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Individualized surgical treatment in patients with advanced gastrointestinal stromal tumor — a case series

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ABSTRACT

In this case series we present the cases of two patients at a metastatic stage of stomach gastrointestinal stromal tumor, who received treatment with imatinib. After a period of disease stability patients showed signs of resistance to the first-line therapy and despite the promising switch to sunitinib, developed life-threatening complications. Salvage surgeries were performed, aimed at preserving patients life and simultaneously reducing the tumor mass. Operation greatly improved patients condition and allowed for successful continuation of tyrosine kinase inhibitor treatment, showing that surgery should be considered a viable complement to the chemotherapeutical treatment.

Key words: gastrointestinal stromal tumors, neoplasm metastasis, salvage therapy, imatinib mesylate, fistula

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Introduction

Gastrointestinal stromal tumors (GIST) are considered the most common mesenchymal neoplasms of the gastrointestinal tract [1]. Their overall incidence is estimated to be between 10 and 20 cases per million, occurring predominantly in patients above 50 years old, with equal distribution between men and women [2, 3]. Typically, GIST is located in the stomach or the small intestine, originating from the interstitial cells of Cajal, which act as pacemaker cells regulating peristalsis in the gastrointestinal tract [4]. Most commonly GIST arises as an effect of gain of function mutation in the KIT proto-oncogene or less predominantly in the *PDGFRA* gene [2, 5, 6].

The diagnosis of GIST comprises recognizing its clinical and molecular features, as well as a character-

istic anatomic location of the tumor. The majority of GISTs show a positive expression of characteristic KIT (CD117), DOG-1, and CD34 markers in the immunohistochemical analysis [7].

Gastrointestinal stromal tumors range in size and aggressiveness, but all of them can eventually give metastases. Patients may present with symptoms such as gastrointestinal bleeding, abdominal pain, and dysphagia, but are often fully asymptomatic. Due to a lack of specific symptoms, patients frequently seek medical advice when the disease is already in its advanced stage, with 20% to 30% of presenting patients having metastases at the point of the initial diagnosis [8].

Here we present two cases of patients at a metastatic stage of stomach GIST.

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Case report

Case 1

A 55-year-old woman was referred by her general practitioner to the Department of Gastrointestinal Cancer with a 3-month history of discomfort in the abdominal region as the only symptom. On physical examination, the patient had a mildly enlarged liver, with a palpable, uneven border.

The patient was immediately taken for a computed tomography (CT) scan of the abdomen, revealing a growth in the left epigastrium measuring 106×76 mm and multiple metastases in the liver. Gastroscopy was performed, displaying a massive, ulcerated infiltration on the posterior wall of the stomach. Additional peritoneal metastases were shown in the following positron emission tomography-computed tomography (PET-CT) scan. A liver metastasis biopsy was performed. Tissues were analyzed with immunohistochemical staining, which revealed a set of markers characteristic for GIST: CD 117 (+), DOG-1 (+), and CD 34 (+), confirming the diagnosis. Due to the diffuse metastases, a radical operation was not possible, thus systemic therapy with imatinib was administered.

A follow-up CT scan after 5 months revealed an area of elevated radiodensity in the tumor on the gastric wall (from 27 HU to 48 HU). The patient was taken for gastroscopy, which showed a spot of changed tissue on the inner surface of the stomach, associated with the large, submucosal tumor. The observed symptoms of tumor progression resulted in the introduction of second-line treatment with sunitinib. The new treatment caused a moderate regression, as the tumor measured consecutively: 90×70 mm, 82×65 mm, and finally 76×60 mm (the best response) in the successive follow-up CT scans. Despite a good response to the treatment, the disease remained in the dissemination phase (metastases to the liver and peritoneum).

After 3 years of treatment, the patient presented to the clinic again, with signs of esophageal erosion and esophagitis [endoscopically classified as grade B in the Los Angeles (LA) classification], as well as anemia. The patient was promptly taken for a CT scan, which revealed development of a fistula in the gastric wall damaged by the neoplastic process (Fig. 1).

