upto 90%). Historically Unresectable/metastatic GIST has a median survival of 12 months(Roberts PJ et al;2002). Imatinib mesylate, a specific tyrosikine kinase inhibitor has produced a paradigm shift in the treatment of GIST, due to the targeted molecular therapy. Imatinib produce sustained clinical response in more than 50% of the patients with advanced GIST and one year survival in these patients was 88%(Demetri GD et al;2002). Surgery with negative surgical margins and no tumor rupture is a necessary and adequate means of treating such tumors. Extensive lymph node dissection is unnecessary, because GISTs rarely metastasize to the regional lymph nodes(Pidhorechly I et al;2000, Emory TS et al;1999, Dematteo RP et al;2000, Pieri JPEN et al;2001). When technically feasible, this makes duodenal resection preferable to pancreatoduodenectomy(Uehara K et al,2001). However, the optimal surgical treatment for duodenal GISTs has never been fully assessed. Recent anatomical knowledge of the head of the pancreas(Sakamoto Y et al;2000) has facilitated various methods of pancreatic resection for low-grade malignancies (52,53,54 Nakagohri T et al;2000, Thayer SP et al;2002, Sakamoto Y et al; 2002), and duodenal resection preserving the pancreatic head can now be performed safely.

5. Colon and rectum

GISTs are an extremely rare subset of colonic tumors that are difficult to distinguish grossly from the commonly encountered adenocarcinoma. GISTs are found commonly in the

stomach (60 – 70%) and small intestine (20 – 30%), and rarely in the colon and rectum (5 – 10%) and esophagus (less than 5%).(Graadt van Roggen JF et al;2001). When in a colonic location, about two thirds of these GISTs occur in the left or transverse colon(57 Miettien M et al;2000) . These tumours predominantly occur in middle aged or older persons, the median age at presentation being sixty years, and are uncommon below forty years of age(Graadt van Roggen JF et al;2001, Mukhopadyay S et al;2002). Males and females are affected equally, but a peculiar subset occurs in female patients below the age of 21 years, either singly or in association with pulmonary chondromas and extra-adrenal paraganglionomas (Carney's syndrome)(Graadt van Roggen JF et al;2001).

Grossly, GISTs may vary greatly in size. Smaller tumours (2 cm or less) are usually asymptomatic and are usually detected incidentally during investigations or at surgery for unrelated pathology. These often exhibit a benign nature, but at times, may present with metastasis to the liver and lungs(DeMatteo RP et al; 2000). Larger tumours usually behave like malignant tumors, and may present with abdominal pain and gastrointestinal bleeding due to ulceration of the overlying mucosa, abdominal mass, or with nonspecific symptoms such as weight loss, vomiting, fever and anemia. Depending on the site, the tumor may also present with obstruction, dysphagia, altered bowel habits, or rarely, obstructive jaundice(Burkill GJC et al;2003, Ludwig DJ et al;1997). Complete gross excision of the tumor is the treatment of choice; routine lymph node excision is not recommended since they are rarely involved. However, it must be stressed here that in the absence of a clear cut diagnosis of colonic GIST, surgery must proceed as if for adenocarcinoma and radical clearance should be done. Care must be taken to avoid tumour rupture during surgery, since this has been implicated as one of the causes of recurrence(Mukhopadyay S et al;2002, DeMatteo RP et al; 2000). Colorectal GISTs are relatively rare, frequency being reported at approximately 5%(Miettinen M et al;2000).Moreover, the pathobiological features of malignant GISTs of the colon remain unclear. Most rectal tumours are of epithelial origin. Only a small number of rectal tumours originate from the smooth muscle cells in the rectal wall. Such stromal tumours are either benign (leiomyoma) or show malignant characteristics (formerly known as leiomyosarcoma), and may have a submucosal, subserosal or intraluminal location(Dufresne AC et al; 1999, Buckley JA et al;1998). Malignant stromal tumour of the rectum represents 0.5% of all rectal tumours and 7% of gastrointestinal stromal tumours (GIST)(Wolf O et al;1994, Randleman CD Jr et al;1989). Macroscopically the tumour originates from the muscularis propria of the rectum, and the mucosa generally remains intact. Microscopic findings consist of a proliferation of spindle cells arranged in fascicles(Dufresne AC et al;1999). On endorectal ultrasound, a GIST is seen as a hypoechoic, heterogeneous polycyclical mass, which at high resolution ultrasound imaging is shown to originate from the muscularis propria(Dufresne AC et al; 1999, Marcy PY et al;1993). Endorectal ultrasound is very helpful in defining the extent of disease(Hsieh JS et al;1999). CT appearances of GIST located in the rectum do not differ from those in other parts of the digestive tract. On nonenhanced CT, a GIST presents as a welldelineated, lobulated, homogeneous soft tissue mass with low attenuation and sometimes with calcification(Buckley JA et al;1998, Pannu HK et al; 1999). Although GIST confined to the rectal wall can be treated by local excision(Cailliez-Tomasi JP et al;1999), the prognosis of GIST of the rectum is poor and the 5-year survival rate ranges from 22% to 66% for high grade malignant and low grade malignant types, respectively(Witzigmann H et al;1995). Tumours with mitotic counts higher than 5 per 10 high power fields, and a size larger than 10 cm have an especially significant risk of recurrence(Miettinen M et al,1998).

