Duodenal gastrointestinal stromal tumor: From clinicopathological features to surgical outcomes

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Abstract

Duodenal gastrointestinal tumors represent an extremely rare subset of stromal tumors arising from interstitial cells of Cajal. In the last 30 years the comprehension of the pathophysiology and natural history of this previously misunderstood clinical entity, in association with developments in endoscopy, imaging technology, and immunohistochemistry has resulted in novel diagnostic and treatment approaches. This is a comprehensive review of the current data of the literature on the various aspects of the diagnosis and treatment of these tumors. The duodenum is the less commonly involved site for these tumors in the digestive tract. Endoscopy and computed tomography can usually establish the diagnosis, confirmed by immunohistochemical staining and occasionally molecular genetic analysis. Endoscopic ultrasound with fine needle aspiration has been recently found to be the gold diagnostic standard with high sensitivity and specificity rates, diagnosing GIST in up to 80% of patients. Due to the complex anatomy of the pancreatico-duodenal region optimal therapeutic strategy of duodenal GISTs are challenging. Nevertheless surgical resection with microscopically clear resection margins seems to be the only potentially curative treatment for non-metastatic primary GISTs of the duodenum. Imatinib mesylate plays a key role in the management of GISTs both as neoadjuvant therapy and in patients with recurrent and metastatic disease. Meanwhile, the advances in the comprehension of the pathophysiology and natural history of this previously misunderstood clinical entity as well as the treatment of these tumors may render feasible, in the near future, the advent of newer and more effective treatment options.

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors arising in the gastrointestinal smooth-muscle muscles in the 1983 by Mazur and Clark.1 Although GISTs are found throughout the digestive tract, from the esophagus to the rectum, the stomach is the most common site of occurrence in more than half of patients while only 3–5% of GISTs occur in the duodenum.2,3 Due to the low incidence and to the complex anatomy of the pancreatico-duodenal region and to the high variability of clinical presentation, the diagnostic assessment and the optimal therapeutic strategy of duodenal GISTs are challenging.4,5 In the last 30 years the comprehension of the pathophysiology and natural history of this previously misunderstood clinical entity, in association with developments in endoscopy, imaging technology, and immunohistochemistry has resulted in novel diagnostic and treatment approaches.6 Several reports have proposed to address clinical and diagnostic characteristics, as well as prognostic factors and therapeutic options for these rare duodenal tumors.5

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In this article, we present the current data of the literature on the diverse aspects of the clinico-pathologic features and the management of GIST located at the duodenum in a comprehensive review.

Methods

A literature search in PubMed, Medline, Cochrane and Ovid databases of all articles published between January 1, 1983, and December 31, 2014 with the medical subject headings (MeSH) keywords “duodenal GIST”, “duodenal gastrointestinal stromal tumors”, “duodenal gastrointestinal stromal tumors of the duodenum”, “gastrointestinal stromal tumors of the duodenum”, “gastrointestinal stromal tumors of the duodenum”, “duodenum GIST”, “benign duodenal tumors” and “benign duodenal tumors” was carried out. The key words were used in all possible combinations to retrieve the maximal number of articles. All types of study designs were included. Exclusion criteria included: articles in non-English language, experimental studies in animal models, abstracts and editorials. The bibliography of each selected article was reviewed for other potentially relevant citations.

Epidemiology

The true epidemiology of gastrointestinal stromal tumors has been unclear until the 2000, when the diagnostic coding of GISTs was introduced in the third edition of the International Classification of Disease for Oncology (ICD-O).7 All population-based epidemiologic data obtained and published before this period included non-GIST benign and malignant mesenchymal lesions as well as not further classified abdominal neoplasms resulting in an overestimation.7,8

Nevertheless, an increasing GIST incidence was demonstrated in a Norwegian database over three decades, with 1.8 cases per million in the 1980s and 12.5 per million during 2000–2004, with an estimated GISTs prevalence of 129 cases per million.9 Also a Dutch registry revealed a similar increase in annual incidence of 2.1 cases per million in 1995 to 12.7 per million in 2003,10 as well as recent data from the United Kingdom that estimate the GIST annual incidence from 1.32 to 1.50 cases per million.11,12 In this way the reports from Sweden and Hong Kong have estimated prevalence at 12.9 cases per million8 and 13.4–15.6 cases per million,13 respectively. These increases in incidence are probably due to progresses in radiographic imaging, endoscopic and immunohistochemical diagnostic tools.

