GIST:
Personalizing surgery in advanced disease

Peter Hohenberger
Div. of Surgical Oncology & Thoracic Surgery
Medical Faculty Mannheim
University of Heidelberg, Germany
Disclosure slide

- Received research support and honoraria from Novartis, Pfizer, and Bayer.
Facts and assumptions

- Surgery is unable to control resistant GIST
- But imatinib, sunitinib, regorafenib are also .... on the long run
- Development of secondary mutations depends on tumor load (?)
Indications for surgery in M1 GIST patients

- Removal of residual disease
- Resection of focal progressive lesions
  - of multifocal progression
- (Palliation, like in other cancer types)
Hepatic resection for residual liver metastasis
(really no viable cells?)
Which part of the tumor do we attack with drugs?

IM, SU, REG
no effect!

Surgery?

Bardsley, Gastroenterology 2010: 139: 942-52
Heinrich, Lancet Oncology 2010; 11:910-911
S.H. *20.1.39, m, 73 yrs

Spring 2011

Abdominal distention, umbilical hernia, sent to surgery

April 2011

Omphalectomy and direct suture of the umbilicus, 'strange tissue' below abdominal wall, biopsy taken

Dg: GIST, referred for further treatment

CT scan
April 2011: omental cake + hepatic metastases
S.H. *20.1.39, m

Spring 2011

Abdominal distention, umbilical hernia, sent to surgery

Omphalectomy and direct suture of the umbilicus, April 2011

strange tissue below abdominal wall, biopsy taken

Dg: GIST, referred for further treatment

Dg: peritoneal and hepatic metastatic GIST,

exon 11 mutation  V559G

no primary tumor detected

Start treatment with imatinib 400mg/d
## Surgery in M1 GIST: Residual tumor resection

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>FU (mon.)</th>
<th>Survival (mon)</th>
<th>Progression-free survival (mon.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raut et al. 2006</td>
<td>69</td>
<td>15</td>
<td>95 % (12 mon)</td>
<td>80 % (12 mon)</td>
</tr>
<tr>
<td>Rutkowski et al. 2006</td>
<td>32</td>
<td>12</td>
<td>100 % (12 mon)</td>
<td>100 % (12 mon)</td>
</tr>
<tr>
<td>DeMatteo et al. 2007</td>
<td>40</td>
<td></td>
<td>100 % (24 mon)</td>
<td>60 % (24 mon)</td>
</tr>
<tr>
<td>Gronchi et al. 2007</td>
<td>38</td>
<td></td>
<td>100 % (24 mon)</td>
<td>69 % (24 mon)</td>
</tr>
<tr>
<td>Mussi et al. 2009</td>
<td>80</td>
<td>31</td>
<td>83 % (60 mon)</td>
<td>65 % (24 mon)</td>
</tr>
</tbody>
</table>

References:

- Rutkowski et al. J Surg Oncol 2006;93;304-311
- Raut et al. JCO 2006;24:2325-2331
Surgery of residual disease after imatinib in M1 disease

Progression-free survival

Overall survival

Raut et al. J Clin Oncol. 2006
Residual disease (A) vs. single progressive (B)
80 patients Mannheim / Milano

**Progression-free survival**

**Overall survival**

Don’t we have better data?

- Is not this selection bias
- Patients who respond to therapy do always better

- No, at least not prospectively and randomized against continued drug therapy (EORTC study failed)

- But, new data from a large, multicentric study
Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib — Analysis of prognostic factors (EORTC-STBSG collaborative study)∗

S. Bauer a,∗, P. Rutkowski b, P. Hohenberger c, R. Miceli d, E. Fumagalli e, J.A. Siedlecki b, B.-P. Nguyen a, M. Kerst f, M. Fiore g, P. Nyckowski h, M. Hoiczyk a, A. Cats f, P.G. Casali e, J. Treckmann i, F. van Coevorden j, A. Gronchi k

