

Efficacy of surgery and imatinib mesylate in the treatment of advanced gastrointestinal stromal tumor: a systematic review

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ABSTRACT

Aims and background. In patients with localized gastrointestinal stromal tumors, surgery remains the elective treatment. Nowadays, imatinib therapy has been standardized in advanced gastrointestinal stromal tumors, showing continuous improvements in progression-free and overall survival. A combination of imatinib therapy and surgery may also be effective in a subset of patients with metastatic or unresectable gastrointestinal stromal tumors. In this review, the authors analyzed the role of imatinib mesylate associated to surgery in unresectable and/or metastatic gastrointestinal stromal tumors.

Methods and study design. We searched for all published and unpublished randomized controlled clinical trials and controlled clinical trials. We conducted the review according to the recommendations of The Cochrane Collaboration. We used Review Manager 5 software for the statistical analysis.

Results. There are currently no randomized controlled clinical trials or controlled clinical trials on this issue. We performed a subgroup analysis in the patients preoperatively treated with imatinib mesylate. This subgroup revealed a minor incidence of recurrent or metastatic gastrointestinal stromal tumors and a greater incidence of locally unresectable gastrointestinal stromal tumors in the responsive disease group ($P = 0.001$). In this patient group, more complete resections were observed ($P = 0.00001$). Furthermore, in the same patient group we observed a more significant 12 and 24-month disease-free survival after imatinib treatment and complete resection (respectively $P = 0.06$ and $P = 0.003$) and also a better 24-month overall survival ($P = 0.004$).

Conclusions. There is actually only one ongoing European randomized study evaluating surgery of residual disease in patients with metastatic gastrointestinal stromal tumors responding to imatinib mesylate. Imatinib mesylate represents the standard treatment as preoperative supplement for locally unresectable and/or metastatic gastrointestinal stromal tumors, and a trial to compare the approach *versus* surgery alone is not necessary. For patients responding to imatinib or patients with prolonged stable disease, resection of residual disease should be considered. A phase III randomized study evaluating surgery of residual disease in patients with metastatic gastrointestinal stromal tumor responding to imatinib mesylate, EORTC 62063, has been opened. Moreover, surgery should be considered for patients at higher risk of complications during pharmacological debulking. In advanced gastrointestinal stromal tumors, the advantages of the integrated treatment are significant in the complete or partial response disease group in terms of more complete resections and better disease-free and overall survival. Free full text available at www.tumorionline.it

Key words: advanced gastrointestinal stromal tumors, imatinib mesylate, surgery.

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Received April 27, 2009; accepted June 30, 2009.

Introduction

Gastrointestinal stromal tumors (GIST) include the most common subset of mesenchymal tumors of the gastrointestinal tract. Most GIST have an activating mutation in the KIT protooncogene or, occasionally, in the PDGFR-gene. Constitutive overexpression of the tyrosine kinase receptor results in increasing cell proliferation and survival^{1,2}. The essential role of KIT in GIST pathogenesis has been proven by the therapeutic success of imatinib mesylate (STI571, Gleevec or Glivec, Novartis Pharmaceuticals, Basel Switzerland), a selective molecular inhibitor against these defects³. In patients with localized GIST, surgery remains the elective treatment⁴. Nowadays, imatinib therapy has been standardized in advanced GIST, and it is showing continuous improvements in progression-free and overall survival^{5,6}. A combination of imatinib therapy and surgery may also be effective in a subset of patients with metastatic or unresectable GIST⁷⁻¹¹. In this review, the authors analyze the role of imatinib mesylate associated to surgery in unresectable and/or metastatic GIST.

Methods

Research methods for identification of studies

We searched for all published and unpublished randomized controlled trials and controlled clinical trials. We asked authors of relevant papers to provide further information by using a data extraction form. We did not restrict searches by language, date, or publication status. We searched into the following electronic data bases: Cochrane Central Register of Controlled Trials (latest issue), MEDLINE (1966 to date), Science Citation Index (1981 to date), ISI Proceedings (1990 to date), Current Controlled Trials metaRegister (latest issue), Zetoc (latest issue), CINAHL (1982 to date) and EMBASE (1980 to date). We based the electronic data base searches on the following MEDLINE strategy, which we adapted, as appropriate, for each database: “surgery”; “imatinib mesylate”; “Gleevec”; “Glivec”; “gastrointestinal stromal tumors”; “GIST”. We checked the reference lists of all relevant studies obtained from our search and from previously published systematic reviews in order to identify other possible articles.

Data collection and analysis

We conducted the review according to the recommendations of The Cochrane Collaboration¹².

Statistical analysis

We used Review Manager 5 software to conduct the review¹³.