Although most studies report no differences regarding the gender,14,15 a population-based consecutive 52 cases of GIST from Norway found a female prevalence (62% female versus 38% male)9 while an higher risk in male resulted from a study on 6142 GISTs in the United States (rate ratio (RR) = 1.35).7 GISTs were also more common in non-Hispanics than Hispanics (RR = 1.23), and blacks (RR = 2.07) or Asians/Pacific Islanders (RR = 1.50) than whites.7,16 Gastrointestinal stromal tumors are typically diagnosed in people between 60 and 70 years old (median age 60–67 years) with 75% of cases occurring in patients over the 50 years.9,13,17 Furthermore, although these neoplasms can arise in patients of any age, the occurrence before 30 years is extremely rare.18

All these epidemiological data should be correlated to the real entity of duodenal GISTs, that account for 1–5% of all gastrointestinal stromal tumors1,6,14,17,19 still representing approximately 30% of primary duodenal tumors.2

Clinical presentation

Similarly to gastrointestinal stromal tumors of other digestive tracts, duodenal GISTs may occur as part of an hereditary-familial syndrome, such as Carney’s triad (GIST, paraganglioma, pulmonary chondroma),20 type 1 Neurofibromatosis (cutaneous café-au-lait spots, axillary freckling, skeletal dysplasias, both benign and malignant nervous system tumors, and predominately spindle cell type of multifocal GIST),21–23 Von Hippel Lindau disease (central nervous system and retinal hemangioblastomas, clear cell renal carcinomas, pheochromocytomas, pancreatic neuroendocrine tumors, pancreatic cysts, endolymphatic sac tumors and epididymal papillary cystadenomas), or as a recently identified genetic syndrome involving a combination of multifocal GISTs and multiple functional paragangliomas with autosomal dominant transmission,24 accounting for 5–10% of all GISTs.3 Otherwise they represent sporadic disease.

Duodenal GISTs arise at the central layers of duodenal wall and can extend through the serosal layer spreading to adjacent organs with displacement free from neoplastic invasion, as well as through the mucosa leading to an intramural mass centrally ulcerated with consecutive bleeding.15,25,26 The clinical manifestations of duodenal GISTs are non specific and extremely varied depending on their size, growth pattern, the presence or absence of mucosal ulceration and location.2,15,26 Furthermore these tumors rarely cause symptoms and are often diagnosed incidentally, especially for small lesions (generally less than 2 cm) without mucosal ulceration, or for GISTs that invade through the serosa and spread extraluminally.25

For symptomatic lesions the gastrointestinal bleeding including melena, hematemesis or symptomatic anemia, and abdominal discomfort or epigastric pain represent the most commonly reported symptoms.2,24–30 Particularly, compared to other tumor localizations, duodenal GISTs are associated with a dramatically increased incidence of digestive bleeding, accounting in 75% compared to 54% of gastric and 28% of ileo-jejunal GISTs.31

Although the duodenal GISTs are mainly located in the second portion of the duodenum and less often the third, fourth, and first portions,2,26 symptoms caused by obstruction of the periampullary structures such as obstructive jaundice and cholangitis are very rare.2,25,32,37 Sporadically
some Authors also described back pain, intestinal obstruction and palpable mass.

