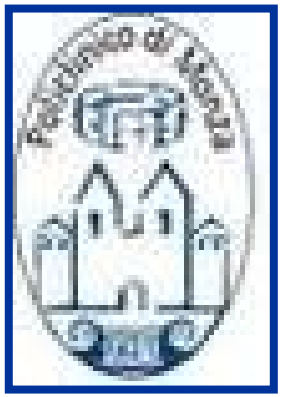
# GIST

## SURGICAL TREATMENT OF LIVER METASTASIS



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# Why talking about GIST liver metastasis?

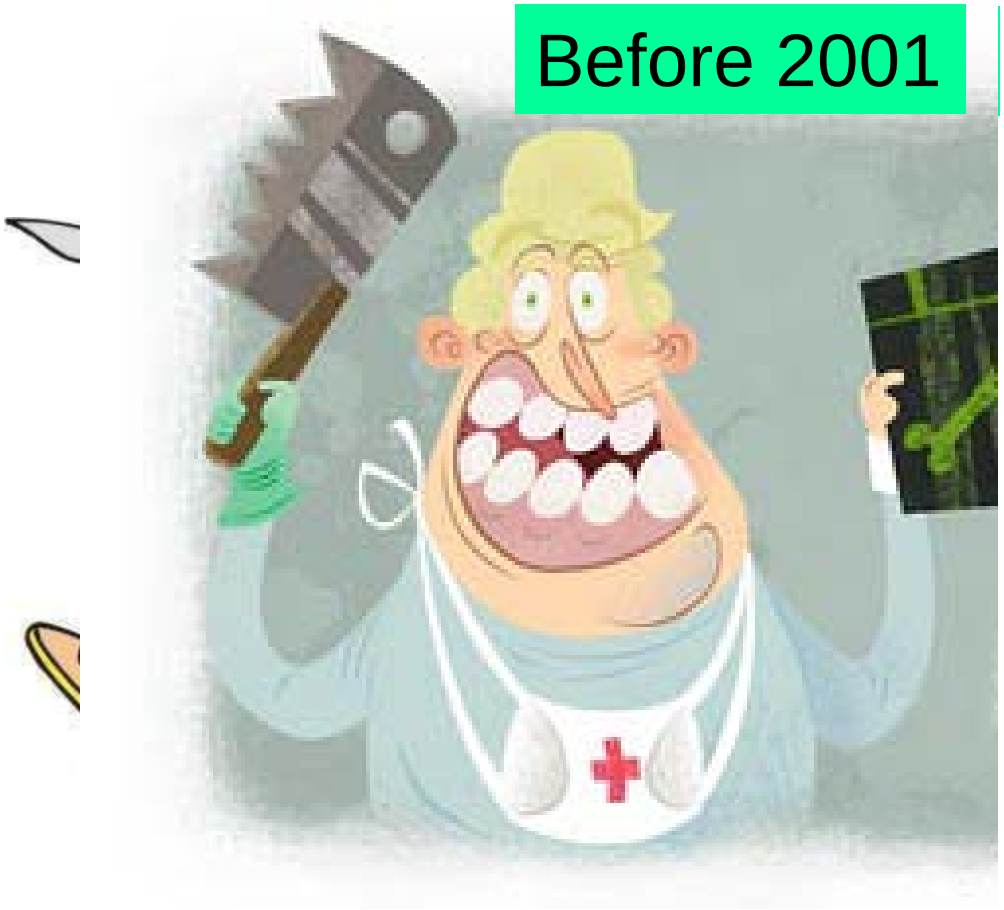
- The rate of liver metastasis was reported as 15.9% in primary GISTs

- Up to 40% of patients who undergo complete resection of GIST primaries have recurrence within a median time ranging from 18 to 24 months. The peritoneum and the liver are the most common metastatic sites.

- Resectable disease in 26-30% of cases

Zalinski et al Hematol Oncol Clin N Am 23 (2009)

# Hepatic resection in the Tyrosine Kinase Inhibitor era




# Before 2001….

- The only effective therapy was surgery
- The limit was technical: safety of liver resection is clearly linked to the volume and function of the liver remnant.
- The recurrence rate following surgical resection for hepatic metastasis from GIST had been reported as 70-77%
- The outcome was poor (5years survival 27-34%)

# GIST consesus conference

- “The goal of surgery is complete resection of visible and microscopic disease, possibly avoiding the occurrence of tumor rupture and achieving negative margins
- Laparoscopic surgery should be avoided, owing to the higher risk of tumor rupture and subsequent peritoneal seeding (SOR expert agreement, NCCN level 2A).
- A laparoscopic resection might be accepted in cases of small (<2 cm) intramural tumors. Margins should be negative,
- GIST metastasize only rarely to local regional lymph nodes, and thus lymphadenectomy is warranted only for evident nodal involvement (SOR expert agreement, NCCN level 2A).
- Adjuvant imatinib should only be given in clinical trials

DeMatteo RP, Lewis JJ, Leung D et al. Two hundred gastrointestinal stromal tumors. Recurrence patterns and prognostic factors for survival. Ann Surg 2000; 231: 51–58.