Data extraction

Two authors (RC, FL) assessed titles or abstracts of all the studies identified by the initial search and excluded

clearly non-relevant studies. They obtained the full text of articles for all the potentially relevant studies and also for those studies with unclear methodology. Disagreements on inclusion were resolved by discussing and, if necessary, by involving an independent third author (EF). The following information for each included trial was extracted independently by the two investigators (RC, FL): method of outcome, blinding of outcome evaluators, and balance of prognostic factors.

Inclusion criteria

To be included in the analysis, studies had to compare neoadjuvant treatment with imatinib mesylate and surgery *versus* surgery alone in the unresectable and/or metastatic GIST.

Exclusion criteria

Studies were excluded from the analysis if: the outcomes of interest were not reported for the two techniques; it was impossible to extrapolate or calculate the necessary data from the published results; there was a considerable overlap between authors, centers or patient cohorts evaluated in published literature.

Outcomes of interest

The outcomes overall survival and disease-free survival were used to compare the surgery group with the preoperative imatinib mesylate treatment associated to surgery.

Methodological quality

RC and EF assessed the methodological quality of each trial independently. Each unclear or missing information was resolved by contacting the authors of the specific trial. Different opinions between the extracting data authors were resolved through discussion. DC acted as an arbitrator in case of persistence of different opinions.

Measures of treatment effect

Dichotomous data were analyzed for relative risk ratio and odds ratio (OR). The absolute effects were measured with the risk differences. 95% confidence intervals (CI) were calculated for these measures of effect. The Mantel-Haenszel method was used for meta-analysis^{14,15}. Results were presented on a forest plot graph.

Assessment of heterogeneity

The chi square test was used for heterogeneity assessment. The outcomes were measured with continuous scales, whereas data of treatment effects were analyzed with mean difference. If different trials used different scales, we standardized and combined the results.

Results

Eligible studies for meta-analysis

There are currently no randomized controlled trials or controlled clinical trials on this issue to compare surgery alone with the use of imatinib as preoperative supplement for unresectable and/or metastatic GIST.

Subgroup analysis

We performed a subgroup analysis in the patients preoperatively treated with imatinib mesylate.

Inclusion criteria of subgroup analysis

We evaluated disease status after imatinib mesylate use as preoperative supplement for locally unresectable and/or metastatic GIST. Response to imatinib mesylate in the literature can be classified in two groups¹⁶: complete or partial response disease (RD), progressive or stationary disease (PD).

Eligible studies for subgroup analysis

A total of 238 abstracts were identified by searching through the aforementioned key words. Abstract examination left 14 adequate studies viable for full evaluation. Two studies showed overlap of authors or institutions, whereas data were not extractable from five studies for meta-analysis purposes so these trials were also excluded. A total of seven studies (1 prospective non-randomized study and 6 retrospective studies) remained included in the final analysis, with a total of 256 patients (139 RD; 117 PD)¹⁷⁻²⁷ (Figure 1) (Tables 1 and 2).

Results from subgroup analysis

In the PD group, a minor incidence of locally unresectable GIST and a greater incidence of recurrent or metastatic GIST were noted (OR, 0.10; 95% CI, 0.02-0.40; $P = 0.001$) (Figure 2). There was a small localization difference in the PD group: gastric GIST *versus* other GIST (OR, 0.32; 95% CI, 0.06-1.63; $P = 0.17$) (Figure 3).

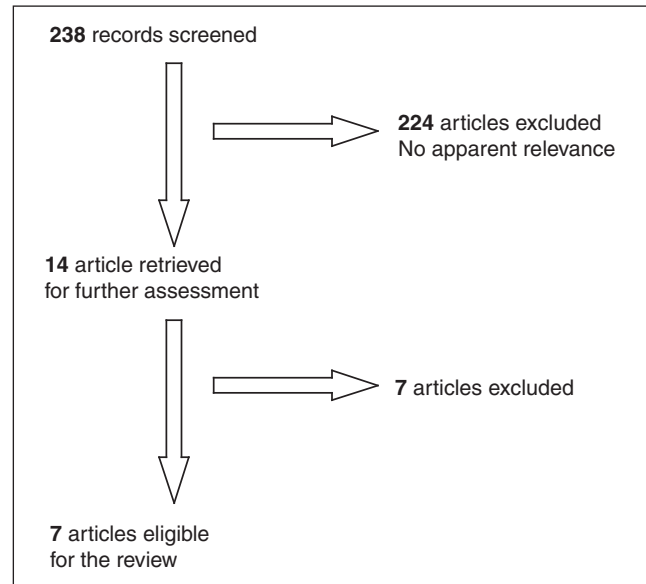


Figure 1 - Systematic review study flowchart - search reporting instruments for identification of published articles subgroup analysis in the group treated preoperatively with imatinib mesylate.

A more significant difference in favor of small bowel localization was detected considering gastric GIST *versus* small bowel GIST as a subgroup of localization (OR, 0.23; 95% CI, 0.05-1.21; $P = 0.08$) (Figure 4).