**Diagnosis**

**Histopathology**

From a pathologic perspective duodenal GISTs are not different from other GISTSs. Over the last decades the histopathologic knowledge had uncommon development: in the 1983 Mazur and Clark introduced the term “gastrointestinal stromal tumors” to identify the main group of mesenchymal gastrointestinal tract tumors that could not be distinguished from smooth muscle or neural tissue origin tumors. In the 1998 Kindblom found that GISTs show phenotypic characteristics of the interstitial cells of Cajal, innervated cells associated with the Auerbach’s plexus. Macrosopically the GISTs cannot be distinguished from malignant neoplasms. They present well circumscribed margins, with overlying mucosal surface that can appear normal or lifted up and ulcerated. The cut surface is generally granular with hemorrhage, necrosis, or cystic features. Microscopically these tumors are composed of thickly packed spindle cells with abundant fibrillar cytoplasm and interposed delicate thin-walled vessels predisposing to stromal hemorrhage. The cells vary in size and shape to a minor degree and are typically arranged in three different cellular growth patterns, spindle cell, epithelioid or mixed, with limited prognostic relevance. It is suggested, in fact, that the mitotic threshold for malignancy is lower for epithelioid compared with spindle cell growth pattern. Characteristically, GISTs in the duodenum often present with spindle cell differentiation, which is more frequent than epithelioid cell differentiation or mixed types. Furthermore the histopathological characteristics of duodenal GISTs show peculiar features compared with gastric and small intestinal cases. First of all, GISTs of the duodenum are relatively smaller in size resulting the median size of these lesions of 4 cm compared to a median size of gastric and small bowel GISTs of 6—7 cm, respectively. Secondly, duodenal GISTs are diagnosed earlier and need less invasive therapeutic approach being smaller. In addition, due to the lower median mitotic count of <5 per 50 high power field (HPF) found in 72—75% of duodenal stromal tumors as opposed to median mitotic count of >5 per 50 HPF found in more than 30% of GISTs from other sites of the gastrointestinal tract, duodenal location may also imply a better prognosis.

**Immunohistochemical features**

Although GISTs are the most common mesenchymal tumors of the gastrointestinal tract, the differential diagnosis must include all the other neoplasms occurring in this location. The diagnosis of gastrointestinal stromal tumors is supposed histologically and confirmed by immunohistochemical staining and occasionally molecular genetic analysis which represent invaluable tools in distinguishing these tumors among others. The most sensitive and universal marker of GISTs is CD117 (c-kit) which is expressed in more than 95% of these tumors. However, due to the CD117 false positivity and to the approximately 5% of CD117 negative GISTS (generally with alpha-type platelet-derived growth factor receptor-PDGFRα mutations) a complementary stain with similar sensitivity and specificity to CD117 staining is needed. Polyclonal antibodies against DOG1 (discovered in GIST 1), a gene found to be overexpressed in GISTS, have been found to mark GIST independently of CD117/PDGFRα mutational status. In addition CD34, another antigen recommended as a GISTs marker, is found in approximately 60—70% of GISTS. Finally, other proteins such as smooth muscle actin, calponin, caldesmon, nestin, S100 and desmin have been identified as potential markers of GIST, but they are only very rarely expressed and are nonspecific for the accurate diagnosis. As of late a protein kinase theta, a protein involved in neuronal differentiation processes, has been suggested to be an undeniable marker of GISTS.

**Molecular features**

The KIT gene product is a transmembrane growth factor receptor with tyrosine kinase activity, the c-kit protein and its antigenic determinant CD117, which is the activator of an intricate cell-signaling cascade that control essential cell functions in tumorigenesis, including proliferation, adhesion and differentiation. A mutation in the c-kit proto-oncogene (chromosome 4q11-q12), found in most GIST, leads to constitutive activation of the KIT receptor with continuous stimulating action for proliferation. In approximately 5—10% of GISTS, KIT staining may be negative and the mutational analysis of KIT may show mutations of exon 11 of the gene in chromosome 4 in 68% of cases and of exon 9 in 11% of GISTS, resulting in a poorer outcome compared with GIST lacking these mutations. In addition, a small percentage of GISTS (0.6—4%) contain mutations of KIT exons 9, 13 or 17 in the same chromosome, as well as mutation of the platelet-derived growth factor receptor alpha (PDGFRA). Finally other important cell-cycle proteins such as the tumor suppressor proteins ki-67, p53 and p16, are frequently associated with the pathogenesis or progression of more malignant GISTS. Yang WL et al. (reported that duodenal GISTS differ from other GISTS (gastric and small bowel)) in the expression of these prognostic factors, resulting in a lower prevalence of p16 loss and ki-67 which are both indicated as negative prognostic factor. Probably also for these reasons duodenal GISTS usually have prognosis better than GISTS from other sites of the gastrointestinal tract, even if further observational studies are needed to confirm the prognostic meaning of tumor suppressor proteins.
Prognostic factors