DeMatteo RP, Heinrich MC, El-Rifai WM et al. Clinical management of gastrointestinal stromal tumors: before and after STI-571. Hum Pathol 2002; 33: 466–477

# Randomized phase III trials "adjuvant" Imatinib

| Trial | Target population | Design | Primary end-point | Interventions | Median follow-up (months) | Results |
|---|---|---|---|---|---|---|
| **ACOSOG Z9001** | KIT-positive GIST, localized, ≥3cm | Double-blind, multicentre (USA, Canada) | RFS<br><br>Secondary (OS) | Imatinib (400mg/day for 1 year; n=359) vs placebo (for 1 year; n=354) | 19.7 | **1-year RFS: 98% vs 83% (HR=0.35; 95% CI 0.22-0.53; p<0.0001)**<br>1-year OS: 99.2% vs 99.7% (HR=0.66; 95% CI 0.22-2.03; p=0.47) |
| **SSGXVIII/AIO** | KIT-positive GIST, high risk or tumor rupture EXCLUDED INOPERABLE OR METASTATIC | Open-label, multicenter (Finland, Germany, Norway, Sweden) | RFS<br><br>Secondary (OS and treatment safety) | Imatinib (400mg/day for 3 years; n=200) vs Imatinib (400mg/day for 1 year; n=200) | 54 | **5-year RFS: 65.6% vs 47.9% (HR=0.46; 95%CI 0.32-0.65; p<0.0001)**<br>***5-year OS: 92% vs 81.7% (HR=0.45; 95CI 0.22-0.89; p<0.019)*** |

Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial

www.thelancet.com Vol 373 March 28, 2009

One vs Three Years of Adjuvant Imatinib for Operable Gastrointestinal Stromal Tumor
A Randomized Trial