The difference was instead very poor for the subgroup of gastric GIST *versus* colorectal GIST (OR, 0.86; 95% CI, 0.10-7.34; $P = 0.89$) (Figure 5).

As for resection status, there were significant differences between RD and PD groups: incomplete resections (R1/R2) were significantly fewer in the RD group (OR, 0.06; 95% CI, 0.03-0.11; $P = 0.00001$) (Figure 6).

The difference was significant in favor of the RD group in disease-free survival within 12 months of imatinib treatment and complete resection (R0) for advanced GIST between RD and PD groups (OR, 0.10; 95% CI, 0.01-1.12; $P = 0.06$). In the analysis, there was a sig-

Table 1 - Descriptions and summary of studies eligible for the review

Authors	Year	Location	Type of study	No. patients with advanced GISTs	Surgery associated with preoperative imatinib treatment (no. patients)	Examined outcome
Andtbacka <i>et al.</i> ¹⁷	2007	USA	Retrospective	56	56	DFS, OS
Bonvalot <i>et al.</i> ¹⁸	2006	France	Retrospective	180	22	PFS
Gold <i>et al.</i> ¹⁹	2007	USA	Retrospective	40	40	OS
Gronchi <i>et al.</i> ²⁰	2007	Italia	Retrospective	159	38	PFS, DFS
Raut <i>et al.</i> ²¹	2006	USA	Retrospective	69	69	DFS, OS
Rutkowski <i>et al.</i> ²²	2006	Poland	Prospective not randomized	141	24	PFS, OS
Sym <i>et al.</i> ¹⁰	2008	Korea	Retrospective	256	34	PFS, DFS

DFS, disease-free survival; OS, overall survival; PFS, progression-free survival.

Table 2 - Descriptions and summary of studies excluded from the review

Authors	Year	Location	Type of study	No. patients with advanced GISTs	Surgery associated with preoperative imatinib treatment (no. patients)	Examined outcome
Al-Batran <i>et al.</i> ²³	2007	Germany	Retrospective	38	38	PFS, OS
An <i>et al.</i> ²⁴	2007	Korea	Retrospective	111	111	OS
Bauer <i>et al.</i> ²⁵	2005	Germany	Prospective	113	90	PFS, OS
Haller <i>et al.</i> ⁷	2007	Germany	Case report	1	1	*
Hasegawa <i>et al.</i> ²⁶	2007	Japan	Retrospective	16	16	PFS, Median TTP
Ruka <i>et al.</i> ⁸	2009	Poland	Case series	4	4	PFS, OS
Wu <i>et al.</i> ²⁷	2003	USA	Retrospective	57	0	PFS, OS

OS, overall survival; PFS, progression-free survival; TTP, time to progression. *Not indicated.

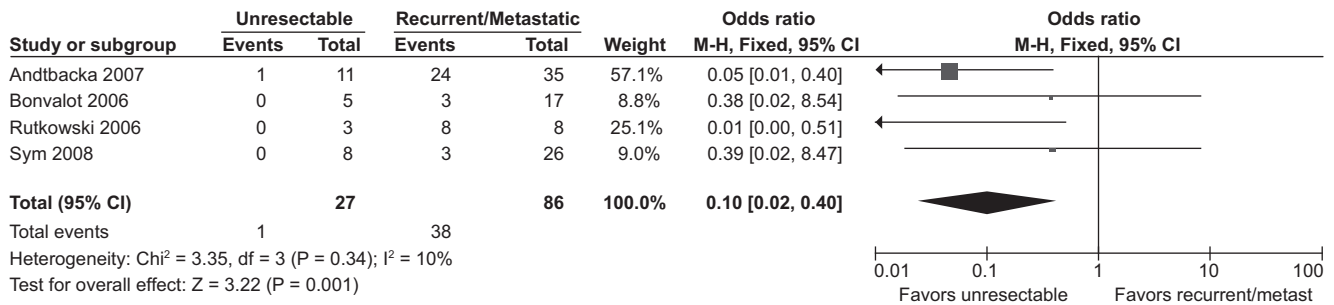


Figure 2 - Disease status after preoperative imatinib treatment in advanced GIST: PD patients in locally unresectable versus recurrent or metastatic GIST.

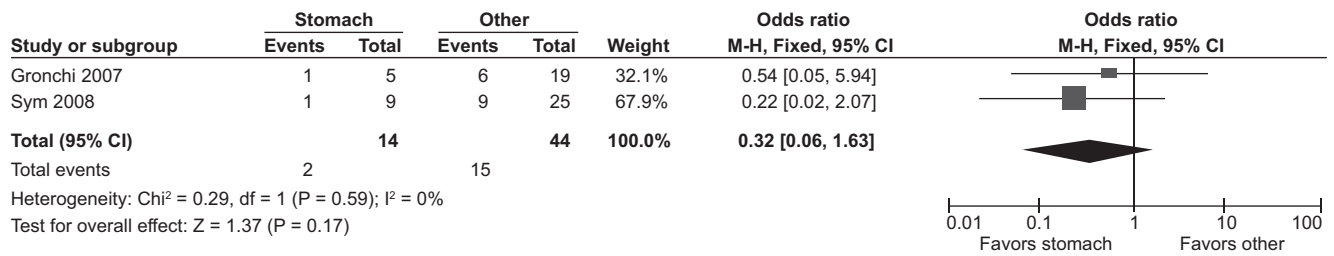


Figure 3 - Disease localization in PD patients: gastric GIST versus other GIST.

