THE ROLE OF THE SURGERY IN THE GIST AFTER TARGETED THERAPY INTRODUCTION. CASE REPORT AND REVIEW OF THE LITERATURE

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[Il ruolo della chirurgia nel GIST dopo l'introduzione della terapia molecolare "mirata". Caso clinico e revisione della letteratura]

ABSTRACT

We report a case of gastric primary localized GIST 12 cm in size on 62 year-old male patient underwent complete surgical resection R0 by subtotal gastrectomy and starting adjuvant therapy with imatinib mesylate 400 mg. a day. The follow-up by endoscopy and PET-TC total body hasn't been shown relapse after 2 year from surgical resection. The author makes a review of the literature about the current role of the surgical therapy in the primary localized as well as in recurrent and metastatic GIST after targeted therapy introduction.

Key words: Gastrointestinal Stromal Tumor (GIST), Surgical Resection, Targeted Therapy, Combined medical and surgery therapy.

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Introduction

Gastrointestinal Stromal Tumours (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract even if they represent only the 0.2% of all gastrointestinal neoplasms. The term was coined in the 1983 by Mazur and Clark, however the identification as separate entity has been possible in the 1998 with the identification by Hirota et al. of immunohistochemical staining pattern positive for CD 34 and Tyrosine Kinase Receptor Kit mutation (CD 117), a protooncogene common to up to 85% of GIST considered the key of cell proliferation, while another 3% to 5% have a PDGRFa mutation. This immunohistochemical pattern common with the Interstitial Cells of Cajal suggests a hystologic origin of the GIST from Cajal cells, or alternatively a common origin from a stem cell. Recent guidelines by National Comprehensive Cancer Network (NCCN) estimate the annual incidence in 10 - 20 cases for million of inhabitant; near 5000 annual cases in the U.S. with a equal distribution in men and women with the largest incidence in patients between 40 - 80 of age, although all ages may be interessed. Approximately 60% of GIST occur in the stomach, 30% in the small intestine 5% in the rectum and 5% in esophagus. Rarely GIST may develop outside of the alimentary tract as the mesentery, omentum, pancreas or other retroperitoneal structures. Because of the rarity of this tumour the preoperative diagnosis requires a high degree of suspicied because the clinical presentation is not specific and the symptoms are related to the presence of a mass or bleeding. Approximately 30% of patients are asymptomatic and the diagnosis is found incidentally. C.T. and M.R.I. are the most used indagings to detect primary GIST. PET is now used for functional information about the response of tumour to the treatment, because the tumour regression can not be accompanied by changes in tumour size; Endoscopy is useful in the diagnosis of gastric or colorectal GIST, that appears as submucosal mass.

Endoscopic ultrasounds (EUS) confirm the origin from the gastric wall and not from the mucosa. Percutaneos biopsy can theorically precipitate the tumour rupture and lead to dissemination or hemorrhage, and should not be used. EUS FNA should be considered today the procedure of choice to secure diagnosis of GIST, and has been associated with a diagnostic accuracy of 80% - 85%.

Clinical behaviour of the GIST is uncertain, and theese tumours always have a malignant potential. Multiple parameters have been considered as predictors of malignancy.

A recent Consensus Conference by the National Institute of Health considered sizes and mitotic count the most useful predictor of the malignant behaviour, and a scheme has been developed to predict the risk of recurrence or metastasis after surgical resection of primary GIST and published by Fletcher et al. (Tab. 1).

	SIZE	MITOTIC COUNT
Very Low Risk	< 2 cm	< 5/50 HPF
Low Risk	2 - 5 cm	< 5/50 HPF
Intermediate Risk	< 5 cm. 5 - 10 cm	6-10/50 HPF < 5/50 HPF
High Risk	> 5 cm. > 10 cm.	> 5/50 HPF Any Mitotic Rate

Tab.1: GIST Risk Stratification (Fletcher et al. 2002)

Generally tumours less 2 cm in size with mitotic index of 5 or less for 50 HPF are considered a very low risk. Because of the observation that gastric GIST have a more favourable outcome than tumour arising from other location, Miettinen et al. propsed a risk scheme that separates gastric GIST from intestinal GIST.

Case presentation

A 49 year old male patient presented a history of 30 day duration of post-prandial upper left abdominal pain, nausea and weight loss of 5 kg. Physical examination revealed abdominal mass in left flank, ematochemistry and oncologic markers appeared normal. A abdominal U.S. has showed a hypoechoic mass complex on left flank of 12 x 7 cm in size arising probably from the stomach. A C.T. scan disclosed a 12 x 9 cm. large mass with pour contrast enahancement not dissociable from gastric posterior wall, whitout secondary lesions, nodes or abdominal amounts, suggestive of the Gastrointestinal Stromal Tumor (GIST) of the stomach. A gastroduodenal endoscopic examination has showed a submucosal mass of the posterior wall of the gastric body.