JAMA, March 28, 2012—Vol 307, No. 12

# Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial

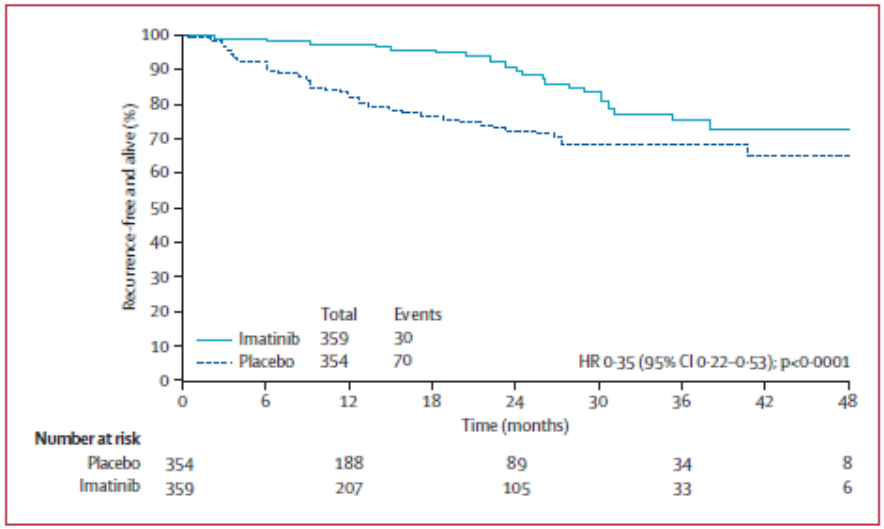



*Figure 2:* Recurrence-free survival

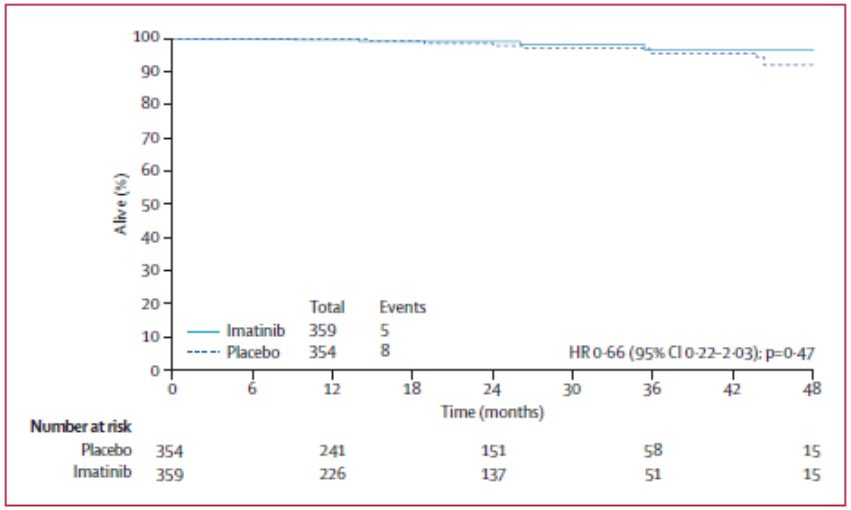


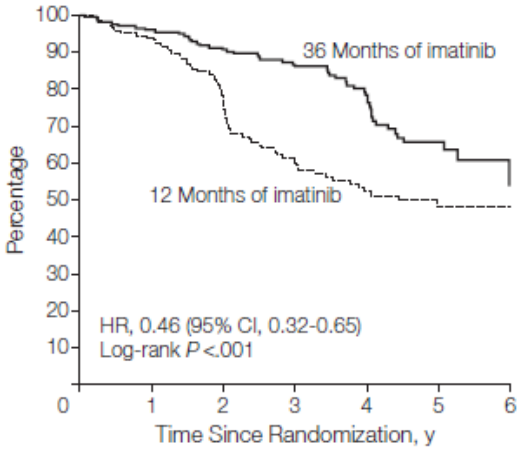

*Figure 4:* Overall survival

DeMatteo et al The Lancet vol 373 March 28, 2009

# One vs Three Years of Adjuvant Imatinib for Operable Gastrointestinal Stromal Tumor

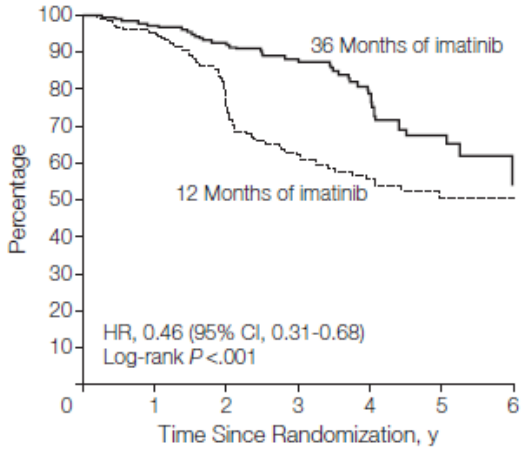
## A Randomized Trial

A Recurrence-free survival: intention-to-treat population




| No. of patients | | | | | | | |
|---|---|---|---|---|---|---|---|
| 36 Months of imatinib | 198 | 184 | 173 | 133 | 82 | 39 | 8 |
| 12 Months of imatinib | 199 | 177 | 137 | 88 | 49 | 27 | 10 |

B Recurrence-free survival: efficacy population




| No. of patients | | | | | | | |
|---|---|---|---|---|---|---|---|
| 36 Months of imatinib | 177 | 167 | 157 | 121 | 71 | 35 | 7 |
| 12 Months of imatinib | 181 | 163 | 126 | 81 | 46 | 25 | 10 |

Joensuu et al JAMA, March 28, 2012-vol 307, No 12

# Randomized phase III trials metastatic and unresectable GIST

| Trial | Target population | Design | Primary end-point | Interventions | Median follow-up | Results |
|---|---|---|---|---|---|---|
| **EORTC 62005** | CD117+ GIST, Advanced or metastatic (Feb 2001-Feb 2002) | Open-label multicenter (Europe, Australia, New Zealand , Singapore) | PFS<br><br>Secondary (OS, toxic effect, response to treatment) | Imatinib (400mg/day n=473) vs Imatinib (400mg twice/day, n=473) until disease progression or unacceptable toxicity | 760 days | Estimated Median PFS : 22months for standard-dose, vs 27months for high-dose<br><br>OS: 69% at 2-years (standard dose) vs 74% at 2 years (high-dose) |
| **SWOG S0033** | CD117+ GIST , incurable (metastatic or unresectable) (Dec 2000-Sep2001) | Open-label, multicenter (USA, Canada) | PFS/OS | Imatinib (400mg/day n=345) vs Imatinib (400mg twice/day, n=349) until disease progression or unacceptable toxicity | 4.5 years | Median PFS : 18months for standard-dose, vs 20months for high-dose 2years PFS: 41% (95%CI, 36-47) vs 46% (95%CI, 41-51)<br><br>Median OS: 55months for standard-dose, vs 51months for high-dose |

# Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial

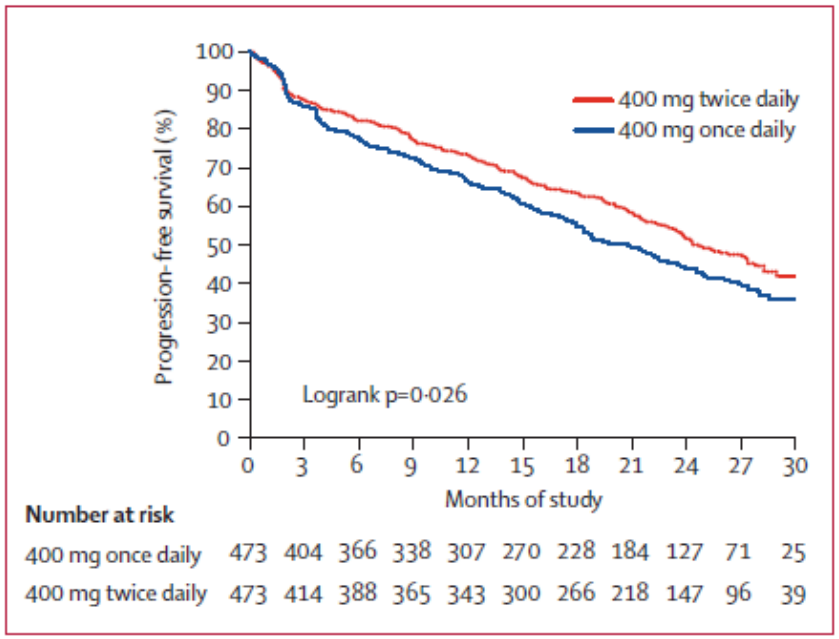



*Figure 5:* **Progression-free survival**

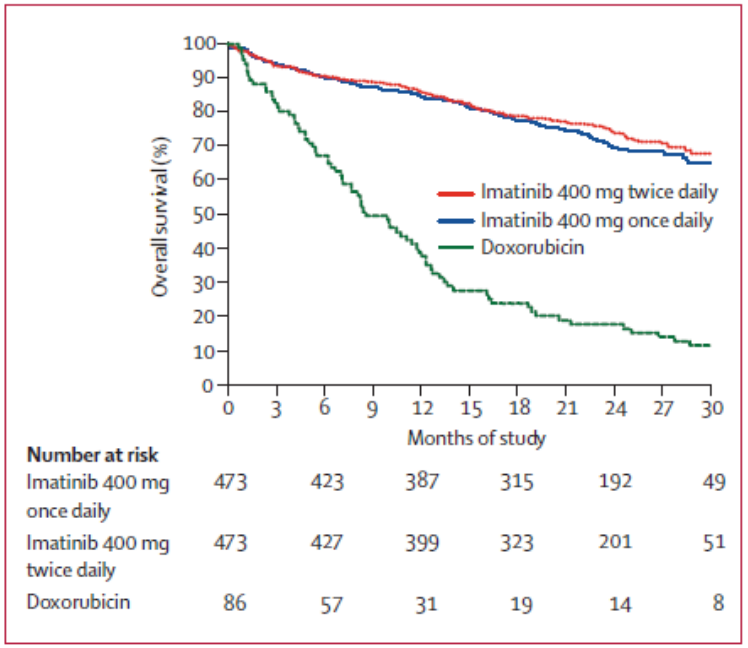



*Figure 6:* **Overall survival for total study population**
Data are compared with historical (GIST) controls from the EORTC database. Dox=doxorubicin-based regimen

Statistically significant advantage in PFS with high dose imatinib
This Trial confirm effectiveness of imatinib for incurable GIST, but did not show any advantage in OS to higher dose treatment

Verweij et al The Lancet vol 364 Sept 25, 2004
EORTC 60025

# Phase III Randomized, Intergroup Trial Assessing Imatinib Mesylate At Two Dose Levels in Patients With Unresectable or Metastatic Gastrointestinal Stromal Tumors Expressing the Kit Receptor Tyrosine Kinase: S0033