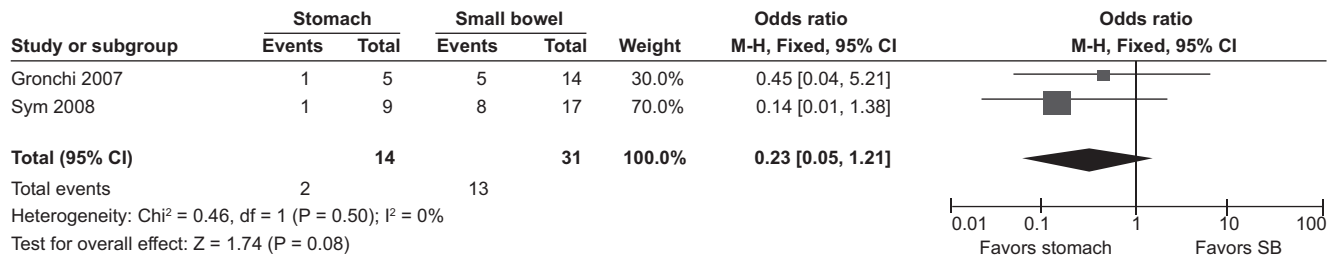


Figure 4 - Disease localization in PD patients: gastric GIST versus small bowel GIST. PD, progressive or stationary disease.

nificant heterogeneity ($\chi^2 = 1.97$; I^2 49%), and for this reason we used the M-H random test instead of the fixed one for the OR calculation (Figure 7).

This difference in disease-free survival was still signif-

icant at 24 months after the integrated treatment (OR, 0.13; 95% CI, 0.03-0.50; $P = 0.003$) (Figure 8).

Furthermore, there was a relevant difference in favor of the RD group in overall survival within 24 months of ima-

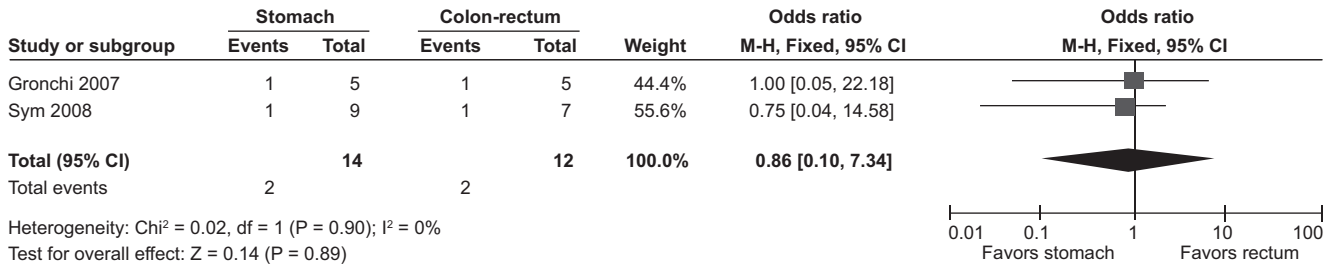


Figure 5 - Disease localization in PD patients: gastric GIST versus colon-rectal GIST.

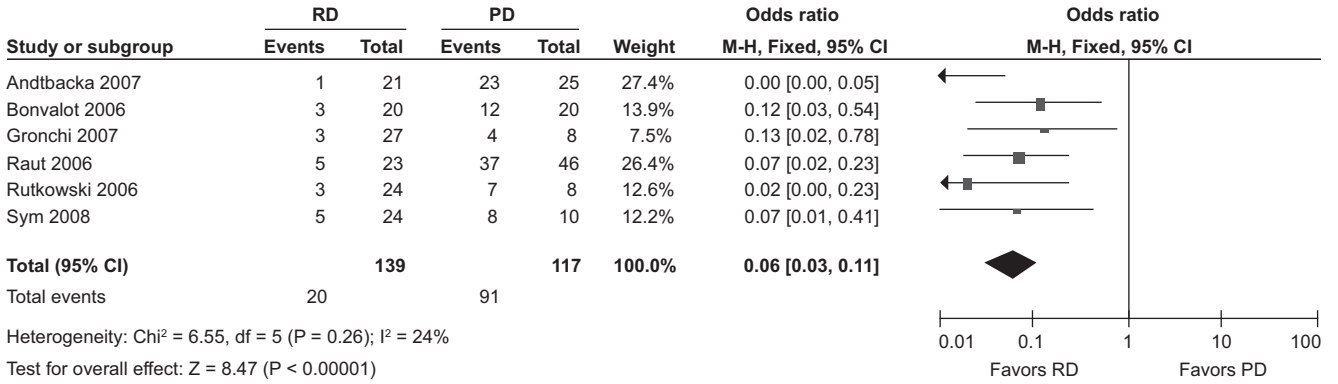


Figure 6 - Incomplete resection (R1-R2) after imatinib treatment in advanced GIST: RD versus PD groups.