At the laparotomy a large tumour measuring 12 x 10 cm has been seen arising from posterior wall of the gastric body with integrity of the capsule, no metastases or node were found. A subtotal gastrectomy was performed with trans-mesocolic gastrojejunostomy. Post-operative course was complicated by anastomotic leakage treated with TPN and the patient was discharged on the 15° day.

Histopatological examination showed a GIST 13 x 9 x 5 cm. in size CD117 (c-KIT) positive. Mitotic Index was 1-2 mitoses/50 HPF. S 100 and NSE focal positivity. Actina anti-muscle and anti-smooth-muscle negatives. Pan-cytocheratina negative. 7 node and margin of resection was negative.

The patient started after 30 day targeted therapy with imatinib mesylate 400 mg. a day for 1 year. Follow-up by PET-TC total body and upper gastrointestinal endoscopy has not been shown disease relapse after 2 year from surgical treatment.

Discussion

The surgery has traditionally been the only potential curative treatment for the primary localized GIST because theese neoplasms are resistant to radiotherapy and chemotherapy and also in the imatinib era the complete surgical resection “R0” with negative microscopic margin remains the most important prognostic factor. Like other sarcoma, GIST rarely metastasize to lymph-nodes, therefore lymphadenectomy is not routinely necessary unless locoregional* lymph-nodes are enlarged.

Unfortunately a R0 resection can be achieved only on the 40% - 60% of all GIST and approximately in 70% of the patients with primary localized GIST because more than half of the patients at the time of diagnosis have locally advanced or metastatic disease.

Long term follow-up indicates moreover that the surgery alone is generally non curative because more of the 50% of patients underwent potentially curative resection will show local recurrence or metastases within 18 -24 months and 5 year survival is usually 50% (De Matteo)). The recurrence involves the liver in the 65%, the peritoneal surface in the 50% and both in about 20%[11].

Tumour rupture or perforation are assimilable to residual gross disease and reduce the 5 years survival to rate inferior to 10%, therefore during the operation every precaution must be found to preserve capsule integrity because GIST are soft and friable neoplasms.

In locally advanced, recurrent and metastatic GIST, the surgery has played traditionally a palliative role because of the low resectability rate; essentially all patients after excision of peritoneal disease or hepatic resection develop recurrent disease with a median survival estimate on 15 months[1-7] (Muddan - De Matteo). A dramatic change in the management of the GIST happened in the 2001 when Joensuu et al. discovered imatinib mesylate to be highly effective against GIST. Imatinib is a tyrosina kinase receptor inibitor that inhibits proliferation and promotes apoptosis in GIST cells by interrupting tyrosine kinase-mediated and PDRGFa intracellular signaling. Initial clinical trials testing the efficacy of imatinib in unresectable and metastatic GIST have shown survival dramatically better than historical controls in over 80% of patients, with a partial tumor response approximately on 50% of patients, while about 30% have a least stable disease (Raut - De Matteo). Approximately 70% of patients with metastatic disease will be alive 2 years after the start of the therapy and about 50% will be free of progression.

In the recurrence and metastatic GIST imatinib is now considered the first-line treatment. Nevertheless long term follow-up has showed that complete responses are rare (5%)[6] and that moreover most of patient who initially respond to medical treatment, became resistant within 2 years from the start of the imatinib therapy with disease progression, because of molecular evolution of Kit mutation resistant clones. Even after introduction of the suntinib, approved for the patients intolerant or refractory to imatinib, the development of drug resistance remains a challenge. The limited possibility to continue a long-term medical therapy has prompted numerous studies to asses the role of combined medical and surgery therapy in the hope to improve the outcomes of GIST treatment, and several trials are ongoing to plan the best integration between surgery and medical adjuvant and neoadjuvant combined therapy. In the adjuvant therapy field a phase II trial by the ACOSOG Z9000 cnducted in high risk patients defined as tumour size > 10 cm., intraperitoneal rupture or multifocal tumour at dose of 400 mg/day for 12 months have shown that imatinib prolongs recurrence-free survival (RFS) and improved overall survival(OS) after the resection of primary GIST, when compared with historical controls.