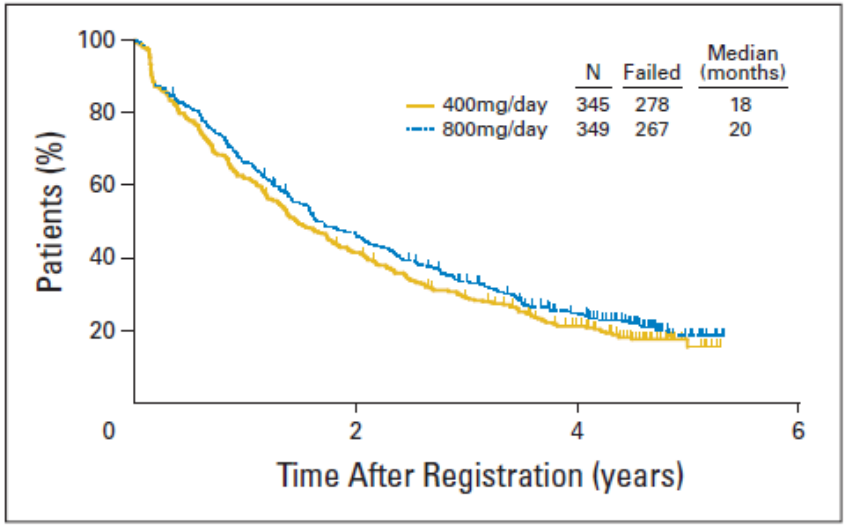



**Fig 2.** Progression-free survival.

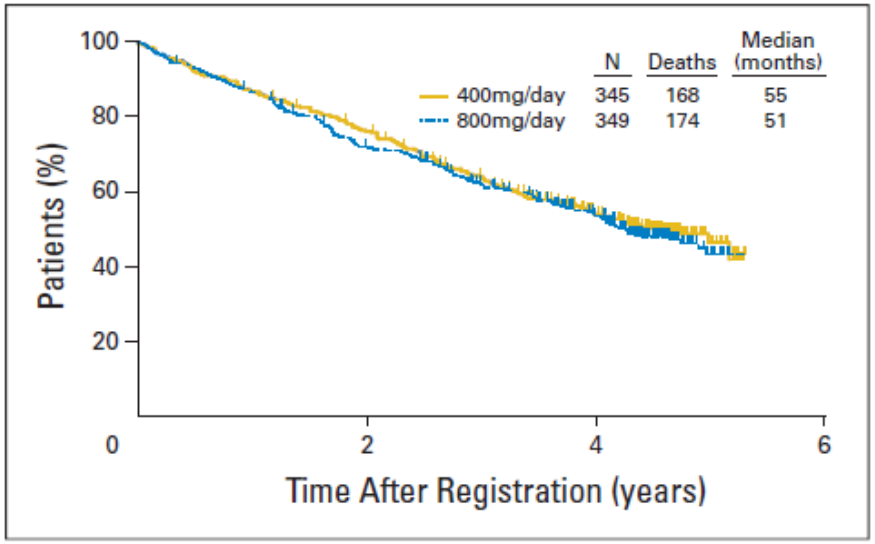


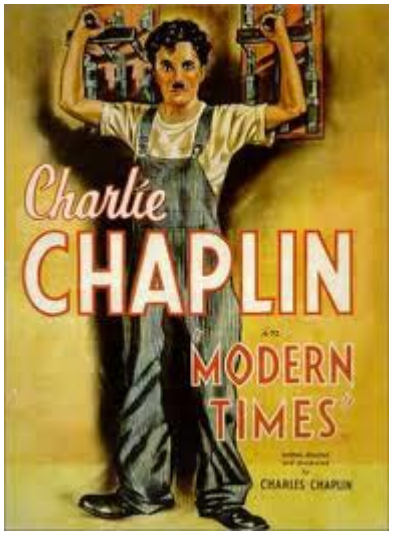

**Fig 3.** Overall survival.

No statistically significant differences in objective response rates, PFS and OS. This Trial confirm effectiveness of imatinib for incurable GIST, but did not show any advantage to higher dose treatment

Blanke et al JCO vol 26 Feb 1, 2008
SWOG S0033

# What about surgery

GIST in the Tyrosine Kinase Inhibitor Era



# Why considering surgery?

- Rates of PFS for patients responding to TKI therapy: 70-96% at 1 year after surgery
- At least half of all patients **develop resistance** to imatinib within 2 years of starting treatment through the acquisition of secondary gene mutations
- Downsizing tumor after therapy may allow parenchymal preservation
- Downsizing or cystic transformation may suggest “favorable” biology, could be shown to enhance **patient selection** for hepatectomy
- The significance of radiologic response should not be overinterpreted, because **pathologic CR is rare** (5-10%) and virtually all patients treated with imatinib ultimately develop resistance
- There are **no data yet** to support replacement of resection with target therapy

Zalinski et al Hematol Oncol Clin N Am 23 (2009)

# After 2001.....

**Categories of disease response**

1. Stable diasease (radiographically stable or responding to drug therapy)
2. Limited (localized) disease progression on drug therapy at one or few sites
3. Generalized disease progression on drug therapy

**The role of surgery**

1. $R_0$ or Cytoreductive resection
2. All sites of progressing disease could be resected, along with other sites of stable disease if associated morbidity was relatively low and if feasible
3. Surgery offered no survival benefit

Y.-jiang Ye et al. / EJSO 35 (2009)

## PRINCIPLES OF SURGERY FOR GIST

**Primary (Resectable) GIST**

The surgical procedure performed should aim to resect the tumor with histologically negative margins.

- Given the limited intramural extension, extended anatomic resections (such as total gastrectomy) are rarely indicated. Segmental or wedge resection to obtain negative margins is often appropriate.
- Lymphadenectomy is usually not required given the low incidence of nodal metastases.

**Metastatic GIST**

Imatinib is the primary therapy for metastatic GIST. Surgery may be indicated for:

- Limited disease progression refractory to systemic therapy.
- Locally advanced or previously unresectable tumors after a favorable response to preoperative imatinib.

If persistent metastatic or residual tumor remains after surgery, then imatinib should be continued as soon as the patient is able to tolerate oral intake.

- All oncologic principles of GIST resection must still be followed, including preservation of the pseudocapsule and avoidance of tumor spillage.
- Resection specimens should be removed from the abdomen in a plastic bag to prevent spillage or seeding of port sites.

**Metastatic GIST**

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- Limited disease progression refractory to systemic therapy.
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If persistent metastatic or residual tumor remains after surgery, then imatinib should be continued as soon as the patient is able to tolerate oral intake.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

# When considering surgery?

The crucial point is…..the timing….