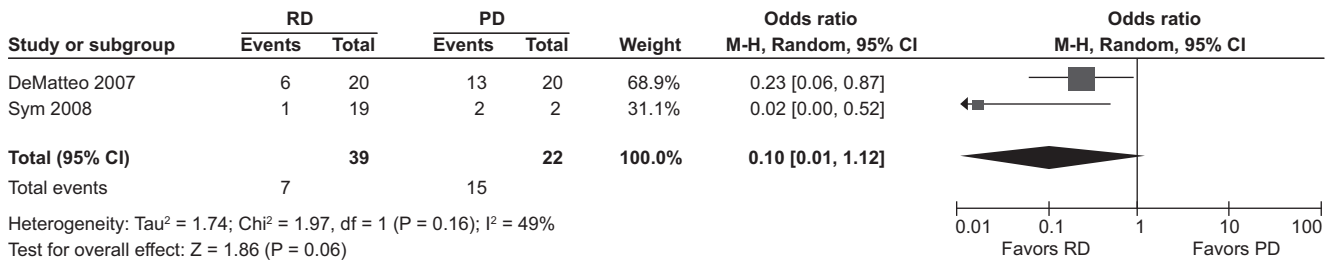


Figure 7 - Recurrence within 12 months of imatinib treatment and complete resection (R0) in advanced GIST: PD groups.

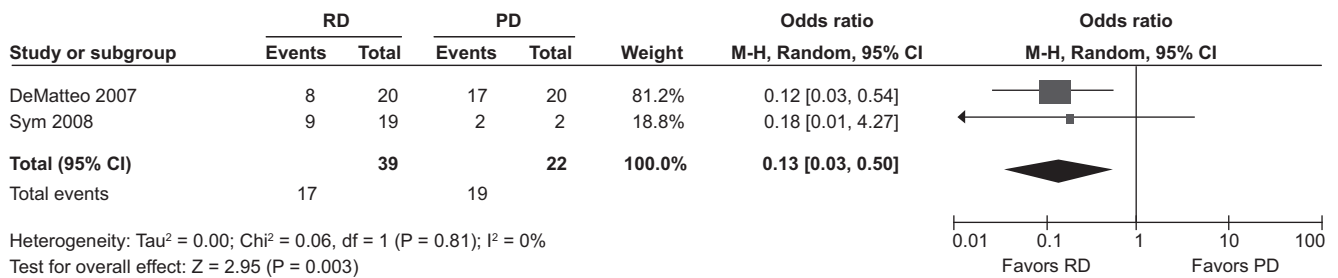


Figure 8 - Recurrence within 24 months of imatinib treatment and complete resection (R0) in advanced GIST: RD versus PD groups. RD, complete or partial response disease; PD, progressive or stationary disease.

tinib treatment and complete resection (R0) in advanced GIST (OR, 0.04; 95% CI, 0.00-0.37; $P = 0.004$) (Figure 9).

Discussion

In the pre-KIT era, surgery represented the only successful therapy for GIST treatment at every disease stage.

Nowadays, complete surgical excision is the standard treatment only for localized GIST. Indeed, even if a radical resection might be possible in up to 70-95% of the cases, 5-year overall survival is 42-54%. The risk of relapse remains relevant, depending on mitotic count, tumor size and localization. In advanced GIST, the role of surgery has always been palliative, with a mean overall sur-

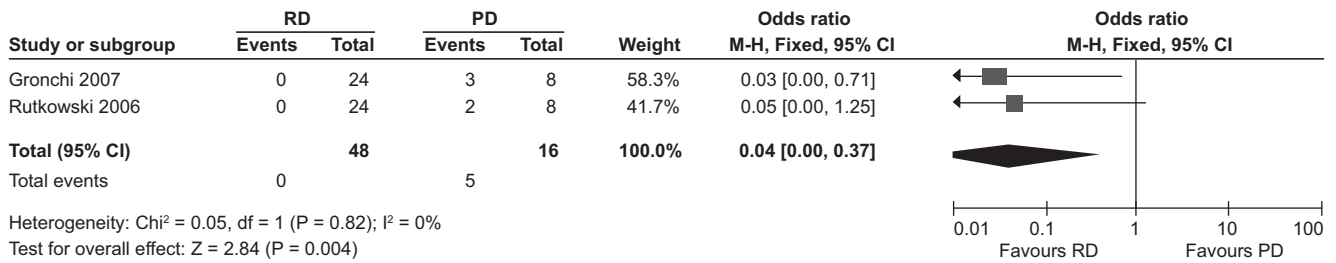


Figure 9 - Death within 24 months of imatinib treatment and complete resection (R0) in advanced GIST: RD versus PD groups.

vival of 13 months²⁸⁻³¹. Since 2001, imatinib has represented the standard treatment in locally unresectable patients and metastatic patients. These approaches are unambiguous and shared by all recent NCCN guidelines in the USA³² and ESMO guidelines in Europe³³.

