Poster discussion Sarcoma Abstracts 1484PD-1486PD

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Disclosure slide

- No conflicts of interests

Poster discussion Sarcoma
Abstract 1484PD-1486PD

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"Choose your battles wisely"

Battles

- All three abstracts address important issues, so wisely chosen battles

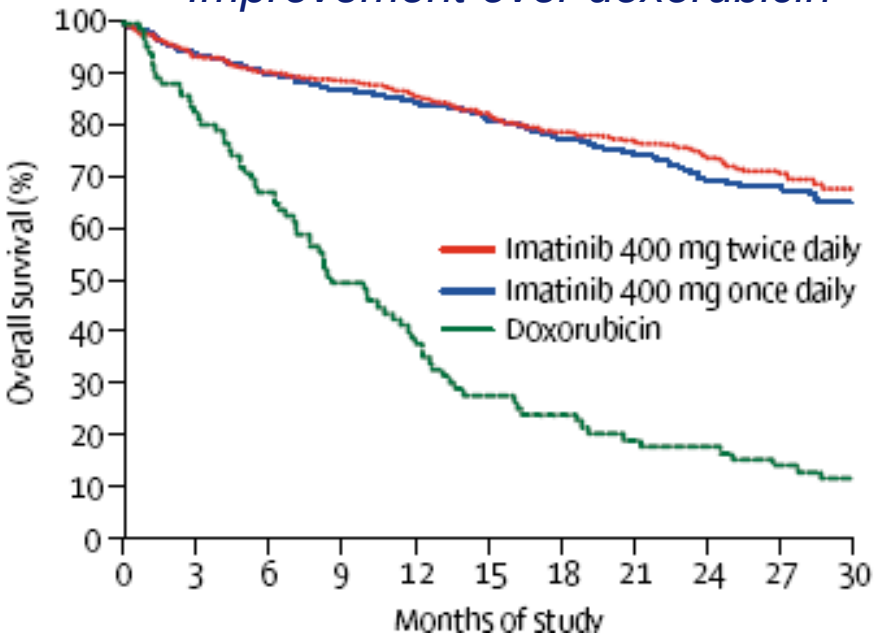
- Hohenberger et al (1484PD):
  - Metastatic GIST: Selective internal radiation therapy against focal progressive hepatic lesions

- Wardelmann et al (1486PD):
  - Localized GIST: Tumor aggressiveness of *c-KIT* exon-9 mutated GIST affected by tumor location?
    - Traditional risk scores + mutational status against traditional risk scores

- Miyazaki et al (1485PD):
  - Small gastric submucosal lesions: outcome of surgery for tumors with size enlargement during watchful waiting
    - Watchful waiting against early invasive procedures