To combat the swift decline in the patient's overall condition, it was decided that a salvage surgery is necessary. A wedge resection of the stomach with the primary tumor was performed, with tumor tissues submitted for a histopathological examination. The tumor showed histopathological signs of regression, probably responsible for the formation of the fistula. The patient's condition substantially improved after surgery although the disease was still in the stage of dissemination (metastases to the liver and peritoneum).

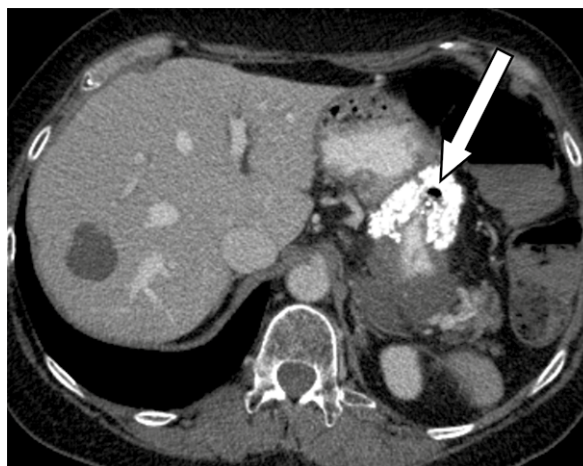


Figure 1. Computed tomography image of the abdomen showing a partially calcified tumor, with signs of decay in the central section. Visible fistula canal to the gastric lumen (arrow)



Figure 2. Computed tomography image of the abdomen 3 months after surgery. Status after partial resection of the tumor

A follow-up CT scan with contrast, performed 3 months later, confirmed a successful closure of the fistula (Fig. 2). The tumor measured 42×30 mm, which demonstrated a further shrinking of the tumor in the postoperative period. In the 40-month course of follow-up examinations after surgery, the patient's condition remains stable despite the diffuse neoplastic process. The patient continues the treatment with sunitinib.

Case 2

A 49-year-old man was admitted to the Department of Gastrointestinal Cancer with a suspicion of a neoplastic process of unknown character recognized by a primary care practitioner. On a physical examination,

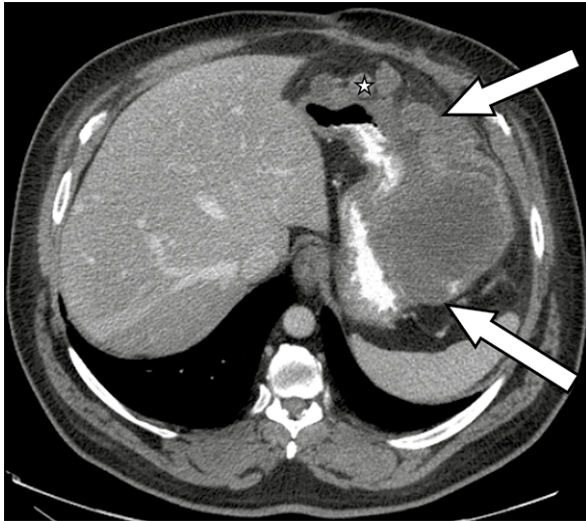


Figure 3. Computed tomography image of an exophytic tumor in the gastric wall (arrows). Visible metastasis in the peritoneum (*)

an atypical mass in the patient's left epigastrium with a diameter of around 20 cm was detected.

In order to remove the abnormality, laparotomy was performed; however, it revealed a diffuse neoplastic process affecting the stomach, as well as segment VI of the liver, the pancreas, distal part of the duodenum, spleen, the greater omentum, and the peritoneum (Fig. 3). A radical operation was not possible, thus treatment with imatinib was introduced instead.