Currently, there are numerous trials on the management of tyrosine kinase inhibitors (TKI) as adjuvant and neoadjuvant therapy, and in the years to come, an integration in different combinations, between surgery and TKI, is to be expected. Multidisciplinary treatment planning, leading to the best treatment choice, the correct patient selection and the right timing of integrated treatments, is thus necessary. On the basis of the data reported by two phase I-II trials on the use of imatinib in metastatic diseases, partial responses to the treatment were obtained in 45-50% of the patients, with disease stabilization in 28-32%. Instead, complete responses were rare (5%)^{34,35}. An ongoing European randomized study evaluating surgery on residual disease in patients with metastatic GIST responding to imatinib mesylate suggests that adjuvant imatinib therapy is safe and seems to improve recurrence-free survival compared with placebo after the resection of primary GIST³⁶. Glivec has been approved in the adjuvant setting in the US and Europe after publication of the study³⁶.

Application of the orally bioactive TKI as targeted therapy for GIST has given prodigious results in terms of overall survival (1-year survival of 90% vs 25% in pre-TKI era) and of progression-free survival (18-26 months) compared to the same parameters previously evaluated in trials employing doxorubicin as conventional therapy³⁵. Imatinib has dramatically influenced the treatment of patients affected by GIST. However, the matter of secondary resistance is still limiting long-term TKI use. Therefore, complete excision of residual metastatic disease in advanced tumors, weeding out cellular clones that have acquired resistance in order to increase complete remissions, is still a topic of discussion.

Nowadays, it is clear that an objective response (30% reduction in tumor size evaluated through following controls compared to the initial tumor mass) is often obtained after about 4 months of treatment. An 80% reduction in tumor size is obtained within 6 months, with a plateau at 12 months after the onset of TKI therapy, but yearly 20% of patients acquire secondary resistance^{11,34,35}.

It would be convenient to consider a surgical resection of residual disease, in advanced disease, as soon as the greater response is achieved. A greater response can be defined as no signs of improvement in two following computed tomography evaluations. For the reasons stated above, surgery should be planned after at least 6 months of treatment with TKI and before the appearance of secondary resistance (within 12-24 months).

Furthermore, another group of patients benefiting from surgery of residual disease has to be considered. Such patients, which represent about 5% of all treated patients, have a high probability of developing complications during pharmacological debulking of the tumor. In particular, the most common surgical complications during selected molecular-targeted therapy are hemorrhage, abscesses, intestinal occlusion, perforation and fistulization. In these cases, morbidity and mortality for emergency surgery are particularly high. Therefore, surgery should be considered in a multidisciplinary setting pool. Molecular-targeted therapy, in the case of preventive surgery, should not be suspended until 24 h before surgery.

From our analysis, we found a lower incidence of recurrent or metastatic GIST and a higher incidence of locally unresectable GIST in the RD group ($P = 0.001$), although in this patient group there were more complete resections (R0) ($P = 0.00001$). Neoadjuvant imatinib therapy for primarily unresectable GIST commonly results in "down-sizing" and allows curative surgical resection or function-sparing surgery. Imatinib therapy showed an improvement following radical surgical resection (R0) in patients in the RD group. Furthermore, in the same patient group we verified a better 12 and 24-month disease-free survival after imatinib treatment and complete resection (R0) (respectively $P = 0.06$ and $P = 0.003$). A better 24-month overall survival ($P = 0.004$) was also noted. Patients exhibiting complete or partial response appeared to have a better clinical outcome compared to patients with PD. Moreover, the higher incidence of small bowel localized GIST concerned the patients with PD after imatinib treatment (PD group), whereas gastric GIST more frequently ($P = 0.08$) showed a complete or partial response. GIST localization is probably an important prognostic factor that could be highly relevant in the future.

There is actually only one ongoing European randomized study evaluating surgery of residual disease in patients with metastatic GIST responding to Imatinib mesylate³⁶. Imatinib mesylate represents the standard treatment as preoperative supplement for locally unresectable and/or metastatic GIST, and it is not necessary to perform a trial to compare this approach *versus* surgery alone. It is also unlikely that randomized controlled trials or controlled clinical trials will be available in the future. For patients responding to imatinib or patients with prolonged stable disease, resection of residual disease should be considered if the tumor has become resectable. In general, surgery should be planned when the maximal response to molecular-targeted therapy is reached. This usually happens within 6-12 months after the onset of TKI therapy. Moreover, surgery should be considered for patients at higher risk of complications during pharmacological debulking.