# When considering surgery?

- Secondary resistance to treatment occurs at a median of 20 to 24 months after treatment initiation, but most response occurs within the first few months, which raises the question as to the optimal timing for surgery

- Most experts recomend surgery after 6-12 months of disease stability or response

Y.-jiang Ye et al. / EJSO 35 (2009)

# The role of surgical resection, today

- It is crucial to understand that, though an operation may be technically feasible, presently there is no evidence for the role of surgical resection plus TKI therapy over TKI therapy alone in patients with advanced disease.

- This question can only be answered by randomized clinical trials

Y.-jiang Ye et al. / EJSO 35 (2009)

# Ongoing Phase III TRIALS

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Study 1 of 1 for search of: NCT00956072
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## Imatinib Mesylate With or Without Surgery in Treating Patients With Metastatic Gastrointestinal Stromal Tumor That is Responding to Imatinib Mesylate

**This study is ongoing, but not recruiting participants.**

First Received on August 8, 2009. Last Updated on March 19, 2011 History of Changes

| | |
|---|---|
| **Sponsor:** | European Organization for Research and Treatment of Cancer - EORTC |
| **Information provided by:** | National Cancer Institute (NCI) |
| **ClinicalTrials.gov Identifier:** | NCT00956072 |

### Purpose

RATIONALE: Surgery may remove residual disease in patients with gastrointestinal stromal tumor that is responding to imatinib mesylate. It is not yet known whether surgery is more effective than continued imatinib mesylate in treating patients with metastatic gastrointestinal stromal tumor.

PURPOSE: This randomized phase III trial is studying giving imatinib mesylate therapy together with surgery to see how well it works compared with imatinib mesylate alone in treating patients with metastatic gastrointestinal stromal tumor that is responding to imatinib mesylate.

# Resection Combined with Imatinib Therapy for Liver Metastases of Gastrointestinal Stromal Tumors

- 41 patients with GIST and liver metastases
- Random:

  20 pts: neoadjuvant therapy+resection+ adjuvant therapy with imatinib

  21 pts: imatinib alone
- Follow-up 36 months
- Characteristics:
  - ✓ R0 surgical resection of the primary tumors
  - ✓ Recurrent tumors and liver metastases after resection of the primary tumor
  - ✓ liver tissue encroached by GIST was <50% and Child-Pugh classification was A

Lin Xia et al Surg Today (2010) 40:936–942

# Resection Combined with Imatinib Therapy for Liver Metastases of Gastrointestinal Stromal Tumors

- The operation group received imatinib treatment for 6 months preoperatively and it was continued for 2-4 weeks after surgical resection of GIST liver metastases

- The primary end-point was Overall Survival (from the first dose of imatinib to the date of last follow-up or death)

- Evaluable patients: 19 pts from the operation group and 20 pts from the nonoperation group

Lin Xia et al Surg Today (2010) 40:936–942

# Resection Combined with Imatinib Therapy for Liver Metastases of Gastrointestinal Stromal Tumors

**Table 2.** Responses to imatinib therapy[a]

| | Operation group ($n = 19$) | Nonoperation group ($n = 20$) |
|---|---|---|
| Complete response | 0 | 2 |
| Partial response | 13 | 6 |
| Stable disease | 6 | 9 |
| Progressive disease | 0 | 3 |

[a]The operation group response was evaluated before surgery and the nonoperation group response was evaluated at the end of follow-up

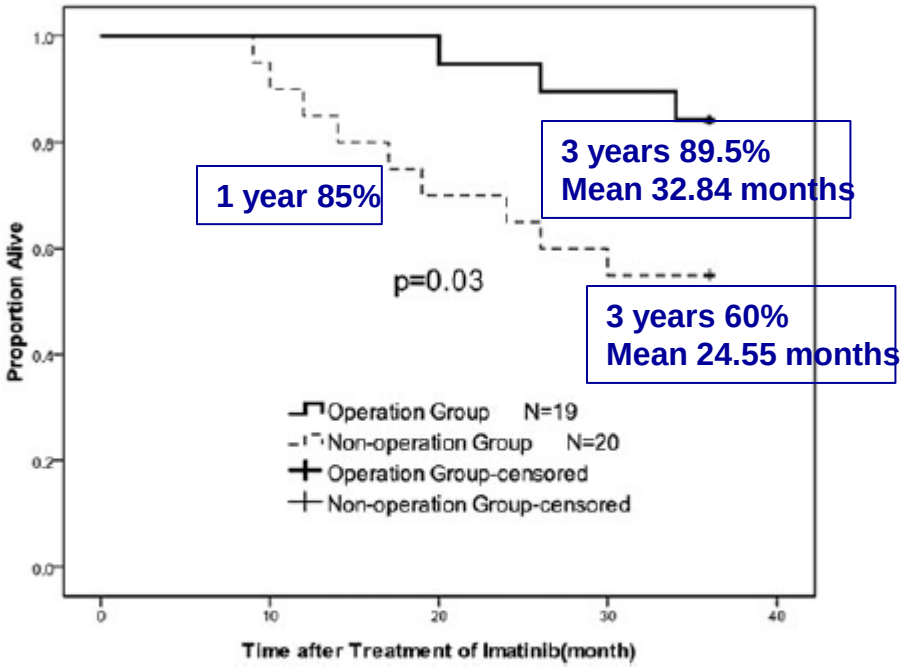


**Fig. 1.** Impact of surgical resection on gastrointestinal stromal tumor (GIST) liver metastases after imatinib treatment. A significant difference was observed in the overall survival rates of the operation and nonoperation groups ($P = 0.03$)