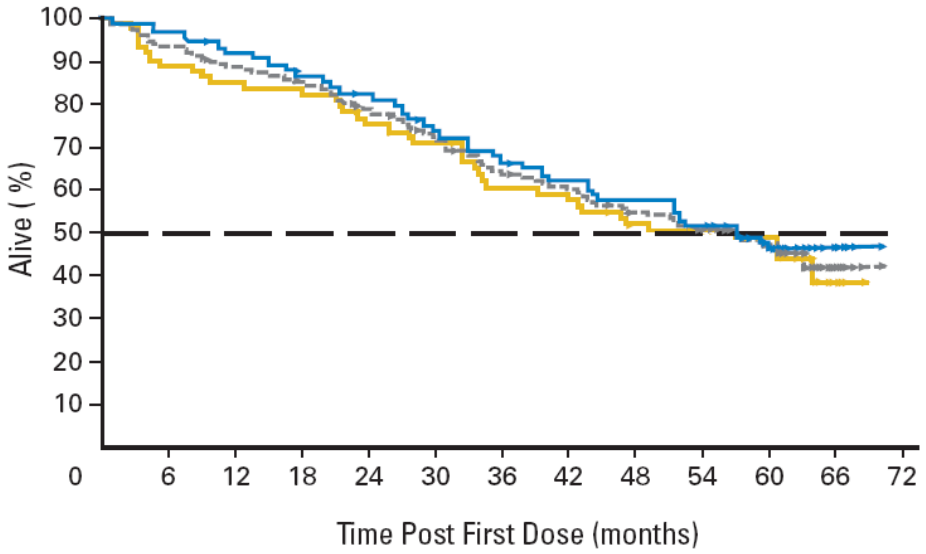
Great success of TKIs in GIST

Improvement over doxorubicin



Verweij, Lancet 2004

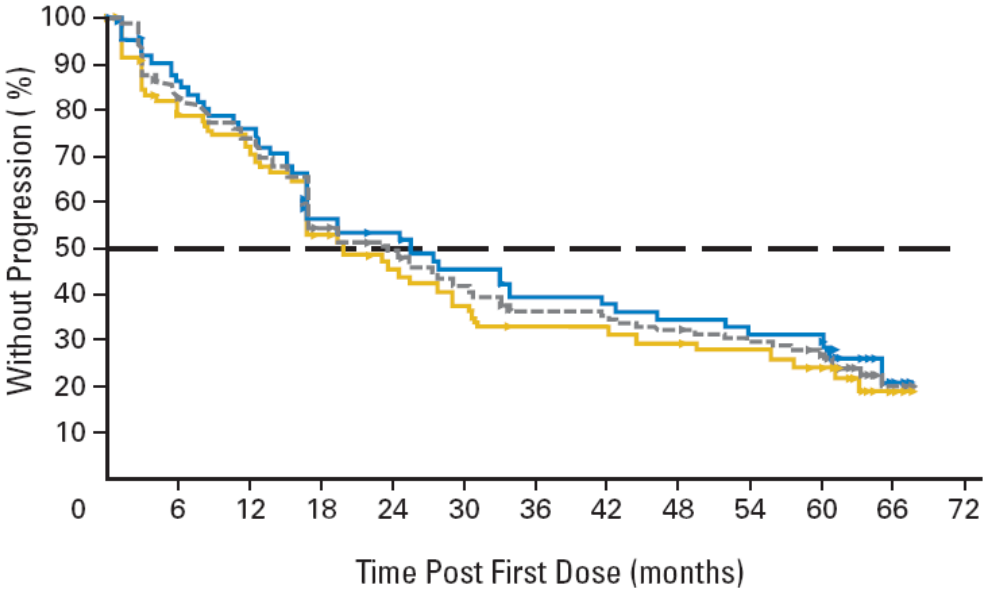
Median overall survival of 5 years



Blanke, JCO 2008

Great success of TKIs in GIST

- The longer on imatinib, the lower the chance to develop resistance



Blanke, JCO 2008

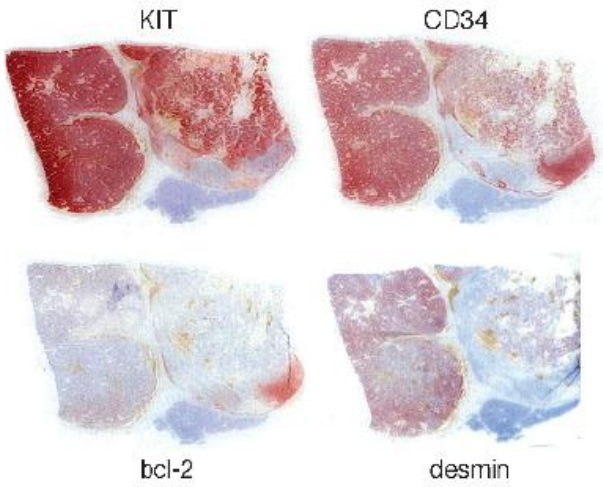
- 10% metastatic GIST: > 10 yrs benefiting from 1st line treatment

- "Making cancer a chronic disease"