<table>
<thead>
<tr>
<th>Total number</th>
<th>239</th>
</tr>
</thead>
<tbody>
<tr>
<td>male : female</td>
<td>51 : 49</td>
</tr>
<tr>
<td>Median age at diagnosis</td>
<td>55 yr</td>
</tr>
<tr>
<td>Median age at surgery for M1</td>
<td>58 yr</td>
</tr>
<tr>
<td>Liver</td>
<td>25%</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>46%</td>
</tr>
<tr>
<td>Liver &amp; peritoneum</td>
<td>18%</td>
</tr>
<tr>
<td>Other</td>
<td>11%</td>
</tr>
<tr>
<td>R0/R1 resection</td>
<td>189 (79%)</td>
</tr>
<tr>
<td>R2 resection</td>
<td>50 (21%)</td>
</tr>
</tbody>
</table>
## Survival after start of imatinib for M1

<table>
<thead>
<tr>
<th>Indication/Condition</th>
<th>Result</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0/R1 resection</td>
<td>median OS: 8.7 years</td>
<td></td>
</tr>
<tr>
<td>R2 resection</td>
<td>median OS: 5.3 years</td>
<td>.0001</td>
</tr>
<tr>
<td></td>
<td><strong>Resected in remission:</strong></td>
<td></td>
</tr>
<tr>
<td>R0/R1 resection</td>
<td>median not reached</td>
<td></td>
</tr>
<tr>
<td>R2 resection</td>
<td>median OS: 5.1 years</td>
<td>.0001</td>
</tr>
<tr>
<td></td>
<td><strong>TTRrec:</strong> median not reached</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median TTRrec: 1.9 years</td>
<td>.0001</td>
</tr>
</tbody>
</table>
### Indication/Condition

<table>
<thead>
<tr>
<th>Indication/Condition</th>
<th>Result</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resected in progression:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0/R1 resection</td>
<td>It does not matter!</td>
<td></td>
</tr>
<tr>
<td>R2 resection</td>
<td>Not significantly different</td>
<td>ns</td>
</tr>
</tbody>
</table>

---

S.Bauer et al., Eur J Surg Oncol 2014
Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib — Analysis of prognostic factors (EORTC-STBSG collaborative study)
### Multivariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female &gt; male</td>
<td>1.9 (1-3.6)</td>
<td>.038</td>
</tr>
<tr>
<td>Interval of IM to surgery</td>
<td>2.04 (1.14-3.6)</td>
<td>.044</td>
</tr>
<tr>
<td>R0/1 vs R2</td>
<td>2.26 (1.1-4.7)</td>
<td>.001</td>
</tr>
<tr>
<td>PR/SD vs PD</td>
<td>3.98 (1.95-8.1)</td>
<td>.00001</td>
</tr>
<tr>
<td>Site of mets: liver vs other</td>
<td>3.24 (.06-16.6)</td>
<td>.012</td>
</tr>
</tbody>
</table>

S.Bauer et al., Eur J Surg Oncol 2014
Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib — Analysis of prognostic factors (EORTC-STBSG collaborative study)∗

Interval of IM to surgery

S.Bauer et al., Eur J Surg Oncol 2014
Locally advanced
  ↓
Imatinib neoadjuvant
  ↓
Remission
  ↓
Resection
  ↓
Ok, fine
  ↓

Metastatic
  ↓
Imatinib
  ↓
Remission
  ↓
Resection
  ↓

No definitive proof to be advantageous
R0/R1 required
No morbidity allowed
Some hints that further course could be better
Metastatic

Imatinib

Remission

Resection

Progression, multifocal

Progression, unifocal

DRUG!

No effective drug

Location? HEP, PER, OSS, BRAIN, STS

Surgery
  if, no mutilation low morbidity

No definitive proof to be advantageous
  R0/R1 required
No morbidity allowed
Some hints that further course could be better
Unusual location of metastases
first: exon 11, then exon 13, now exon 17 mutation
Liver resection in 2004
RFA ablation in 2006
Radiation therapy for rib met in 2009
IM, SUN, IM800, IM+RAD, NILO, DASA
Small bowel metastasis in 2010 while being treated with sorafenib
Exon 9 mutation (A504_Y505ins)
New: D820Y in exon 17
Metastatic

Imatinib

Remission

Resection

Progression, multifocal

Progression, unifocal

DRUG!