A month later the patient presented again with signs of significant anemia and melena. Emergency gastroscopy was performed, showing stomach contents resembling "ground coffee" and a clotted ulceration on the greater curvature of the stomach. A following CT scan revealed an underlying nodular tumor, measuring 150 × 120 mm. The biopsied mass was analyzed with immunohistochemical staining, which unveiled the presence of characteristic markers such as CD 117 (+), DOG-1 (+), and CD 34 (+), confirming the diagnosis of GIST. Additionally, a genetic test showed a deletion affecting exon 11 of the KIT gene, further reinforcing the diagnosis.

In the follow-up CT scans, the tumor was gradually shrinking (104 × 92 mm), unfortunately, two years later, the patient presented with a fever and lack of bowel movement. Another CT scan revealed a sudden growth of the tumor (144 × 107 mm) as well as visible bubbles of gas within the tumor, suggesting a formation of a fistula between the tumor and the splenic flexure of the colon (Fig. 4). That progression prompted the introduction of second-line treatment with sunitinib, but despite the change in medication and extensive ambulatory care, the patient's condition deteriorated. A loss of over 30 kg of weight in two months was reported as well

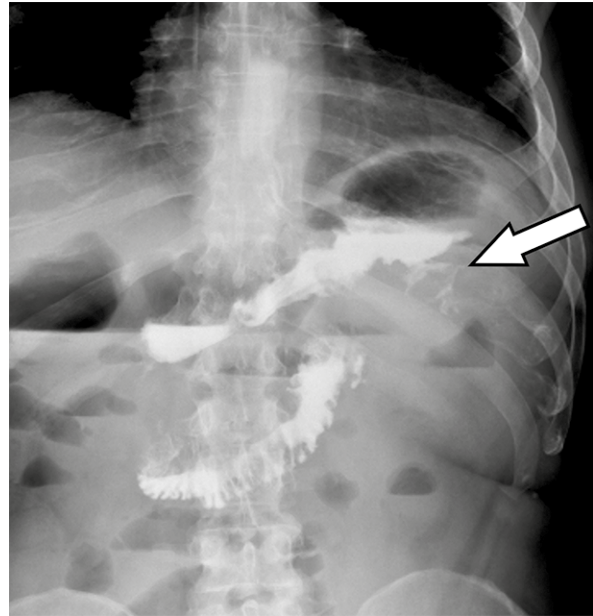


Figure 4. Computed tomography image of the abdomen, revealing the presence of a fistula to the tumor mass (arrow)



Figure 5. Computed tomography image of the abdomen after surgery. Status post total gastrectomy

as a development of life-threatening anemia, with signs of upper gastrointestinal bleeding.

In order to improve the patient's quality of life, palliative surgery was performed, consisting of transverse colectomy, gastrectomy, splenectomy, and partial pancreatectomy with a reconstruction of the gastrointestinal tract by a roux-en-Y gastric by-pass (Fig. 5). Following surgery, the patient's condition was gradually improving. After the withdrawal of life-threatening symptoms, the patient was referred to the Department of General Surgery and Clinical Nutrition for further treatment. The patient died 19 months after surgery due to disease progression.

Discussion

Before the application of specific tyrosine kinase inhibitor (TKI) — imatinib, GIST was considered resistant to any form of conventional chemotherapy or radiotherapy [9]. The standard therapy for a patient with GIST diagnosis was limited to surgery, with no established method of complex treatment for advanced tumors. The introduction of Imatinib mesylate in the treatment of GIST has changed treatment capabilities, allowing for clinically validated suppression of tumor growth, thus making GIST treatment a paradigm in the treatment of solid tumors with molecularly targeted therapy. Imatinib is an inhibitor targeting multiple receptor tyrosine kinases which are responsible for carcinogenesis of most GIST [2]. It blocks the signaling via KIT, the pathway which malfunctions. Imatinib's affinity to the etiology of GIST resulted in a global change in the therapeutic approach, as it allows approximately 65–80% of patients to achieve a partial response, with another 15–20% having a stable disease [2, 10].

