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The role of surgery after Imatinib therapy in GIST

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INTRODUCTION

Imatinib (IM) is considered the standard treatment for patients with metastatic GIST (1) and the standard adjuvant therapy for those with localized GIST at significant risk of recurrence (2). In the past few years, the possible role of combination of IM with surgery has been explored in specific settings (localized or metastatic disease). IM has been offered before surgical treatment (neoadjuvant therapy) in localized disease in order to improve the results of surgery and/or to simplify the operation. In patients with metastatic GIST, surgery has been used after IM with the aim of reducing the risk of secondary resistance.

In this review we discuss the role of surgery after IM therapy in patients with localized and metastatic disease.

LOCALIZED DISEASE

Until 2006 the use of IM in the pre-operative setting for patients with primary but inoperable GIST was anecdotal with only few cases published (3). The definition of inoperability of primary disease is difficult to standardize and it can vary in different centers being usually surgeon-dependent. With the introduction of target therapy in the treatment of solid tumors, the parameters used to define the resectability of a lesion changed. In fact, prior to the development of IM, surgical resection was attempted for nearly all localized primary GISTs and eventually a tumor was considered unresectable during the intra-operative procedure (4). To date, according to the reports of referral centers, GISTs are defined locally advanced based on the radiological evidence of significant involvement of a single organ and/or extension of the tumor to adjacent organs (5) or involvement of critical anatomic structures, i.e. superior mesenteric vessels (6).

In patients with clearly unresectable localized GIST, the therapy of choice should be IM eventually followed by surgery, if technically feasible (1).

In patients with resectable localized GIST the use of pre-operative therapy should be considered in the following situations:

– potential multivisceral resection or major organ resection, such us total gastrectomy, addomino-perineal resection, pancreaticoduodenectomy (to possibly spare organs and function and reduce surgical morbidity)

– risk of bleeding or tumor rupture, based on preoperative radiological imaging (to reduce the potential risk of contamination, known to have a significant impact on outcome) (6).

The meaning of neoadjuvant therapy is to decrease tumor volume in order to perform more conservative but complete excision avoiding multivisceral or critical structure resection. This pre-operative approach is usually associated with a decrease in surgical morbidity and to a potential organs and/or function sparing. For example, in esophageal or duodenal GISTs, the extent of surgery does not change even after consistent tumor shrinkage, but the surgical procedure could be safer in case of size reduction. In fact, the critical structures surrounding the tumors at these sites can

be more safely handled and the rate of complications possibly reduced. On the contrary, an evident change in surgical procedure is expected for gastric or rectal lesions. In particular, patients with tumors located close to the oesophagogastric junction may benefit from tumor shrinkage: in this case a wedge resection preserving oesophagogastric sphincter can be performed obtaining a better functional outcome. Patients with low rectal GIST, who require abdomino-perineal resections, after volume reduction on IM could potentially undergo a conservative procedure. Tumor shrinkage in this specific location can also reduce the risk of sexual and urological dysfunctions (6).

In general, in order to properly plan surgical resection after IM therapy, the response assessment is of crucial importance. Tumor response is evaluated with serial contrast enhanced CT imaging, even if for specific location such as the rectum, MRI with gadolinium is preferable due to the better characterization of the soft tissue of pelvic floor.

Pre-operative IM does not guarantee the completeness of the surgical resection, but in the series published in literature, complete surgery was achieved in the vast majority of patients with locally advanced disease (Table 1) (5-10). These data are different from the one obtained in the metastatic setting where the completeness of the resection is more difficult to achieve (Table 2).

Surgical resection after IM therapy is safe and feasible, especially in patients treated for localized disease (6,8). Complications are usually mild and include wound infection, intra-abdominal abscess/fluid and delayed gastrointestinal function. The rate and the type of complications depend on the extent of surgery. Due to the small number of patients included in the series available in the literature and to the heterogeneity of the population (localized/metastatic disease), larger studies are needed to evaluate the impact of neoadjuvant IM on the rate of surgical complications.

