Gastrointestinal stromal tumours and other primary gastrointestinal neoplasms.
A single-center experience

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BACKGROUND: *In our surgical daily activity, we report the observation of rare tumour as Gastrointestinal Stromal Tumours (GIST). We report the incidence and behaviour of new cases of GIST operated in our Center during the last decade, from 2008 to 2018 and here we also describe the concomitant observation of a second gastroenteric tumor.*
METHOD: *We have examined all the case files and histological examinations of patients with CD 117-positive GISTs treated in our Institute from 2008 to 2018. We have gathered data regarding clinical symptoms at the time of diagnosis, tumour site, type of surgery performed, tumour size, histopathological data and follow up data.*
RESULTS: *We have analysed 950 cases of patients who underwent surgery for gastrointestinal neoplasia in our department from 2008 to 2018.*
We have found 12 cases affected by GIST and in 4 cases it was also a second tumour. In two cases GIST were incidentalomas and in the others two patients a second tumour was incidentally observed in primary GIST.
CONCLUSION: *Patients with GIST run the risk of developing a second neoplasm, nearly twice as high as the general population with a negative impact on survival; also, incidental GIST is often observed requiring a better molecular characterization for the high risk of developing second neoplasms with the aim of achieving an early diagnosis.*

KEY WORDS: Gist, Second neoplasm, Surgery

Introduction

Gastrointestinal Stromal Tumours (GISTs) are neoplasms deriving from a common mesenchymal stem cell of the gastrointestinal tract or, rarely, from other intra-abdominal tissues: the interstitial cell of Cajal. The stomach is the most commonly affected site (50-60%) followed by the small intestine (30-35%); colon-rectum (5%) and esophagus (<1%) are rarer. Other sites within the abdominal cavity, such as omentum, mesentery and retroperitoneum (<5% of total GISTs) are classified as extra-gastrointestinal [1,2]. Advances in immunopathology have identified a mutation activating proto-oncogene c-KIT (75-80% of cases) and in a minority of cases (5-10%) PDGFR-[a] gene. In the last few years numerous studies in molecular biology have demonstrated that KIT/PDGFRA WT GISTs represent extremely heterogenous entities from both a biological and clinical point of view [3]. GISTs can develop at any age: the average occurrence age is 60-65 years old. The diagnosis is often made on the basis of imaging examination an abdominal mass [4]. Tumours develop mainly in submucosal sites, but they can also develop as extraluminal masses. Small intestinal GISTs are often asymptomatic until they grow to a such a large size to be accompanied by clinical symptoms. Surgical removal is possible

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in about 60% of cases. Adjuvant treatment with tyrosine kinase inhibitors is recommended in patients with a high/intermediate risk of recurrence and in tumours with a KIT or PDGFR-a mutation. In case of WT GISTs it is useful to include patients in specific protocols in virtue of limited sensitivity to imatinib both in adjuvant phase and in locally advanced and metastatic phase. Tyrosine kinase inhibitors substantially improve the survival of these patients [5].

Materials and Methods

We have examined all the case files and histological examinations of patients with CD 117-positive GISTs treated in our Institute from 2008 to 2018. We have gathered data regarding clinical symptoms at the time of diagnosis, tumour site, type of surgery performed, tumour size, histopathological data and follow up data.