No effective drug

Location? HEP, PER, OSS, BRAIN, STS

Surgery

RFA

SIRT

No definitive proof to be advantageous
R0/R1 required
No morbidity allowed
Some hints that further course could be better
GIST metastases by angiogram
Local treatment for liver metastases: TACE

Hepatic Artery Chemoembolization for 110 Gastrointestinal Stromal Tumors

Response, Survival, and Prognostic Factors

85 patients:
PR 12 (14%), SD 63 (74%), PD 10 (12%)

PFS-liver rates:
31% at 1 year
8% at 2 years
5% at 3 years

median PFS time: 8.2 months

OS rates:
62% at 1 year
32% at 2 years
20% at 3 years

median OS time: 17.2 months

Katsuhiro Kobayashi, MD
Sanjay Gupta, MD
Jonathan C. Trent, MD, PhD
Jean-Nicolas Vauthey, MD
Savitri Krishnamurthy, MD
Joe Ensor, PhD
Kamran Ahrar, MD
Michael J. Wallace, MD
David C. Madoff, MD
Ravi Murthy, MD
Stephen E. McRae, MD
Marshall E. Hicks, MD

Cancer 2006; 107: 2833
Local treatment for liver metastases: RFA

GIST \(n=36\)
Leiomyosarcoma \(n=18\)
Sarcoma \(n=12\)

Resection +/- RFA, RFA alone

Results of a Single-Center Experience With Resection and Ablation for Sarcoma Metastatic to the Liver

Timothy M. Pawlik, MD, MPH; Jean-Nicolas Vauthey, MD; Eddie K. Abdalla, MD; Raphael E. Pollock, MD, PhD; Lee M. Ellis, MD; Steven A. Curley, MD

Pawlik, Arch Surg 2006; 141: 537
Local treatment for liver metastases: RFA

DFS at 1 yr: 52%
DFS at 3 yrs.: 16%

DFS of resection: 18 months
DFS of RFA +/- resection: 7.4 months

OS at 1 yr: 91%
OS at 5 yrs.: 27%

Recurrence rate of RFA alone: 84%

> Continuation of TKI treatment is absolutely crucial

Pawlik, Arch Surg 2006; 141: 537
Locoregional therapy for multiple liver mets: SIRT (Selective Internal Radiation Therapy)
Locoregional therapy for multiple liver mets: SIRT

Treatment of Inoperable Primary Pancreatic and Liver Cancer by the Intra-Arterial Administration of Radioactive Isotopes (Y^{90} Radiating Microspheres)

IRVING M. ARIEL, M.D., F.A.C.S.

From the Pack Medical Foundation, and the Division of Radioactive Isotopes, Department of Radiation Therapy, Hospital for Joint Diseases, New York, New York

Male, * 1956
03/2006 GIST small bowel, size 9 x 14 cm, mitoses 6/50 HPF, high risk, exon 9 mutation
10/2006: liver metastases
03/2007: Progressive liver mets, dose escalation to 800 mg IM
02/2011: Tumor progression, switched to sunitinib, > SD
02/2012: RFA of solitary progressive metastasis, segm IV
04/2013: again PD liver, biopsy: 2ndary mutation exon 17, N822Y
05/2013: participated in 3rd line trial
10/2013: Progressive liver metastases
          Liver resection, segments 5/6, and S4a (prior RFA)
Conclusions

- Surgery in M1 GIST patients is still an individual decision.
- No prospective/randomized data are available.
- Residual tumor resection is safe.
- Resection of progressive tumor is less rewarding.
- Other local treatment measures like SIRT or RFA must not be forgotten.
- Site, time interval, mutation status must influence the decision-making.