In advanced GIST, the advantages of integrated treatment (neoadjuvant imatinib mesylate associated with surgery) are significant in the RD group in terms of more complete resections and better disease-free and overall survival.

References

- Singer S, Rubin BP, Lux ML, Chen CJ, Demetri GD, Fletcher CD, Fletcher JA: Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. *J Clin Oncol*, 20: 3898-3905, 2002.
- Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CD, Fletcher JA: PDGFRA activating mutations in gastrointestinal stromal tumors. *Science*, 299: 708-710, 2003.
- Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, Silberman S, Capdeville R, Dimitrijevic S, Druker B, Demetri GD: Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med*, 344: 1052-1056, 2001.
- Duffaud F, Blay JY: Gastrointestinal stromal tumours: biology and treatment. *Oncology*, 65: 187-197, 2003.
- Verweij J, Van Oosterom A, Blay JY, Judson I, Rodenhuis S, Van der Graaf W, Radford J, Le Cesne A, Hogendoorn PC, Di Paola ED, Brown M, Nielsen OS: Imatinib mesylate (STI-571 Glivec, Gleevec) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target. Results from an EORTC Soft Tissue and Bone Sarcoma Group phase II study. *Eur J Cancer*, 39: 2006-2011, 2003.
- Demetri GD, Von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H: Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*, 347: 472-480, 2002.
- Haller F, Detken S, Schulden HJ, Happel N, Gunawan B, Kuhlitz J, Fuzesi L: Surgical management after neoadjuvant imatinib therapy in gastrointestinal stromal tumours (GISTs) with respect to imatinib resistance caused by secondary KIT mutations. *Ann Surg Oncol*, 14: 526-532, 2007.
- Ruka W, Rutkowski P, Szawlowski A, Nowecki Z, Debiec-Rychter M, Grzesiakowska U, Dziewirski W, Siedlecki JA, Michej W: Surgical resection of residual disease in initially inoperable imatinib-resistant/intolerant gastrointestinal stromal tumor treated with sunitinib. *Eur J Surg Oncol*, 35: 87-91, 2009.
- Scaife CL, Hunt KK, Patel SR, Benjamin RS, Burgess MA, Chen LL, Trent J, Raymond AK, Cormier JN, Pisters PWT, Pollock RE, Feig BW: Is there a role for surgery in patients with "unresectable" cKIT + gastrointestinal stromal tumors treated with imatinib mesylate? *Am J Surg*, 186: 665-669, 2003.
- Sym SJ, Ryu MH, Lee JL, Chang HM, Kim TW, Kim HC, Kim KH, Yook JH, Kim BS, Kang YK: Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). *J Surg Oncol*, 98: 27-33, 2008.
- Blay JY, Bonvalot S, Casali P, Choi H, Debiec-Richter N, Dei Tos AP, Emile J-E, Gronchi A, Hogendoorn PCW, Joensuu H, Le Cesne A, MacClure J, Maurel J, Nupponen N, Ray-Coquard I, Reichardt P, Sciot R, Stroobants S, van Glabbeke M, van Oosterom A, Demetri GD; GIST consensus meeting panelists: Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. *Ann Oncol*, 16: 566-578, 2005.
- Higgins JPT, Green S (editors): *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.0 [updated February 2008]. The Cochrane Collaboration 2008. Available from www.cochrane-handbook.org.
- Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2008.
- Greenland S, Robins J: Estimation of a common effect parameter from sparse follow-up data. *Biometrics*, 41: 55-68, 1985.
- Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*, 22: 719-748, 1959.
- Choi H: Critical issues in response evaluation on computed tomography: lessons from the gastrointestinal stromal tumor model. *Curr Oncol Rep*, 7: 307-311, 2005.
- Andtbacka RHI, Ng CS, Scaife CL, Cormier JN, Hunt KK, Pisters PW, Pollock RE, Benjamin RS, Burgess MA, Chen LL, Trent J, Patel SR, Raymond K, Feig BW: Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. *Ann Surg Oncol*, 14: 14-24, 2007.
- Bonvalot S, Eldweny H, Le Péchoux C, Vanel D, Terrier P, Cavalcanti A, Robert C, Lassau N, Le Cesne A: Impact of surgery on advanced gastrointestinal stromal tumors (GIST) in the imatinib era. *Ann Surg Oncol*, 13: 1596-1603, 2006.
- Gold JS, van der Zwan SM, Gönen M, Maki RG, Singer S, Brennan ME, Antonescu CR, De Matteo RP: Outcome of metastatic GIST in the era before tyrosine kinase inhibitors. *Ann Surg Oncol*, 14: 134-142, 2007.
- Gronchi A, Fiore M, Miselli F, Lagonigro MS, Coco P, Messina A, Pilotti S, Casali PG: Surgery of residual disease following molecular targeted therapy with imatinib mesylate in advanced/metastatic GIST. *Ann Surg*, 245: 341-346, 2007.
- Raut CP, Posner M, Desai J, Morgan JA, George S, Zahrieh D, Fletcher CD, Demetri GD, Bertagnolli MM: Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. *J Clin Oncol*, 24: 2325-2331, 2006.
- Rutkowski P, Nowecki Z, Nyckowski P, Dziewirski W, Grzesiakowska U, Nasierowska-Guttmejer A, Krawczyk M, Ruka W: Surgical treatment of patients with initially inoperable