The optimal duration of preoperative IM has not yet been established (3) even if longer is the treatment smaller becomes the lesion and consequently less difficult is the operation. In the series published, surgery is performed after a median time of 9 months from the beginning of IM therapy (5-10). In fact, the majority of patients achieve tumor shrinkage within 6 months from IM initiation. As observed in a previous phase III EORTC trial for metastatic patients, tumor shrinkage starts from the 4th month of therapy

Table 1 – **Surgery after IM in patients with localized disease**

References	#Pts	Median length of preop. IM (mo.)	% Response to preop. IM[a]	% CR pts	Median postop. FU (mo.)	% of NED pts at last FU	% of pts alive at last FU
Andtbacka et al., 2006[5]	11	11.9	90.9	100	19.5	90.9	100
Bonvalot et al., 2006[7]	5	12	100	100	32	NR	NR
Fiore et al., 2009[6]	15	9	80	100	25	73	86.7
Eisenberg et al., 2009[8]	30	2	90	80	36	NR	NR
CST1571-BDE43[9]	40	6	NA	NA	NA	NA	NANA
Blesius et al., 2011[10]	9	7.3	89	89	53.5	78	100

[a] Including complete, partial response and stable disease

#Pts, number of patients; preop., preoperative; mo., months; IM, Imatinib; CR, complete resected; postop., postoperative; FU, follow-up; NED, not evidence of disease; NR, not reported; NA, not available

Table 2 – **Surgery after IM in patients with recurrent/metastatic**

References	#Pts	Median length of preop. IM (mo.)	% Response to preop. IM[c]	% CR pts	Median postop. FU (mo.)	% of NED pts at last FU	% of pts alive at last FU
Andtbacka et al., 2006[5]	35	15.2	31.4	31.4	11.8[d], 30.7[e]	51.4	85.7
Bonvalot et al., 2006[7]	17[a]	12	88.2	58.8	32	NR	NR
DeMatteo et al., 2007[16]	40	15	97.5	62	15	52.5	70
Eisenberg et al., 2009[8]	22	2	95	54	36	NR	NR
Mussi et al., 2010[13]	80	15 (Group A), 21 (Group B)[b]	Unknown	71	31, 13[f]	61	86

[a] Including 5 patients who underwent to emergency procedure

[b] 15 months for patients who were operated upon clinical response (Group A);21 for patients in whom surgery was carried out with the aim of resecting single progressive lesions (Group B)

[c] Including complete, partial response and stable disease

[d] For incomplete resected patients

[e] For complete resected patients

[f] 31 months for patients in Group A; 13 months for patients in Group B

#Pts, number of patients; preop., preoperative; mo., months; IM, Imatinib; CR, complete resected; postop., postoperative; FU, follow-up; NED, not evidence of disease; NR, not reported

and continue for several months (11). Further volume reductions after the 9th month can occur, but in general they are minimal. In patients with responding disease, potential resection should not be considered before 3-4 months of therapy (4, 12). Theoretically, if surgery is carried out too early, the benefit of preoperative treatment may be less and complete resection of all tumor tissue might be more difficult. If it is planned too late, secondary resistance might develop (13). The best operating time is then between the 6th and the 12th month.

The challenge in the group of patients with localized disease who respond to pre-operative IM therapy is to explain to them the need of surgical approach. In fact, due to the well tolerability of the drug and the absence of symptoms in case of response, patients could refuse the surgical option even if it represents the only potential curative treatment.

Few studies give information on the safety and efficacy of IM in the preoperative setting for patients with localized disease. In the first trial, RTOG S0132, patients received preoperative IM (600 mg/day for 8-12 weeks) followed by surgical resection if the disease was considered completely resectable. Then, patients received adjuvant IM for 2 years. Preoperative IM was shown to be safe and associated to 57% PFS, 77% DSS and 77% OS at 5 years (14).

CST1571-BDE43 is a recently completed prospective non randomized, neoadjuvant phase II study that evaluated the use of preoperative IM in patients with localized disease potentially resectable. Patients received IM 400 mg once daily for 6 months. The results are still pending.

Recently, a sub-analysis of the patients with localized GIST who received preoperative IM in the context of BFR14 prospective trial was published. The PFS and OS of patients operated (36%) at 3 years were 89% and 67%, respectively (10).

Preoperative therapy in localized disease is therefore an option that should be considered every time surgical morbidity is not expected to be minimal. When a sufficient shrinkage is obtained, surgery might be performed, since it remains the only potentially curative procedure in this phase of the disease.

METASTATIC DISEASE

The standard treatment of metastatic disease is IM (1). In the pre-imatinib era, long-term survival of metastatic patients was observed only in a subset of patients who underwent complete resection of the disease (15). In the metastatic setting surgical resection can play a role in reducing the tumor volume, which has been shown to correlate with PFS (5, 7, 17,16).