Results

We have analysed 950 cases of patients who underwent surgery for gastrointestinal neoplasia in our department from 2008 to 2018.
We have found 12 cases affected by GIST: 5 women (5/12, 41,66%) and seven men (7/12, 58,33%). 9 cases were gastric (9/12, 75%), 2 GISTs originated in jejunum-ileal (2/12, 16,6%), and 1 in the duodenal (1/12, 8,3%) (Table I). In 8 cases the size was less than 5 cm, in 3 cases less than 10 cm and in 1 case more than 10 cm (Table II).
2 cases (2/12, 16,6%) were incidentalomas: GIST was diagnosed accidentally during the staging CT for a second neoplasia of the gastroenteric tract. In one of these two cases (a primary tumour of the sigmoid-rectum) a jejunal resection has been performed as well (Fig. 1, Fig. 2); in the other case (a primary tumour of the ascending colon) a gastric resection has also been performed.
In 2 cases (2/12, 16,66%), involving primary GIST, the definitive histological examination has revealed a concomitant neoplasia. One case concerned a small gastric GIST of low malignant potential and the definitive histological examination has revealed also the presence of a neuroendocrine tumour. In the other case (a gastric GIST as well) a cholecystectomy for lithiasis has been performed, which resulted to be the site of a second neoplasia (adenocarcinoma) on histological examination.
As to the cases of gastric GIST, the clinical symptoms at the time of diagnosis were dyspepsia (7/9, 77,77%) and loss of weight (4/9 44,44%). In all cases a gastric resection has been performed.
In regard to the cases of GIST of the ileal, the symptoms were abdominal pain and bowel alteration, whereas clinical symptoms of duodenal GIST were dyspepsia and nausea. In the case of GIST originating in the jejunum no symptoms have been noticed since it dealt with incidentaloma.
The site, the tumour diameter and mitotic index have been taken into account for risk prediction. In 8 cases (6 gastric, 1 duodenal and 1 jejunum-ileal) the tumour diameter was ≤5 cm and the number of mitotic figures < 5/50 HPF and therefore they have been classified as very low risk. 3 cases of GIST whose size was less than 10 cm (1 originating in the ileal and 2 originating in the stomach) and whose mitotic index was > 5/50 HPF have been classified as high risk. Even the last case, a gastric GIST with a diameter >10 cm but a mitotic index > 5/50 HPF, was classified as high risk (Table III). All cases have been evaluated for mismatch Repair System (MMR) with immunohistochemical technique MLH1/PMS2 and MSH2/MSH6. It has shown the expression of all proteins in the neoplastic cells. During follow up, which started 10 years ago and is still ongoing, 2 patients were lost, 3 patients died of disease progression and 7 patients had no recurrence. R0 resection has been achieved in all procedures. In patients with synchronous tumours the resection of GIST and of the second tumour has been performed in one single surgery time. After surgery, 8 patients have received no treatment for a low risk of recurrence according to classification criteria, in 4 cases a precautionary treatment with Glivec (imatinib mesylate) has been given to patients.

TABLE I - *Tumour site.*

Site	M/F
Stomach 9/12 (75%)	5F (41,66%)
Small intestine 2/12 (16,6%)	7M (58,33%)
Duodenum 1/12 (8,3%)	

TABLE II - *Tumour Size*

Size	Num. of cases
<5 cm	8
5-10 cm	3
>10 cm	1

TABLE III - *Risk predicition according to size, site and mitotic index (from miettinen et al.)*

Size	Mitotic Index	Stomach	Duodenum	Jejunum/Ileal	Risk
< 5 cm	< 5	6	1	1	Very Low
5-10 cm	> 5	2		1	High
> 10 cm	> 5	1			High

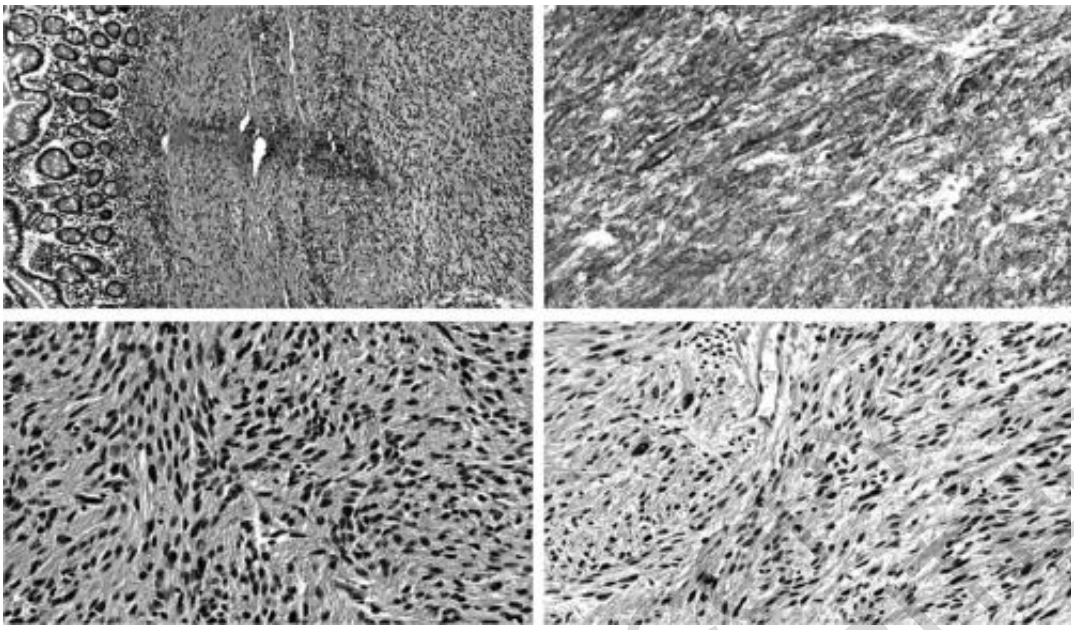

Fig. 1: Neoplasia specials with fusate cells with moderate cellularie and positives for cd117, ingrandiments 10x and 20x.