It is difficult to predict GISTs metastatic potential: the National Institutes of Health (NIH) Consensus workshop for GISTs, held in 2001, proposed a risk stratification dividing tumors into very low — low — intermediate — high “risk of recurrence after complete resection” categories based on tumor size (with threshold levels of 2 cm, 5 cm and 10 cm) and mitotic index (number of mitoses per 50 high-power fields (HPFs) with threshold levels of 5, 10 and more than 10). Prognostic tools include the measurement of cellular proliferation by means of markers such as proliferating cell nuclear antigen (PCNA) or Ki-67, assessment of DNA ploidy, and telomerase activity.56,57

Even if Yan et al.57 found no statistical difference in survival based on primary tumor location of 69 cases of GIST, tumor location has been considered an important independent prognostic factor, as patients with small bowel and gastric GIST present a higher rate of recurrence than those with duodenal tumors,28 probably due to the variation in the proliferation mechanisms of different subsets of Cajal-like precursor of the entire digestive tract.59 Also symptomatic presentation, in contrast to incidentally diagnosed GISTs, was independently associated with a poorer outcome and significantly decreased disease-specific 5-year survival,60 resulting duodenal GISTs with better prognosis.2,25,27,32

Diagnostic evaluation

Gastrointestinal endoscopy remains the most common procedure in diagnosing most duodenal GISTs. Even though duodenoscopy are effective to diagnose neoplasms with the typical characteristics of mucosal ulceration or an intramural mass with a centrally ulcerated umbilication.2,25,27 some problems occur for relatively small lesions without the “mass effect” or centrally ulcerated umbilication.2,25,27 It allows forceps biopsy whose role, in ambiguous cases, is still controversial because often reveals only normal mucosa adding few data to the GIST management51 accounting for diagnostic accuracy of approximately 20%.62 Recently, endoscopic ultrasound (EUS) with fine needle aspiration (FNA) to obtain specimens for cytologic examination and immunocytochemical evaluation has been found to be the gold diagnostic standard17 with high sensitivity and specificity rates,63,64 diagnosing GIST in up to 80% of patients.65 EUS can be also performed to clarify the original layer of the intramural lesion.61 Furthermore preoperative histologic diagnosis of GIST might prevent patients from receiving a highly invasive surgical treatment in spite of the theoretical risk for peritoneal seeding of tumor cells by way of the needle tract or tumor rupture during biopsy.66

Alternative diagnostic mean include radiologic examinations such as ultrasound, computed tomography and magnetic resonance imaging, that play an important role in duodenal GIST detection and localization. Ultrasonography may show a homogenous hypoechoic mass in close relation with the gastrointestinal tract in small GISTs and a vascular mass of mixed echogenicity in large GISTs.67 Computed tomography generally revealed a small isodense or hypodense round or oval mass with a clear boundary inside the duodenal cavity and slight uniform enhancement. Large tumor appeared as an irregular and heterogeneous enhancement mass with variable areas of cystic degeneration, necrosis, or hemorrhage.68 Magnetic resonance imaging findings are widely variable depending on factors that affect the signal intensity: tumor necrosis, hemorrhage and cavitation.56 Generally the solid components of GISTs show low signal on T1-weighted images and high signal in T2-weighted images with enhancement following gadolinium administration.67 Despite profound progresses in imaging technology, in several cases reported in the literature the mass was misdiagnosed as ectopic pancreas, neuroendocrine tumor or solid pseudopapillary tumor.58,69