Unfortunately, 40 to 50% of patients show signs of disease progression after 2–3 years of therapy. Complete responses are also quite rare (5–7%) [4]. This is likely caused by the tumor forming resistance to Imatinib, probably via the mechanism of additional mutations in the KIT gene limiting the effectiveness of the medication [11]. Patients who do not respond to Imatinib or do not tolerate it are administered a second-line treatment with sunitinib, which is a similar inhibitor of tyrosine kinase. Unfortunately, the tumor tends to form a resistance to it as well. As the quality of response in clinical trials is still far below the intended, we are eager to search for improvements in our methods.

Surgery in GIST therapy remains an important part of the therapeutic process. For all non-metastatic tumors of diameter above 2 cm, a surgical approach is preferred, curing about 60% of patients [12]. The optimal outcome of the operation is a total gross resection of the tumor, with safety margins and no ruptures, which would significantly increase the risk of peritoneal spread. Neoadjuvant treatment is typically administered when the tumor cannot be removed in a radical operation or a size reduction of a potentially resectable tumor is likely to cause life-threatening complications.

Surgery is also considered, after a maximal response to Imatinib, if the tumor masses are fully resectable, as it could decrease the risk of developing resistance to the medication. Crucially, in cases where the tumor masses are not fully resectable after a maximal response to TKI, surgical treatment is neither recommended nor discouraged. There have been reports of successful resections of metastatic lesions with no evidence of disease in long-term follow-up [13]. It remains unknown whether cytoreduction (i.e. conscious partial resection)

for patients with stable disease on Imatinib reduces the chance of tumor developing resistance. Similarly, the benefits of the surgical approach in cases with resistance to Imatinib are yet to be estimated [8].

As TKI treatment can result in massive degeneration of tissues, and life-threatening complications such as tumor ruptures, perforations, hemorrhages, and bowel or bronchus obstructions. In such situations, rescue surgery is a viable method of managing those emergencies and should be performed in cases of an apparent threat to the patient's life [14].

The two cases of patients with advanced GIST of the stomach presented here are precedents in which life-threatening conditions of the patients forced surgeons to perform salvage surgeries on the tumors. Partial resection of GIST (primary tumors in the presence of metastatic lesions) was primarily meant to stop the deterioration of the patient's health, but it also significantly decreased the tumor mass. The striking observation in both of these cases is that the operation proved to be a viable form of cytoreduction. The imatinib and the sunitinib treatments allowed for moderate regression, but eventually proved unable to save the patients from severe complications in the long term. The cases described were different in terms of response to the therapy: in the first case, the patient developed a fistula as a consequence of a good response to the second-line treatment, in the second case, the patient had clinical progression during therapy.

For those patients, performed cytoreduction surgeries enabled the chemotherapeutic agents to function effectively again, resulting in an improvement in their condition. Therefore, cytoreduction should be carefully considered in patients treated for GIST with the TKI, optimally when the maximum effect of the therapy has been achieved [15]. That usually corresponds to the interval between the 6th and the 18th month of TKI therapy [16]. A surgical intervention, preferably through function-sparing surgery, is thus a viable complement to TKI therapy. Our patients in both cases did not fulfill the criteria for maximum effect of TKI therapy because they were in the dissemination phase of GIST from the very beginning of the therapy.

Conclusions

The palliative treatment of GIST with tyrosine kinase inhibitors has major limitations, likely diminished with an introduction of surgical intervention into the therapeutic process. Effective therapy of GIST requires a balance between surgical and chemotherapeutic treatments. Surgery is likely to improve the outcome for patients who respond to TKI treatment and should be considered when the maximum effect of the therapy

has been achieved. Salvage surgery should be considered whenever the patient's condition precludes continuation of TKI and surgery may lead to a reintroduction of the therapy; however, all treatment decisions should be undertaken after individualized assessment by a multi-disciplinary team.

Ethics statement

The retrospective study of all data was conducted in accordance with the Declaration of Helsinki.

Author contributions

The authors confirm contribution to the paper as follows: J. Pałucki, M.L., I.P., A.K., T.O.: clinical investigation; J. Pytlos, T.O.: writing — original draft; all authors: writing — review and editing.

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Conflict of interest

Authors declare no conflict of interest.

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