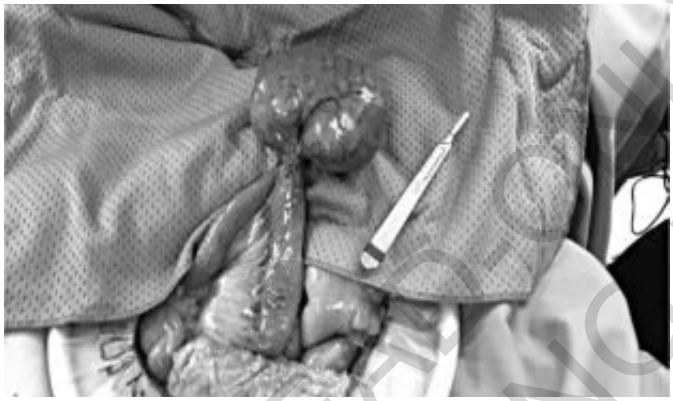

Fig. 2: Jejunal GIST, incidentaloma under resection of a sigmoid-rectum tumour.

Discussion

GISTs are rare mesenchymal tumours of the gastrointestinal tract accounting for about 1% of all the neoplasms originating in the gastroenteric apparatus. Although Mazur and Clark first introduced the term GIST in 1983, this particular group of neoplasms has only recently attracted a wider attention.[6,7] The presence of KIT oncogene mutation in GISTs was noticed in 1998 and in 2001 the introduction of imatinib (a selective inhibitor of KIT) revolutionised the treatment strategy and marked the beginning of the new era of target therapy for these neoplasms [8].

The most important diagnostic tool for GISTs is the evaluation of the CD117 expression, which is positive in 75/80% of cases. Instead, a mutation in the receptor tyrosine kinase PDGFRA has been noticed in about 5-10% of GISTs [9]. In the remaining minority of cases no mutations have been observed neither in KIT nor in PDGFRA (Wild-Type GIST). Moreover, about 20-40% of all KIT/PDGFRA WT GISTs are deficient in succinate dehydrogenase (SDH) and are therefore called SDH-deficient GISTs. About 4-13% of KIT/PDGFRA WT GISTs without SDH deficiency can show a BRAF V600E mutation with intestinal localisation and a likely better prognosis. A small percentage of GISTs can show a NF1 mutation, which is peculiar to GISTs affecting the small intestine, often multifocal, and occurring mainly among women [10,11].

The most common originating sites of the gastroenteric apparatus are the stomach (60%) and small intestine (30%), whereas colon, rectum, appendix, esophagus, mesentery, omentum and retroperitoneum are rarer. In case of GISTs affecting the stomach, the prognosis is better than the other sites, such as small intestine, esophagus and colon where the majority of these tumours is more aggressive [12,13]. The most frequent symptom is gastrointestinal bleeding; the least frequent are abdominal pain, palpable mass, and loss of weight. Rarely, small intestinal GISTs cause intestinal obstruction, hemoperitoneum secondary to tumour rupture and peritonitis secondary to tumour perforation [14].

The complete surgical resection is the elective potentially curative treatment for GISTs. The surgical resection with microscopically free margins is the fundamental therapeutic achievement to reduce the risk of recurrence and it is associated with a 60% global survival rate of 5 years [15]. During surgery a careful manipulation is needed to avoid the rupture of the pseudocapsule and the ensuing spread of tumoral cells and the worsening of prognosis [16].

Lymphadenectomy is not routinely performed because lymph node metastatic spread is rare [17]. Mini-invasive procedures, mainly in small gastric lesions, are particularly suggested owing to the well-known benefits of early operative recovery and low morbidity.

Since 2008 imatinib mesylate has been indicated as adjuvant therapy after surgical resection with a significant reduction in local recurrence rate [18].

The definition of high-risk groups which are amenable to adjuvant therapy is of foremost importance and classically it allows for the mitotic rate, tumour size and primary site, as well as tumour perforation during surgery. GISTs are classified as low, intermediate or high risk of recurrence according to the tumour size, the mitotic rate, the site, and the presence of capsule rupture. The first risk classification model for recurrence was the one by the National Institute of Health (NIH) which was proposed by Fletcher in 2002 and approved by the Consensus Approach. This model classifies four risk groups (very low, low, intermediate, high) considering two principal parameters to predict the biological behaviour of GISTs: tumour diameter and mitotic index (number of mitoses per 50/HPF) [19].