The main rationale for "adjuvant" surgery in metastatic GIST after response to IM is that in almost all patients despite the radiological evidence of complete response, viable disease with active KIT signaling can be demonstrated on surgical specimen (18). The viable cells represent theoretically clones with an acquired mutation in KIT resistant to IM. Currently, once resistance to IM develops, there is only a small chance of rescuing the patient through dose escalation or using a different TKI such as sunitinib (19).

As for patients with localized disease, the best timing for surgical resection after IM therapy in patients with metastatic disease has not yet established, but it is usually considered after a median time of 6-12 months of treatment, to avoid the risk of operating patients once the development of secondary resistance has already occurred.

Radiographic response to IM is based on changes in tumor size, degree and extent of enhancement, and the presence or absence of solid nodules within the tumor. While the vast majority of patients treated with preoperative IM show tumor shrinkage, some may show only changes in tumor density on CT scan. This radiological pattern of response can also be associated to an initial increase in tumor size. To overcome the limits of CT or MRI imaging, FDG–PET scan has been extensively used showing high sensitivity especially in early assessment of tumor response (20). In fact, PET response can be determined after a week or less of treatment and precedes CT response by several weeks (21,22).

In the series published in the literature a benefit of surgery is evident in patients with a response, while for patients with progression, surgical resection does not add significant advantages in terms of progression free survival (PFS) and overall survival (OS) (5,7,16,17,23,24). In fact, despite the completeness of surgery, local relapse occurs before in *non responders* group (5,7,16,17,23,24). This is the main reason to avoid an extensive procedure that can be related to high morbidity in this subgroup of patients.

The vast majority of metastatic patients have more than one lesion especially in the liver or in the peritoneum leading the completeness of surgery difficult to achieve. However, some authors considered the surgical approach also in patients with focal progression assuming these lesions represent the resistant clones of the disease (7,17). Patients with localized progression who underwent surgical resection had a PFS and OS comparable to the one obtained in patients treated with other tyrosine kinase inhibitors (13). Nevertheless, surgical resection in focal/localized disease progression is not universally accepted (24). One of the reasons is that complete resection is not achievable in the vast majority of the patients and PFS and OS are lower than in the responsive patients. Moreover, the risk of complications in patients who underwent R2 was higher (17,23). Therefore, the surgical option in case of focal progression should be discussed into a multidisciplinary fashion, taking into account other therapeutic approaches. On the contrary, in patients with generalized progression, surgery should never be offered except for patients who develop treatment- or progression- related complications. Alternative strategies include second and further line of tyrosine kinase inhibitors as well as IM re-challenging preferably in the context of clinical studies.

For patients who undergo surgical resection in the setting of metastatic disease, discontinuation of therapy after operation is not recommended (26): failure to resume IM postoperatively result in rapid disease recurrence (24). In fact, the actual indication is to continue IM indefinitely even after complete surgical resection (1).

Despite the good prognosis of *responders* after complete surgery for residual metastatic disease, this approach is considered investigational in the guide-

lines available (1). In fact, it is not yet known if the good prognosis is to correlate with the effect of surgical excision or to a selection bias.

However, even in responding patients, complete pathological remissions are not observed. The presence of a subset of cells that remains in a quiescent state might explain the development of progressive lesions after a favorable initial response. In fact, one of the hypothetical mechanism by which IM is able to produce a tumor's shrinkage in the preoperative setting is the anti-vascular effects (27). Further studies on the mechanism of action of IM are ongoing.

Despite the absence of solid data to base the decision upon and waiting for the results of the ongoing trials, surgical resection could always be considered in patients with metastatic disease who respond partially or completely to IM.

A Chinese phase III trial that randomizes patients with metastatic GIST responsive to or stable on IM to either undergo IM alone (current standard of care) or IM plus early cytoreductive surgery, has been recently closed after 3 years with a limited accrual (41 patients over 210 expected) (28). The aim is to evaluate if surgery after IM could improve the PFS. Preliminary results will be soon reported.

Even the EORTC trial (SURGIST), opened to evaluate surgery of residual disease in patients with metastatic GIST responding to IM, has been recently closed for slow accrual. A prospective registry has been proposed. This could include prospectively patients who would have been randomized in the previous study in order to obtain more reliable data to understand whether surgery in responding patients is of any benefit.

To date, surgery after IM therapy in metastatic patients is an option that should be discussed with the patient, explaining all the uncertainties that are waiting for an answer.

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