GIST's of the rectum are most often clinically silent. Symptoms are not specific but highly size-related : the tumors ranged from small asymptomatic intramural nodules to larger masses that bulge into the pelvis, causing compressive symptoms (pain, constipation, occlusion), or rectal bleeding (sudden or occult) together with anemia and urinary symptoms(LI C. F et al;2005). Endoscopy shows a sub-mucosal mass bulging under a normal or ulcerated mucosae. Per-endoscopic guided biopsies can be performed but remained negative in more than 50% of cases(BLAY J. Y et al;2005). Ultra-sonic endoscopy may revealed a hypoechogenic circular lesion with clear edges. Percutaneous needle biopsies have been suggested to be helpful in the diagnosis but may expose to a non-negligible haemorrhage risk and a possible peritoneal diffusion of the tumor(BLAY J. Y et al; 2005).

Timing for surgery is still controversial, although some authors have published indications for surgery(CHANGCHIEN C. R et al;2004): lesions including malignant criteria (Group I), lesions less than 3 cm long with irregular edges and heterogenicity at echoendoscopy screening (Group II). If patients are at high operative risk, periodic biopsies and observation are mandatory. Lesions without malignant criteria (Group III) require echoendoscopy observation every 6 months. lymph node metastasis is considered an infrequent event in the natural evolution of these tumor. Although a limited lymphadenectomy is considered to be the procedure of choice. In this instance, a total mesorectum excision (TME), as strongly recommended for adenocarcinoma, is not mandatory for the resection of rectal GIST. More, extended lymph node dissection doesn't contribute to the improvement of survival(APARICIO T et al;2004).

6. Esophageal GISTs

The presenting signs and symptoms of esophageal GIST depend on the size and location of the tumor. Typically, they cause dysphagia, suggesting the possibility of carcinoma(Miettinen M et al;2000). Less commonly they are detected as large mediastinal masses involving the esophagus. Other manifestations include cough, gastrointestinal bleeding, and weight loss. Occasionally, it may be an incidental finding. There is little information in the literature describing the radiologic appearance of esophageal GISTs. In Miettinen's series, esophageal GISTs ranged from 2.6 to 25 cm in size and were most commonly located in the distal third of the esophagus . This was a distal esophageal mass that distorted and widened the esophageal lumen on barium esophagram(Miettinen M et al;2000). Although complete surgical resection is the standard treatment for localized resectable GISTs, the optimum extent of resection has not been determined. Surgery for esophageal tumors is either enucleation or esophagectomy,with the latter having a higher morbidity rate. Enucleation with clear dissection is sufficient for small-sized,well-capsulated tumors confined to the esophageal muscle layer, without mucosal lesions. Preoperative biopsy and esophagectomy, however, should be considered for larger tumors or tumors accompanied by mucosal lesions. Clear resection margins are also important. In performing enucleation, we shelled out the tumor carefully. with Endo Peanut (U.S. Surgical, Norwalk, CT). And rather than assessing margin status, we determined whether the tumor capsule was maintained in intact condition, as well as confirming mucosal integrity, by intraoperative endoscopic examination. During esophagectomy the external lateral margin as well as the proximal and distal resection margins was confirmed by pathologic examination. Although small intestinal and gastric GISTs may be resected with segmental or

wedge resections, esophageal GIST resections are essentially limited to either simple enucleation or esophagectomy. Successful surgical treatment of GISTs depends on complete local resection. The approach to esophagectomy for GISTs should minimize blunt or blind dissection as this will not reliably include maintaining the thin potential barrier of pleura that may overlie extramucosal tumor. Additionally, poor tumor integrity and lack of esophageal serosa increase the risk of tumor rupture with blunt dissection. Transhiatal esophagectomy would likely violate tumors of the distal and midesophagus that extend beyond the muscularis and cannot be recommended. A transthoracic en bloc resection of the pleura overlying the esophagus and any involved surrounding tissues, including diaphragm, is advisable to avoid microscopically or macroscopically incomplete resection. A left thoracoabdominal approach is advocated for larger tumors at the gastroesophageal junction as this will allow excellent visualization of the parahiatal tissue. Management guidelines for GISTs have been defined by consensus of the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology(Demetri GD et al;2006, Blay JY et al;2005). The NCCN guidelines state that enucleation of small (_2 cm) esophageal GIST may be acceptable and that small intraabdominal tumors might be resected laparoscopically.