The follow-up finished in Dec 2008.
12 pts died, all of tumor progression.
In the operation group , no pts died in the first year

Lin Xia et al Surg Today (2010) 40:936–942

# Resection Combined with Imatinib Therapy for Liver Metastases of Gastrointestinal Stromal Tumors

Good responders

Poor responders

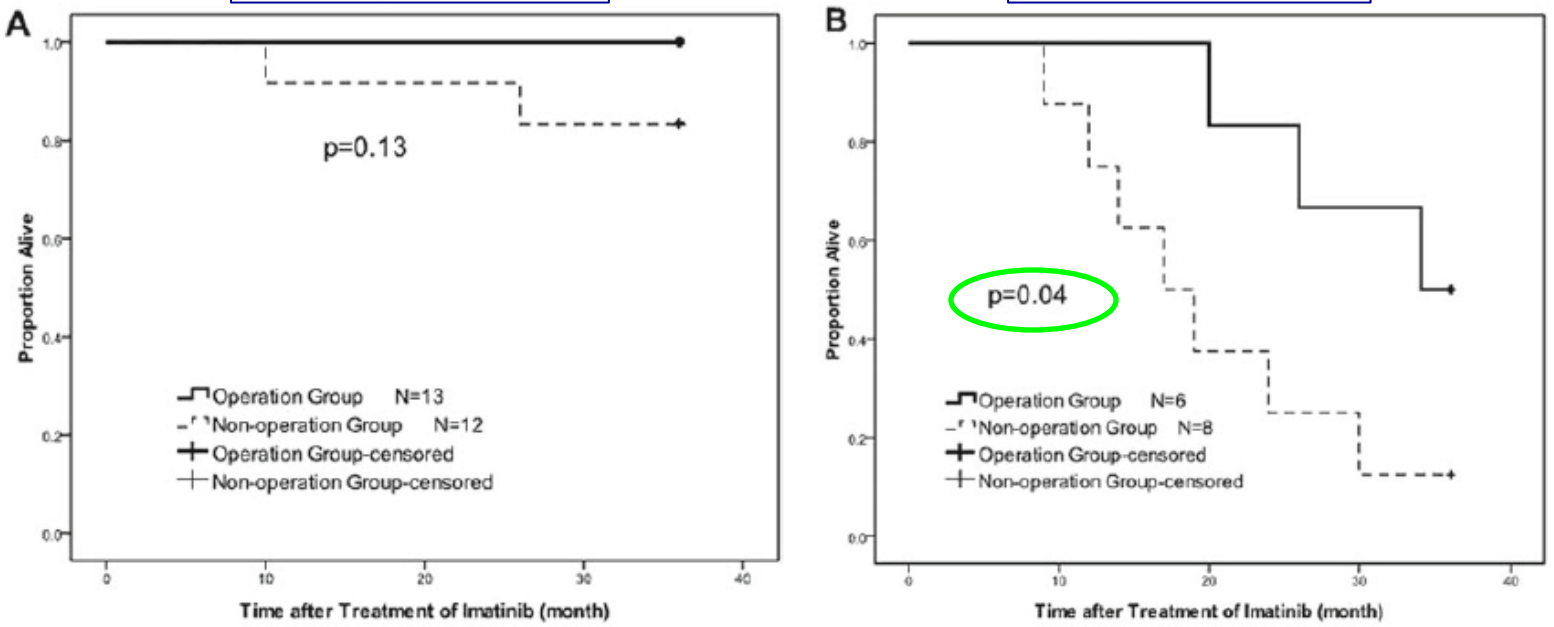


**Fig. 2A,B.** Impact of surgical resection on GIST liver metastases with differential responses to imatinib. **A** No difference was observed in overall survival rates between the operation and nonoperation groups of good responders ($P = 0.13$). **B** A significant difference was observed in overall survival rates between the operation and nonoperation groups of poor responders ($P = 0.04$)

Lin Xia et al Surg Today (2010) 40:936–942

# Resection Combined with Imatinib Therapy for Liver Metastases of Gastrointestinal Stromal Tumors

## Considerations

- "waiting for the largest response" usually means waiting for secondary mutations of GISTs and resistance to imatinib
- Complete resection of liver metastases is important, although the surgery itself is without radical significance
- An appropriate excision range is necessary (at least 1cm)

Lin Xia et al Surg Today (2010) 40:936–942

# Resection Combined with Imatinib Therapy for Liver Metastases of Gastrointestinal Stromal Tumors

**Conclusions**

**Neoadjuvant-Surgery-Adjuvant with imatinib is more effective than imatinib alone against GIST liver metastases.**

**Surgical resection and molecular targeted therapy should be combined.**

**Hepatic resection should be performed within 6 months of preoperative therapy with imatinib and , imatinib should be continued after tumor resection**