TKI-resistant disease

- Vast majority will develop TKI resistance over time and during treatment

Wardelmann, CCR 2006



- Most common mechanisms:
  - Secondary mutations
  - Re-activation of c-KIT by yet unknown mechanisms
- The great challenge: heterogeneity in genetic characteristics:
  - Between metastatic lesions
  - Within metastatic lesions

TKI-resistant disease

- GIST develops from:
  - a homogeneous disease with one major tumor driver mostly sensitive to one TKI
  - to a heterogeneous disease with multiple drivers acting in parallel and differing in TKI sensitivity

- Unlikely that 1 drug will induce stable disease for very prolonged periods in majority of pts progressing after 1st line treatment

TKI-resistant GIST

- Because of heterogeneity under treatment pressure:
  - Isolated/focal progression
  - Remaining lesions still under TKI control

- Local treatment options:
  - Surgery
  - RFA

1484PD

Selective Internal Radiation Therapy (SIRT) for GIST liver metastases resistant to tyrosine kinase inhibitors

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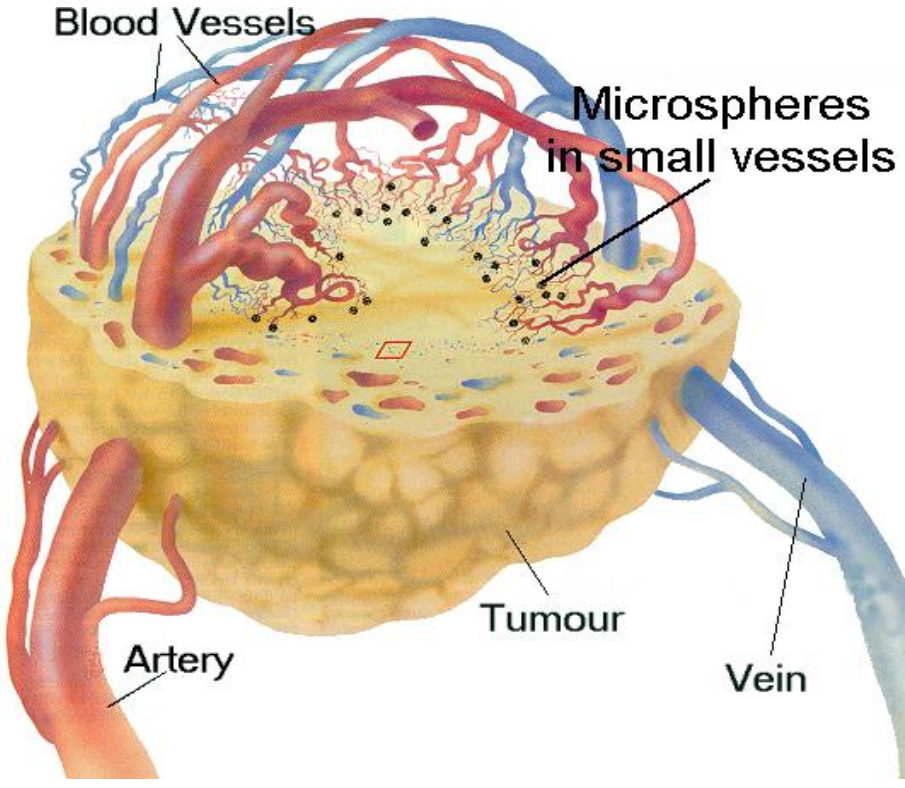
Universitätsklinikum Mannheim

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.