6.1 Treatment of the non-metastatic disease approach to the primary lesion (extra gastrointestinal tumors and Meckel's diverticulum)

GIST also occur in the extra-intestinal abdominopelvic sites such as the omentum, mesentery, or retroperitoneum. A small number may originate not from the omentum, but from outside the gastrointestinal tract; these are designated extra-GISTs (EGISTs)(Reith JD et al;2000). The reported cases of extra-gastrointestinal stromal tumors (EGIST) have included omental, mesenteric, and retroperitoneal tumors. The cellular origin of GIST from the interstitial cell of Cajal (ICC) raises the question of whether these EGIST are truly an entity analogous to GISTs. It is not well known if extra-gastrointestinal stromal tumors (EGIST) originate from pacemaker cells outside of the GI tract or if mesenchymal cells have the ability to recapitulate the phenotype. Sakurai *et al.*(Sakurai S et al;2001), published their results on the cytological, immunohistochemical, and genetic analysis of 5 omental mesenchymal tumors in 2001. They found all five tumors to be positive for CD117 and CD34 staining, while all were negative for smooth-muscle cell markers. More importantly, the authors reported finding KIT immunoreactive CD117 and CD34 cells within specimens of omentum(Sakurai S et al;2001). These findings and those of Yamamoto *et al.*(Yamamoto H et al;2004) underscore the fact that histologically, EGISTs have a similar appearance to GISTs, and that EGIST is a distinctive entity, different from leiomyosarcomas(Miettinen M et al;1999). The most common mutation of the KIT gene occurred in exon 11 in Sakurai's and Yamamoto's experience(Sakurai S et al;2001, Yamamoto H et al;2004).

GIST arising from Meckel's diverticulum are extremely rare(Johnston AT et al;2001). (Figüre 1,3). The tumors are infrequent and observed only in 0.5–3.2% of the Meckel's diverticula. Of these, 12% tumors are GIST. Radiological appearances of GIST may include asymmetrical thickening of the bowel wall initially, but more commonly an exophytic soft tissue mass with relatively well defined margins is seen(Macari M et al;2001). Areas of necrosis are present in up to 70% of tumours(Nicola´s AI et al;1999) and particularly in larger tumours that frequently undergo central necrosis, due to rapid growth, and subsequent ischaemia (Macari M et al;2001). These also demonstrate heterogeneous contrast enhancement (Macari

M et al; 2001). Areas of calcification and haemorrhage are seen within 7% and 64% of tumours, respectively(Nicola´s AI et al;1999).Surgical resection is the treatment of choice for these tumors, which usually have a poor prognosis. Extragastrointestinal stromal tumors arising in the pancreas are extremely rare. A primary localization in the pancreas has rarely been reported on cytology. The clinical symptoms include abdominal pain, early satiety, flatulence, ileus, bleeding, anemia, and weight loss. It can be diagnosed incidentally by radiologic imaging(Miettinen M;2001). There was a distinct female predominance, age ranging from 38 to 72 years including all surgical pathological cases (mean age 55 years). The majority occurred in the body and tail of the pancreas with an average size of 12 cm(Miettinen M;2001). Extraintestinal gastrointestinal stromal tumors (EGISTs) are uncommon and unique neoplasms, usually involving the mesentery, omentum, retroperitoneum, rarely bladder(Nagase S et al;2007) and inguinal hernial sac. EGISTs arising in the rectovaginal septum and presenting as a recurrent vaginal mass is unusual. The current definitive treatment for EGIST is surgical resection, but in majority of the patients, the tumors recur despite complete resection(Dematteo RP et al;2000). An accurate diagnosis is mandatory for EGIST as these are tumors with an aggressive course and a potential for recurrence inspite of complete surgical excision. In addition, the treatment strategy includes kit tyrosine inhibitor, Imatinib which is used for recurrent and advanced disease.