In 2006 a new risk classification model was introduced according to the Armed Forces Institute of Pathology (AFIP) criteria in which the primary tumour site was added to the mitotic index and the tumour size. This classification system shows how gastric GISTs tend to have a more favourable prognosis than intestinal and rectal ones, when the mitotic index and the size are equivalent [20,21]. Recently, the tumour rupture, both spontaneous and intraoperative, is an independent risk factor in comparison with the other parameters. The adjuvant therapy should be carried out for three years and according to the current consensus. It should start as soon as possible after surgery. Although surgery is the best curative treatment, almost 50% of cases subjected to surgery show a risk of recurrence and are submitted to an adjuvant treatment with imatinib mesylate to improve diagnosis. Moreover, imatinib mesylate is considered as the first-line treatment for inoperable cases and metastatic GISTs. Mutational analysis of KIT and PDGFR-a genes is therefore a predictive parameter of response to drugs which inhibit tyrosine kinase activity [22,23].

Currently, two drugs (sunitinib and regorafenib) have been approved by Food and Drug Administration for GISTs after imatinib failure. However, the majority of patients show progression due to primary or secondary resistance.

More recently, neoadjuvant therapy has been taken into account for cases of locally advanced tumours, which could allow radical surgery. It has also been employed to avoid multivisceral resections so as to minimize postoperative morbidity. Neoadjuvant therapy can be administered for 4-12 months and no pre-emptive suspension before surgery is required. Imaging tests are usually repeated one month after starting therapy. According to literature, the association between GIST and the appearance of a second neoplasia is more likely to occur in patients with GIST rather than the general population. It has been reported that GISTs occur synchronously with cases of adenocarcinoma, lymphoma and carcinoid [24,25]. In our study – just as in other works – adenocarcinomas were more frequent in cases of GISTs concomitant with a second neoplasia (¾, 75%). Although the synchronous occurrence of GISTs with other abdominal neoplasms seems to be a mere coincidence, the development of these tumours can involve common cancerogenic agents. It has been demonstrated that microsatellite instability plays an important role in the process of carcinogenesis in malignant tumours of the large intestine and endometrium. In the last few years, the status of microsatellites has been a major interest for molecular oncology, with regard to both the understanding of the process of carcinogenesis and the identification of molecular markers for predictive therapy response [26,27]. Through the investigation of the status of microsatellites in immunohistochemistry on selected cases of GISTs, it has been noticed that microsatellite instability occurs in GISTs originating mainly in the stomach and more frequently related to hereditary syndromes, and in GISTs arising in patients with previous or concomitant neoplastic pathologies. It appears that the determination of MSI status is a marker for new treatments and it can be a predictive indicator for selecting patients who can benefit from pembrolizumab, an anti-PD-1 immunotherapy [28]. The characterization of MSI phenotype in GISTs is scarce and the results are not consensual. A recent study has examined 79 cases – the largest series undergoing MSI status evaluation with the use of molecular techniques – and no occurrence of MSI in the series of GISTs has been noted [29]. Our results agree with this study as well. The first study about the presence of MSI in GISTs is by Lopes et al [30] and it has analysed 33 GISTs. However, other authors have reported the presence of MSI in 5% (3/62) and in 50% (10/22) of cases. These results are divergent and different causes have been suggested. Firstly, the number of cases analysed in the above mentioned studies was not larger enough to obtain coherent results Secondly, different methodologies have been employed for the evaluation of MSI and the accuracy of MSI detection is highly dependent on the selected techniques [31]. In the light of these preliminary data, it is possible to identify the investigation of MSI status in selected cases of GISTs as an important step in the histopathologic diagnosis.

Conclusions

According to what has been analysed in this article, patients with GIST run the risk of developing a second neoplasm, nearly twice as high as the general population. Second neoplasms associated with GISTs can be

of any histology and occur in any organ. The most frequent sites are gastrointestinal tract The survival of patients with second neoplasms seem to be below the average of patients with single neoplasms, hence a deeper study of these patients and a better molecular characterization for the high risk of developing second neoplasms with the aim of achieving an early diagnosis. Through the study of larger case histories and the integration of scientific and clinical-anamnestic data relating to localization and staging of GISTs, the presence of MSI can be added as a valid "objective and reproducible" guide in the clinical management of these rare neoplasms.