- and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. *J Surg Oncol*, 93: 304-311, 2006.
23. Al-Batran SE, Hartmann JT, Heidel F, Stoehlmacher J, Wardelmann E, Dechow C, Dux M, Izbicki JR, Kraus T, Fischer T, Jäger E: Focal progression in patients with gastrointestinal stromal tumors after initial response to imatinib mesylate: a three-center-based study of 38 patients. *Gastric Cancer*, 10: 145-152, 2007.
 24. An YJ, Choi MG, Noh JH, Sohn TS, Kang WK, Park CK, Kim S: Gastric GIST: A single institutional retrospective experience with surgical treatment for primary disease. *Eur J Surg Oncol*, 33: 1030-1035, 2007.
 25. Bauer S, Hartmann JT, de Wit M, Lang H, Grabellus F, Antoch G, Niebel W, Erhard J, Ebeling P, Zeth M, Taeger G, Seiber S, Flasshove M, Schutte J: Resection of residual disease in patients with metastatic gastrointestinal stromal tumors responding to treatment with imatinib. *Int J Cancer*, 117: 316-325, 2005.
 26. Hasegawa J, Kanda T, Hirota S, Fukuda M, Nishitani A, Takahashi T, Kurosaki I, Tsutsui S, Hatakeyama K, Nishida T: Surgical interventions for focal progression of advanced gastrointestinal stromal tumors during imatinib therapy. *Int J Clin Oncol*, 12: 212-217, 2007.
 27. Wu PC, Langerman A, Ryan CW, Hart J, Swiger S, Posner MC: Surgical treatment of gastrointestinal stromal tumors in the imatinib (STI-571) era. *Surgery*, 134: 656-666, 2003.
 28. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF: Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg*, 231: 51-58, 2000.
 29. Crosby JA, Catton CN, Davis A, Couture J, O'Sullivan B, Kandel R, Swallow CJ: Malignant gastrointestinal stromal tumors of the small intestine: a review of 50 cases from a prospective database. *Ann Surg Oncol*, 8: 50-59, 2001.
 30. Pierie JP, Choudry U, Muzikansky A, Yeap BY, Souba WW, Ott MJ: The effect of surgery and grade on outcome of gastrointestinal stromal tumors. *Arch Surg*, 136: 383-389, 2001.
 31. Judson I, Demetri G: Advances in the treatment of gastrointestinal stromal tumours. *Ann Oncol*, 18:20-24, 2007.
 32. Demetri GD, Benjamin RS, Blanke CD, Blay JY, Casali P, Choi H, Corless CL, Debiec-Rychter M, DeMatteo RP, Ettinger DS, Fisher GA, Fletcher CD, Gronchi A, Hohenberger P, Hughes M, Joensuu H, Judson I, Le Cesne A, Maki RG, Morse M, Pappo AS, Pisters PW, Raut CP, Reichardt P, Tyler DS, Van den Abbeele AD, Von Mehren M, Wayne JD, Zalberg J; NCCN Task Force: NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST) – update of the NCCN clinical practice guidelines. *J Natl Comprehensive Cancer Network*, 5 (Suppl 2): S1-29, 2007.
 33. Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY; ESMO Guidelines Working Group: Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol*, 19 (Suppl 2): 35-38, 2008.
 34. Van Oosterom AT, Judson I, Verweij J, Stroobants S, Donato di Paola E, Dimitrijevic S, Martens M, Webb A, Sciot R, Van Glabbeke M, Silberman S, Nielsen OS, European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group: Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet*, 358: 1421-1423, 2001.
 35. Verweij J, Casali PG, Zalberg J, LeCesne A, Reichardt P, Blay JY, Issels R, van Oosterom A, Hogendoorn PC, Van Glabbeke M, Bertulli R, Judson I: Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet*, 364: 1127-1134, 2004.
 36. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, Blackstein ME, Blanke CD, von Mehren M, Brennan MF, Patel S, McCarter MD, Polikoff JA, Tan BR, Owzar K, American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team: Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet*, 373: 1097-1104, 2009.