The preliminary results of a phase III double-blind-placebo controlled randomized multicenter trial by ACOSOG Z9001 has revealed a 97% 1 - year recurrence-free survival in the IM group after the resection of primary GIST compared with 80% in the placebo group. After the publication of these and other trials imatinib has been approved by the FDA for the adjuvant treatment of all resected primary GIST.

In the advanced and metastatic GIST several studies have evaluated the role of the combined medical and surgery therapy in the hope to increase resectability and to achieve R0 – R1 resection in initially unresectable disease responsive to medical therapy or to achieve surgical debulking in disease become drug resistant, in the hypothesis that by resecting clones of disease that have acquired drug resistance at the imatinib or suntinib therapy, surgical debulking may prolong survival as the chance of resistance is proportional to the amount of residual GIST following therapy with tyrosine kinase inhibitor[7].

According oncologist, for GIST metastases that have been downsized by imatinib or suntinib neoadjuvant therapy, surgery should be performed during maximal response to medical therapy, while the tumour is still under control, before of the drug resistant clones development and drug therapy moreover must be continued post-operatively. Although there is not a standardized timing of surgery the most surgeons advocate the resection within one year from start imatinib.

In the papers of Raut e al. the patients included were selected for surgical debulking both to remove disease before secondary resistance developed or to halt disease progression by eliminating resistant clones. 69 patients according the oncologists, were categorized in three group by using serial TC scan in the decision-making, having stable disease, limited progression (1 tumour growing) or generalized progression (more than 1 tumour growing) to the imatinib; R0 or R1 resection was achieved in the 78% of stable disease with 80% of progression free survival(PFS) and 95 % of overall survival (OS) at 1 years respectively while in limited progression disease R0 - R1 resection was achieved only in the 25% with 33% of PFS and 86% of OS at 1 years respectively; conversely none

patient with generalized progression of disease was alive at 1 years.

In the study of De Matteo et al. forty patients categorized in three group, having responsive disease, focal resistance (1 tumour growing) or multifocal resistance (more than 1 tumour growing) to neoadjuvant imatinib, underwent surgery after a median of 15 months from start medical therapy; in 20 patients with responsive disease 2 years progression free survival was 61% and 2 years overall survival 100%; in contrast 13 patient with focal resistance progressed and 2 years overall survival was 36%; none of 7 patients with multifocal resistance was alive a 2 years.

These studies and other more recent[1-13], indicate that today combined molecular and surgery therapy is a reasonable solution in a subset of patients with recurrent and metastatic GIST responsive or with limited progression to the medical therapy; the surgery is not indicate instead in not responsive disease. However they are not randomized studies so it's impossible to asses the specific contribution of the surgery to survival rates in this series; moreover often is required a surgery highly aggressive that may include multivisceral resection, peritonectomy/omentectomy and liver resection, with high morbility rate.

Since the stopping of imatinib is associated with increased risk of disease progression[9], the molecular therapy should be continued post-operatively without a break unless toxicity are unmanageable. The follow-up differ across the institution , however as most of GIST tends to recur within the first 2 years, intense surveillance is required during this period. Recent guideline by the National Comprehensive Cancer Network recommended C.T. scan of the abdomen and pelvis every 3-6-months for 3-5 years and then yearly. The European Society of

Medical Oncology guidelines stratify intensity of surveillance with risk of recurrence. For GIST > 5 cm. in size or with > 5 mitoses /HPF, CT scan is recommended every 3 or 4 months for 3 years followed by every 6 months for 2 additional years and yearly thereafter.

For smaller and less mitotically active tumours, CT scan is recommended every 6 months for 5 years. In general the prognosis of malignant GIST after curative intent surgery is strongly related to tumour size and location.

Conclusion

After twelve years from imatinib introduction, several trials have demonstrated the importance of the combined medical and surgery therapy to improve outcomes of the GIST treatment. In the primary localized GIST, where the complete R0 resection remains the most important prognostic factor, the adjuvant imatinib therapy prolongs RFS and OS after surgery and adjuvant imatinib therapy is now indicated in all resected primary GIST.

In the advanced and metastatic GIST the imatinib is now the first-line treatment, however the develop of drug resistance represents a serious challenge; recent trials have evaluated the integration of the surgery even in the advanced GIST both to achieve complete resection R0-R1, before of the develop of drug resistance, and to achieve surgical debulking of residual resistant disease, to allow the continuation of the medical therapy. However only prospective randomized trials can assess the specific benefit of the surgery beyond the drug therapy in prolonging survival in patients with metastatic or unresectable GIST who have been downsized by imatinib therapy.

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