Surgical treatment

Due to the low incidence of duodenal location of stromal tumors, there was no relevant literature to evaluate the best treatment of the duodenal GISTs. According to some small-sample clinical data, surgical resection with microscopically clear resection margins seems to be the only potentially curative treatment for non-metastatic primary GISTs of the duodenum,27,70,71 which differ from duodenal adenocarcinoma for several specific features affecting the surgical management.25 First, local and regional lymph node involvement is infrequent5,25,27,72 as results from the largest clinicopathologic series of duodenal GIST5 on 167 patients in which no lymphatic spread were detected. Secondly, they represent well encapsulated tumors that, also for those categorized at “high risk”, typically show a tendency to displace, but not to invade, surrounding organs.25,73,74 Thirdly, longitudinal submucosal spread is very limited.32 Finally GISTs generally grow opposite the duodenal lumen towards the abdominal cavity.23 In light of such evidences, lymph node dissection as well as extended resection should not lend a survival advantage in non-metastatic duodenal GIST. Furthermore, although the size of surgical margins along the duodenal tract involved are not rigorously defined, clear margins of 1 or 2 cm are recommended,25,73,74 favorably replacing the duodenum extensive resections with more conservative procedures. For these reasons, the most commonly accepted surgical treatment entails margin-negative resection without lymphadenectomy.23,25,27,72

Nevertheless the optimal surgical procedure for duodenal GISTs has not been well characterized since the surgical choice, differently from the stromal tumors arising from the other sites of digestive tract, depends not only on the tumor size but also on the location in the duodenal wall and the proximity to the pancreatic head, common bile duct, ampulla of Vater and the mesenteric root.27,75—77
Therefore the surgical management swings between major resections such as pancreaticoduodenectomy (PD) or pancreas-sparing duodenectomy (PSD) and conservative surgery (CS) including segmental duodenectomy or wedge resection.80,81

Some authors prefer radical procedures when the tumor is located at the medial wall of the second portion of the duodenum and involves the papilla, pancreas or the duodenal bulb, or if the common bile ducts tend to be smaller causing anastomotic stenosis after reconstruction.2,28 On the other hand Bourgouin S et al.79 stated that only the involvement of the pancreatic side was a determinant in the choice of a PD addressing the distance from the tumor to the ampulla as only distinctive parameter to be considered for the surgical decision precisely assessed by means of intraoperative pancreatic ultrasonography or by opening the second portion of the duodenum. Whereas, others support conservative surgery regardless the above mentioned GISTs pathology: wedge resection with primary closure can be performed for small lesions if the resulting lumen is adequate and the ampulla can be preserved2,28 even by laparoscopy or combined laparoendoscopic surgery even if no studies comparing these different approach are still published10,81; segmental duodenectomy with side-to-end or end-to-end duodenojejunostomy may be done for larger tumors that are located in the third and fourth portions of the duodenum29; partial duodenectomy with Roux-en-Y duodenojejunostomy can be performed for larger tumors involving the antimesenteric side of the second and third portion of the duodenum. A lateromedial anastomosis opposite the papilla or papilloplasty with a temporary stent catheter inserted into the papilla to avoid possible postoperative stenosis are reported even after resections for lesions close to the papilla that require the anastomosis just below the ampulla.82 Recently, Downs-Canner S et al.83 reported for the first time a robotic segmental duodenal resection for 2 duodenal GISTs with encouraging results in terms of several technical advantages that facilitate complex resection and reconstruction during periampullary procedures.