6.2 Treatment of the metastatic and relapsed disease

GISTs have a high risk of metastatic relapse. The usual site of recurrence is the liver (65%), the peritoneal surface (50%) and both (20%). GIST's response to conventional chemotherapy is very poor (<10%), while radiotherapy is only used for analgesic purposes or in cases of intra peritoneal hemorrhage (Gupta P et al; 2008). Surgery has limited efficacy in the treatment of recurrent and metastatic GIST. In the past years, there has been no efficient method to cure recurrent GIST. GIST is also resistant to both chemotherapy and radiotherapy. The development of imatinib has improved the management of GIST. Even though imatinib is effective for most patients with a metastatic GIST, the development of resistance to the drug is a problem that has been increasing(Heinrich MC;2006). Based on the satisfied result for advanced GIST, surgery combined with imatinib adjuvant therapy may give a hope for the patients with high-risk GISTs. A prospective multicenter trial in high-risk patients after complete gross resection of the tumor revealed that imatinib 400 mg daily can reduce the risk of recurrence and metastasis(Zhan WH et al;2006). Based on the satisfied result for advanced GIST, surgery combined with imatinib adjuvant therapy may give a hope for the patients with high-risk GISTs(Zhan WH et al;2006). Although there are several reports of combination therapy of imatinib with surgery for the advanced GIST with metastases, most of the studies used imatinib eoadjuvantly, and the surgery was performed after the reduction of tumor burden by imatinib therapy. For tumours with a larger diameter and/or unfavourable location, primary wedge resection is often not possible and total or subtotal gastrectomy would be required for resection with tumour-free margins. For these cases, the NCCN guidelines(National Comprehensive Cancer Network (NCCN);2008) and ESMO recommendations(P. G. Casali et al;2008) suggest neoadjuvant imatinib therapy to decrease tumour size, thus fallowing for organ-preserving surgery.

7. Laparoscopic resection

The latest ESMO Clinical Recommendations consider a laparoscopic approach "if cancer surgery principles are respected." (P. G. Casali et al;2008). Current NCCN guidelines do not contain a clear statement on whether surgery for GIST should be performed laparoscopically or through open surgery but recommend that surgery should produce minimal surgical morbidity(National Comprehensive Cancer Network (NCCN);2008). Current recommendation(Guitierrez JC et al;2007) is that laparoscopy should be restricted to the treatment of small lesions (up to 5 cm) due to the possibility of tumor rupture as a result of the manipulation of larger lesions(Guitierrez JC et al;2007). Although oncologic success has been reported with laparoscopic resections(Catena F et al;2008), studies with a larger number of cases and long-term follow-up are required in order to define the actual role of laparoscopy in the treatment of this neoplasm. Laparoscopic surgery as the new "gold standard" in the treatment of localised GISTs of the stomach, it would be highly desirable to have results from one or several randomised controlled trials(S. Sauerland et al;1999). As in other laparoscopic procedures, the existence of a "learning curve"must be assumed and it can be expected that operation times further decrease with growing experience(S.Avital et al;2006, M. Lim et al;2006, R. B. Shin et al,2005).

8. Conclusion

Although rare among tumors involving the gastrointestinal system, gastrointestinal stromal tumors are the most frequent mesenchymal tumors. Recommended treatment regimens need to be updated as the multidisciplinary approach to both diagnosis and treatment of the tumor gains importance. Surgery still holds place as the most important constituent of multidisciplinary in current algorythms and ongoing studies. The introduction of imatinib in clinical practice(Joensuu H et al;2001). changed not only the survival of metastatic GIST patients, but also meant breaking through well established paradigms. Nevertheless, despite the advances and the encouraging outcomes with the use of imatinib, the surgeon still has a key role in the management of GIST(Linhares E et al;2006).

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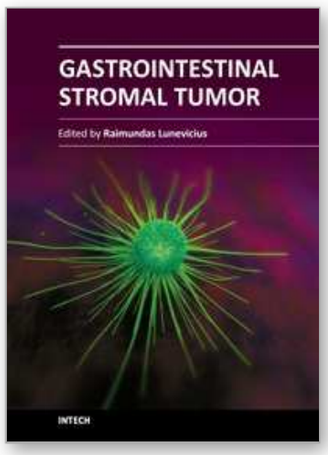

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Almost 30 years have gone by since the postulation that GISTs derive from mesenchymal stem elements, and only 15 years have gone by since the definitive detection of origin of GISTs. Research in the last decade was more focused upon the justification of imatinib mezylate therapy in GISTs and clarification why a secondary resistance that occurred during the kinase inhibitors therapy. The era of therapy for GISTs, targeting the primary activating mutations in the KIT proto-oncogene; is being proclaimed as bringing the message of special importance to the pathologist role in multidisciplinary team that are responsible for treating patients with locally advanced or metastatic GIST. This is the first conclusive message forthcoming from this book. On the other hand, the book provides summarised and case-based knowledge on current management of gastrointestinal and extragastrointestinal stromal tumours. We hope that this book may be considered as a worthwhile timely addition to clinical science dissemination, medical education, further basic and clinical research.

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