Ann Surg 1965; 162: 267 - 278

- ^{90}Yttrium: Local radiation dose up to 120 Gy
- No significant hepatitis beyond of 8 mm of the tumor area



Characteristics and toxicity

- Characteristics:
  - 9 patients (34-73yrs)
  - Progressive hepatic metastases; 4 pts with stable extrahepatic disease
  - 1 pt. excluded: >20% hepato-pulmonary shunt

- Toxicity:
  - Transient elevation of liver enzymes (NCIC grade 3)
  - 1 pt persistent stomach ulcer; surgery needed

Patient characteristics and results of treatment

Patient, sex, age	Initial diagnosis	Start TKI for M1	Mutation status	Location of metastases	Follow-up method	Therapy response	Time to hepatic progression (months)	Time to extrahepatic progression (months)	Status after SIRT
D.B., f, 34	06/99	12/03	exons 11 and 17	right LL	MRI	CR	24	20	AWD at 52 months
M.L., f, 52	09/6	11/06	exon 9	both LL; EHD	MRI	PR	14	5	DOD at 19 months
B.K., m, 73	5/05	2/08	wt*	both LL; EHD	PET CT	PR	24	14	AWD at 33 months
A.H., m, 55	7/03	9/03	exon 11	both LL	MRI	PR	4	4	DOD at 21 months
W.B., m, 55	7/07	7/07	wt	right LL; EHD	MRI	CR	8	2	DOD at 26 months
I.H., m, 61	3/07	3/09	exon 11	both LL	MRI	SD	8+	-	AWD at 8 months
H.G; m, 58	6/08	6/10	exons 11 and 13	both LL; EHD	PET CT	PR	8+	8+	AWD at 8 months
S.N., m, 48	12/04	12/08	wt	right LL	CE CT	CR	9	-	AWD at 30 months

TKI = tyrosine kinase inhibitor, LL= liver lobe , EHD = extrahepatic disease,
AWD = alive with disease, DOD = died of disease;
*Neurofibromatosis type I

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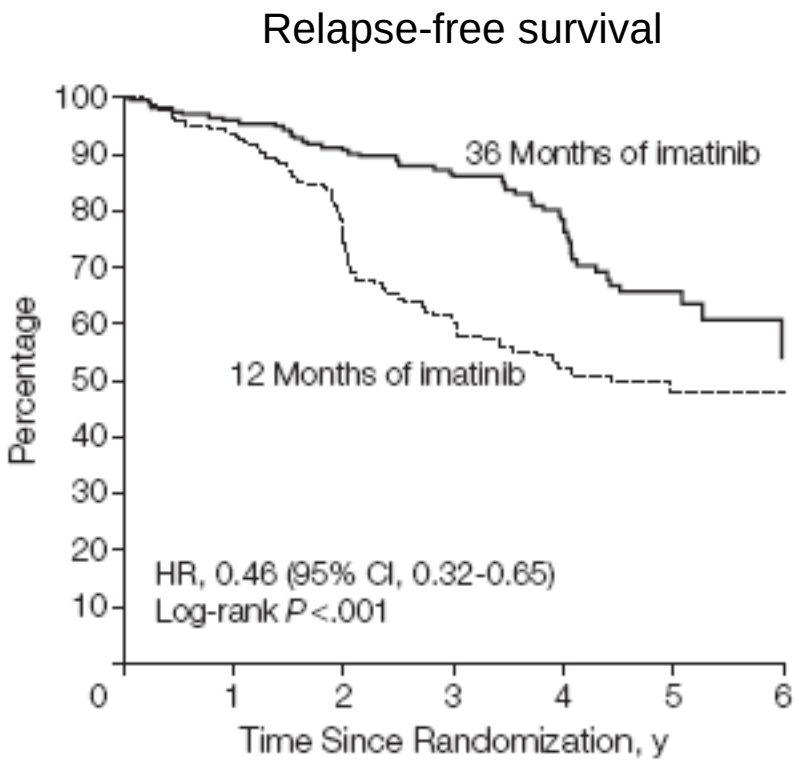
Conclusion & discussion

- Promising approach for durable hepatic disease control
- Not all patients eligible: hepato-pulmonary shunt must be <20%
- Treatment does not control extrahepatic disease
- Impact on overall survival/quality of life?
- Need for randomized studies:
  - In imatinib-resistant pts with focal liver progresssion: switch to 2nd line vs continuation of imatinib + local treatment (SIRT/Surgery)