Although major resections can provide a wider tumor clearance, they are associated with a longer operative time, a longer duration of hospital stay, and a higher rate of post-operative complications than conservative approaches,2 remaining still complex surgical procedures with high post-operative mortality (up to 16%) and morbidity rates (up to 65%) due to pancreatic anastomatic leakage in most cases.29,34,62,71,84–90 Otherwise conservative approaches contribute to a better quality of life, functional preservation of the pancreas and continuity of the gastrointestinal tract25,27 at the expense of the involved margins risk and the increased risk of local recurrence.71 Moreover the main debate is whether conservative surgery is an oncologically correct alternative to a pancreaticoduodenectomy. Even if duodenal GISTs are mostly described in the literature with several case reports and series about the clinico pathological features and frequency of duodenal GISTs, to the best of our knowledge we have reviewed only eight surgical series comparing PD with a conservative approach as regard the surgical as well as oncologic outcomes.29,34,62,71,84–90 Miettinen M et al.72 in their largest series of 156 patients with duodenal GISTs stated that prognosis was associated with tumor grade. In this review, 84 patients (80%) underwent conservative surgery and 21 (20%) underwent pancreaticoduodenectomy but is not reported the effect of surgical choice on disease recurrence after the operation. Johnston et al.91 retrospectively reviewed 96 patients at five institutions, 58 submitted to conservative approach and 38 to pancreaticoduodenectomy. They concluded that tumor size, mitotic count and an NIH high risk classification represent factors associated with a worse recurrence-free survival rather than surgical approach. Tien et al.71 analyzed nine patients who underwent PD and sixteen who underwent CS. They also found that surgical approach was not correlated to disease recurrence. Summarizing, these data indicate that conservative approach represents a reliable and curative option for a significant subset of patients with duodenal GISTs. Moreover, the disease-free survival rate at 1–3 years after complete resection regardless surgical approach, has been reported to vary from 86 to 100%28 addressing the slightly more favorable prognosis of duodenal GISTs compared to gastric or small bowel GISTs.

### Tyrosine kinase inhibitors

#### Imatinib

Imatinib (Gleevec in USA, Glivec elsewhere; Novartis Oncology, Basel), a small molecule tyrosine kinase inhibitor (TKI) with activity against KIT, PDGFR and ABL kinase, was the first TKI approved by the Food and Drug Administration (FDA) for the treatment of metastatic or unresectable GISTs. The effectiveness of this agent was reported in an open-label, randomized, multicenter phase II trial92: approximately two-thirds of 147 patients randomly assigned to receive 400 mg or 600 mg of Imatinib daily showed a sustained objective response at a median follow-up of 288 days, with a manageable toxicities. Furthermore a median overall survival of 57 months in the Imatinib group was reported, compared with 10–20 months reached in the pre-Imatinib era.74 Notably, in the subgroup biomolecular analysis reported by Heinrich MC et al.93 there was a statistically significant partial response rate (PR) in GIST patients with exon 11 KIT mutations. PR was 83.5% versus 47.8% (p = 0.0006) and 0.0% (p < 0.0001) for GIST patients with exon 11 KIT mutations compared to those with exon 9 KIT mutations or no detectable KIT or PDGFRα mutation. Two phase III trials further confirmed the benefit of Imatinib in GIST and also studied the efficacy of higher Imatinib doses (800 versus 400 mg daily)94,95 reporting a small but statistically significant
progression-free survival (PFS) in the higher dose group, with no difference in overall survival. Moving from these results, adjuvant Imatinib therapy for a locally advanced or metastatic duodenal tumors (GISTs) does not differ from that for other GISTs and treatment should be continued indefinitely at a dose of 400 mg/day in advanced metastatic patients because its interruption is generally followed by rapid tumor progression.28

Successful results of Imatinib administration are obtained also in the postoperative treatment for patients at high risk of recurrence after complete resection of a primary GIST tumor. Two randomized phase III clinical trials evaluating the role of Imatinib 400 mg daily in the adjuvant setting demonstrated that adjuvant Imatinib prolongs recurrence-free survival (RFS) compared with placebo.96,97 On these basis current evidence sustains at least 3 years of adjuvant Imatinib as a standard protocol for patients with resected, high-risk GISTs, although the optimal duration of therapy remains unknown since the efficacy on RFS appears to be less evident at the discontinuing adjuvant Imatinib.

Imatinib has recently entered the clinical arena also as neoadjuvant drug, and the in order to downgrade a marginally resectable tumors arising from anatomical complex regions, such as the periampullary region, which would otherwise require extensive surgery. At the best of our knowledge there are no randomized trials evaluating the advantage of neoadjuvant Imatinib, even if promising results from not may retrospective series and prospective phase II trials98 highlight that preoperative Imatinib can reduce tumor size allowing a postponed surgical treatment in patients with locally advanced GIST.