Lin Xia et al Surg Today (2010) 40:936–942

# Hepatic Resection for Metastatic Gastrointestinal Stromal Tumors in the Tyrosine Kinase Inhibitor Era

- Retrospective study
- Three main centers:

Dep.of Surgery, Duke University Medical Center, Durham North Caroline

Dep.of Surgery, Johns Hopkins Hospital, Baltimore, Maryland

Liver Cancer Center, University of Pittsburgh Medical Center, Pittsburgh Pennsylvania

- 39 pts underwent hepatectomy for metastatic GISTs
- 27 pts received postoperative TKI therapy

# Hepatic Resection for Metastatic Gastrointestinal Stromal Tumors in the Tyrosine Kinase Inhibitor Era

**Table 4.** Disease-Free Survival Estimates at 1, 2, and 3 Years

| | Disease-Free Survival, % | | | |
|---|---|---|---|---|
| Survival[a] | 1 Year | 2 Year | 3 Year | *P*[b] |
| Overall (n = 39) | 63.4 | 34.1 | 26.1 | |
| No TKI (n = 7) | 64.3 | 0 | 0 | Referent |
| Any TKI therapy (n = 31) | 63 | 39.3 | 30 | .11 |
| Postoperative TKI only (n = 12) | 63.1 | 39.9 | 34.6 | .13 |
| Perioperative TKI (n = 12) | 61.9 | 30.9 | 6.2 | .25 |

Abbreviations: TKI, tyrosine kinase inhibitor.

[a] The survival analysis excluded 1 perioperative death.

[b] *P* values were calculated using the log-rank test of equality.

# Hepatic Resection for Metastatic Gastrointestinal Stromal Tumors in the Tyrosine Kinase Inhibitor Era

**Table 5.** Overall Survival Estimates at 1 Year, 2 Years, and 3 Years

| | Overall Survival, % | | | |
|---|---|---|---|---|
| Survival[a] | 1 Year | 2-Year | 3-Year | *P*[b] |
| Overall (n = 39) | 96.7 | 76.8 | 67.4 | |
| No TKI (n = 7) | 81.6 | 50.2 | 0 | Referent |
| Any TKI therapy (n = 31) | 96.6 | 77.4 | 71.9 | .005 |
| Postoperative TKI only (n = 12) | 100 | 91.7 | 91.7 | .001 |
| Perioperative TKI (n = 15) | 100 | 52.4 | 38.9 | .24 |

Abbreviations: TKI, tyrosine kinase inhibitor.

[a] The survival analysis excluded 1 perioperative death.

[b] *P* values were calculated using the log-rank test of equality.

# Hepatic Resection for Metastatic Gastrointestinal Stromal Tumors in the Tyrosine Kinase Inhibitor Era

- Limitations of this study

1. Small sample size
2. The use of neoadjuvant and adjuvant therapy was variable and may impact the rates of DFS and OS
3. The exact rationale in determing duration of preoparative TKI therapy could not be fully determined in all pts
4. The duration of postoperative TKI therapy was not available
5. Mitotic rate and prymary tumor size were not available for all pts
6. Retrospective nature

# Hepatic Resection for Metastatic Gastrointestinal Stromal Tumors in the Tyrosine Kinase Inhibitor Era

Despite these limitations, this study provides further evidence indicating that hepatic resection in combination with systemic TKI therapy improves survival for patients with GIST liver metastases with acceptable morbidity and mortality. In light of current evidence reported both here and elsewhere, we recommend that all patients with hepatic GISTs metastases be treated aggressively with both surgery and postoperative TKI therapy before clinical signs of TKI resistance become apparent.

# Unresectable GIST Liver Metastasis

- Liver resections may not be appropriate in patients with bilobar metastases, liver dysfunction, or severe co-morbidities
- For those patients with unresectable disease confined to the liver or unable to tolerate liver resection RFA, HACE, TKI therapy, or any combination of these treatment can be considered.

Y.-jiang Ye et al. / EJSO 35 (2009)

# Take home messages

The optimal therapy for GIST liver metastases is complete resection

The combination of resection with TKI therapy is likely to improve outcome, although the details of TKI administration, including timing (preoperative versus postoperative versus both) and duration of therapy (before and after surgery), have yet to be defined.

Short-duration preoperative therapy (6 months) may not only reduce the extent of needed surgery, but allow for “biologic selection” of the best candidates for surgery, especially when extensive procedures are planned

# Take home messages

Waiting for progression on treatment is a less attractive option, because the development of resistance by means of mutation may have a negative impact on long-term outcome

Use of advanced techniques for hepatic resection should increase the population of patients who have GIST Liver Metastases and can undergo complete resection of disease

The multidisciplinary approach is essential to provide the best treatment


"Trovarsi insieme è un inizio,
restare insieme un progresso…
lavorare insieme un successo."
(Henry Ford)
Grazie per la vostra attenzione!!!!