Riassunto

I Tumori Stromali Gastrointestinali (GIST) sono neoplasie che derivano da una comune cellula staminale del tessuto mesenchimale del tratto gastrointestinale o, raramente, da altri tessuti intra-addominali: la cellula interstiziale di Cajal. Lo stomaco è la sede più comunemente colpita (50-60%) seguita dall' intestino tenue (30-35%) e meno dal colon- retto (5%) e dall'esofago (<1%). Altre sedi nell'ambito della cavità addominale quali omento, mesentere o retroperitoneo (<5% di tutti i GIST), sono indicate come extra-gastrointestinali. I progressi in immunopatologia hanno identificato una mutazione attivante il proto-oncogene c-KIT (75-80% dei casi) e in una minoranza dei casi (5%-10%) il gene PDGFR-a. Negli ultimi anni numerosi studi di biologia molecolare hanno dimostrato che i GIST KIT/PDGFRA WT rappresentano un'entità estremamente eterogenea sotto il profilo sia biologico che clinico). I GIST possono manifestarsi a qualsiasi età: quella mediana di insorgenza è 60-65 anni. Spesso viene posta diagnosi tramite l'evidenza radiologica di massa addominale. I tumori si sviluppano per lo più in sede sottomucosa ma possono manifestarsi anche come masse extra luminali. I piccoli GIST intestinali sono spesso asintomatici fino a quando non raggiungono dimensioni notevoli tali da provocare sintomatologia clinica. L'asportazione chirurgica è possibile nel 60% circa dei casi. Il trattamento adiuvante con gli inibitori della tirosin chinasi è raccomandato per i pazienti con un rischio intermedio/alto di recidiva e nei tumori con una mutazione a KIT o PDGFR-a. Nei casi di GIST wild type è utile inserire i pazienti in protocolli specifici in virtù della minore sensibilita' a imatinib sia in fase adiuvante che localmente avanzata e metastatica. Gli inibitori della tirosina chinasi migliorano sostanzialmente la sopravvivenza di questi pazienti. I pazienti con GIST hanno un rischio circa 2 volte superiore alla popolazione generale di sviluppare un altro tumore (il 4-33% di essi sviluppa una seconda neoplasia, sia sincrona che metacrona. Presentiamo l'esperienza acquisita presso il nostro Istituto di pazienti con diagnosi di GIST singoli e casi associati ad una seconda neoplasia. Abbiamo analizzato 950 casi di pazienti sottoposti a chirurgia per neoplasia gastrointestinale dal 2008 al 2018 trattati presso la nostra divisione. Abbiamo riscontrato 12 casi affetti da GIST di cui cinque donne (5/12, 41,66%) e sette uomini (7/12, 58,33%). Nove casi erano a partenza gastrica (9/12, 75%), due casi a partenza digiuno-ileale (2/12, 16,6%), e un caso a partenza duodenale (1/12 8,3%). In 8 casi le dimensioni erano inferiori a 5 cm, in tre casi inferiori a 10 cm ed in un caso superiori a 10 cm . In 2 casi (2/12, 16,6%) la diagnosi è stata di incidentaloma in corso di stadiazione TC per una seconda neoplasia del tratto gastroenterico. In un caso con diagnosi primitiva di tumore del sigma-retto è stata eseguita in concomitanza anche una resezione digiunale , nell'altro caso con diagnosi di tumore primitivo del colon destro, è stata eseguita anche una resezione gastrica. In due casi (2/12, 16,66%) con diagnosi primaria di GIST è stata riscontrata una neoplasia concomitante all'esame istologico definitivo. Nel caso di un piccolo GIST di basso grado dello stomaco è stato evidenziato all'esame istologico definitivo, compreso nei prelievi, anche la presenza di tumore neuroendocrino. Nell'altro caso, sempre di GIST gastrico, è stata eseguita una colecistectomia per calcolosi, risultata essere poi all'esame istologico definitivo sede di seconda neoplasia (adenocarcinoma). È stata eseguita in tutti i casi la valutazione dello stato del "mismactch Repair System" (MMR) mediante tecnica immunoistochimica verso MLH1/PMS2 e MSH2/MSH6 che ha mostrato presenza di espressione di tutte le proteine nelle cellule neoplastiche. Da quanto è stato esaminato in questo articolo, si può concludere che i pazienti con GIST hanno un rischio quasi doppio rispetto alla popolazione generale di sviluppare una seconda neoplasia. Le seconde neoplasie associate nei pazienti con GIST possono avere qualsiasi istologia e apparire in qualsiasi organo, le sedi più frequenti sono quelle di origine gastrointestinale. La sopravvivenza dei pazienti con seconde neoplasie sembra essere inferiore alla media delle singole neoplasie per cui è necessario uno studio più approfondito di questi pazienti, nonché una migliore caratterizzazione molecolare per l'elevato rischio di sviluppare seconde neoplasie, con l'obiettivo di raggiungere diagnosi precoce.

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