Sunitinib

Sunitinib (Sutent; Pfizer Inc., New York, USA), a multi-targeted small-molecule TKI, has been shown to be an effective second-line therapy following Imatinib failure and is currently approved worldwide for metastatic GISTs in patients with Imatinib resistance or intolerance. A phase III randomized double-blind placebo-controlled study evaluating Sunitinib 50 mg daily, 4 weeks on, 2 weeks off, as second-line treatment for Imatinib-refractory or -intolerant GIST patients, showed significantly longer time to tumor progression (TTP) with Sunitinib (27.3 weeks, 95% CI 16.0—32.1) than with placebo (6.4 weeks, 95% CI 4.4—10.0) (hazard ratio 0.33; p < 0.0001),99 with an acceptable tolerability.

Regorafenib

Regorafenib (Stirvarga, Bayer HealthCare Pharmaceuticals Inc., Montville, NJ, USA) is an orally active multikinase inhibitor recently approved by FDA for the treatment of metastatic or unresectable GIST after failure or intolerance to Imatinib and Sunitinib. An international phase III randomized placebo-controlled trial (GRID trial) evaluating oral Regorafenib 160 mg daily, for the first 3 weeks of each 4 week cycle, was conducted in 199 patients with advanced GIST previously treated with at least Imatinib and Sunitinib.100 A statistically significant improvement in progression-free survival (PFS) was demonstrated among patients treated with Regorafenib (60%) compared with placebo (11%) at 3 months. Median PFS was also statistically significantly longer for patients treated with Regorafenib: 4.8 months compared with 0.9 months in the placebo group [hazard ratio (HR) 0.27, 95% confidence interval (CI) 0.19—0.39; p < 0.0001]. Drug-related adverse events (hypertension, hand-foot skin reaction, diarrhea) were reported in 130 (98%) patients assigned Regorafenib and 45 (68%) patients assigned placebo, with Regorafenib-related adverse events of grade 3 or higher reported in 48%.

Conclusions

Duodenal gastrointestinal tumors represent an extremely rare subset of stromal tumors arising from interstitial cells of Cajal. In the last 30 years the comprehension of the pathophysiology and natural history of this previously misunderstood clinical entity, in association with developments in endoscopy, imaging technology, and immunohistochemistry, has resulted in novel diagnostic and treatment approaches. The duodenum is the less commonly involved site for these tumors in the digestive tract. Furthermore duodenal GISTs have uncertain malignant potential, and they may be asymptomatic, or present with abdominal pain, bleeding, obstructive jaundice or cholangitis. Preoperative diagnosis is difficult to achieve and despite profound progresses in imaging technology, in several cases reported in the literature the mass was still misdiagnosed as ectopic pancreas, neuroendocrine tumor or solid pseudopapillary tumor. Endoscopic ultrasound with fine needle aspiration has been recently found to be the gold diagnostic standard with high sensitivity and specificity rates, diagnosing GIST in up to 80% of patients. Even if duodenal GISTs are pathologically not different from other GISTs, they show some histopathological peculiar features such as a smaller size at diagnosis and a lower median mitotic count. Although surgical resection with microscopically clear resection margins seems to be the only potentially curative treatment for non-metastatic primary GISTs of the duodenum, the optimal therapeutic strategy are challenging due to the complex anatomy of the pancreatico-duodenal region. Small GISTs not involving the papilla of Vater are better resolved performing conservative surgery such as segmental duodenectomy and wedge resection. However limited resections are not always feasible and for large tumors with more extensive involvement major resections such as pancreaticoduodenectomy or pancreas-sparing duodenectomy represent the treatment of choice. The risk of recurrence and disease free survival depend on tumor size, mitotic count and an NIH high risk classification.
rather than surgical approach. Localized GIST is associated with a 1–3 year survival rate of 86–100%. Imatinib mesylate plays a key role in the management of GISTs both as neoadjuvant therapy and in patients with recurrent and metastatic disease. Meanwhile, the advances in the comprehension of the pathophysiology and natural history of this previously misunderstood clinical entity as well as the treatment of these tumors may render feasible, in the near future, the advent of newer and more efficacious treatment options.

Conflict of interest statement

The Authors have no conflict of interest or financial ties to disclose.

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