Adjuvant imatinib

- Based on the success of imatinib in metastatic disease: exploration in adjuvant setting



Joensuu, JAMA 2012

Adjuvant imatinib

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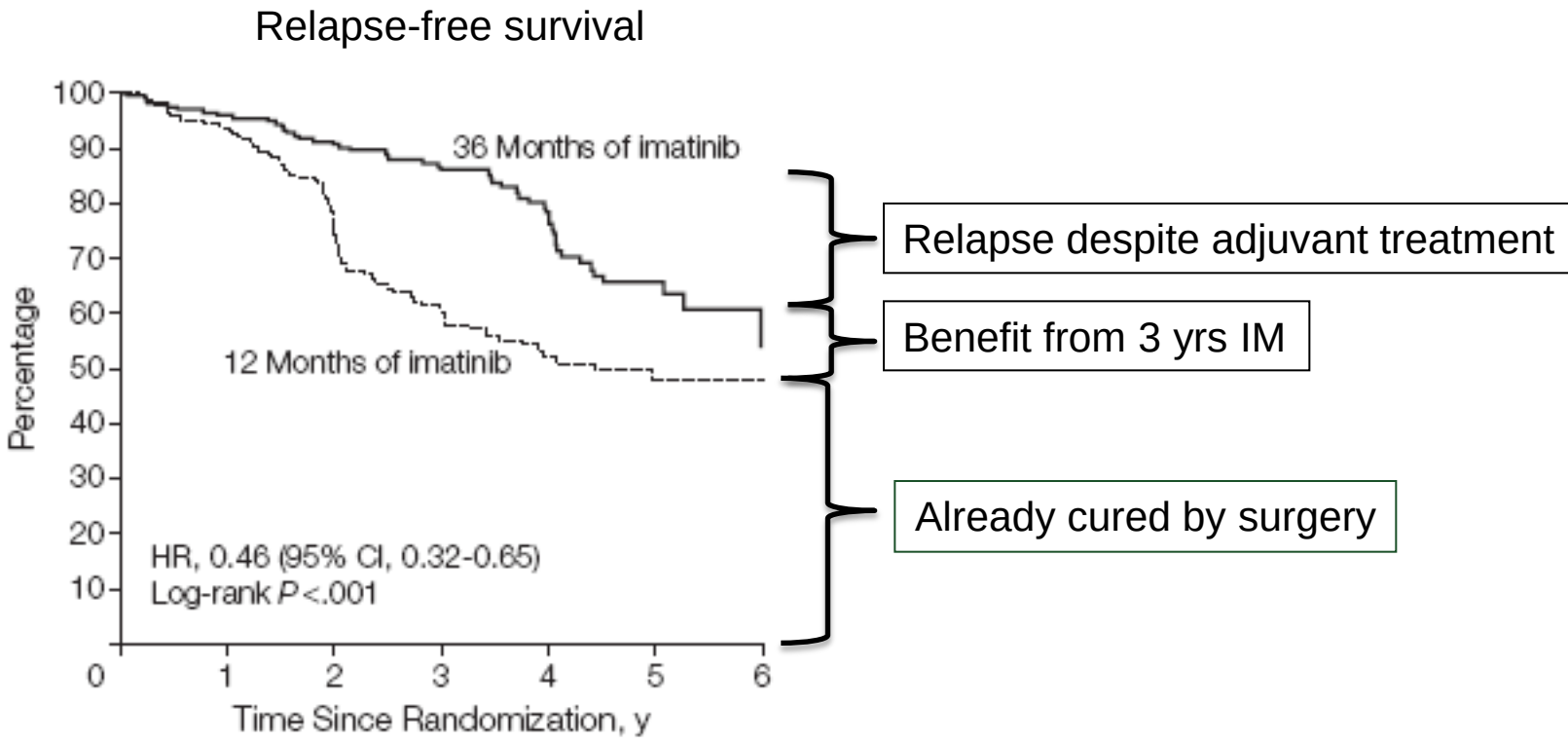
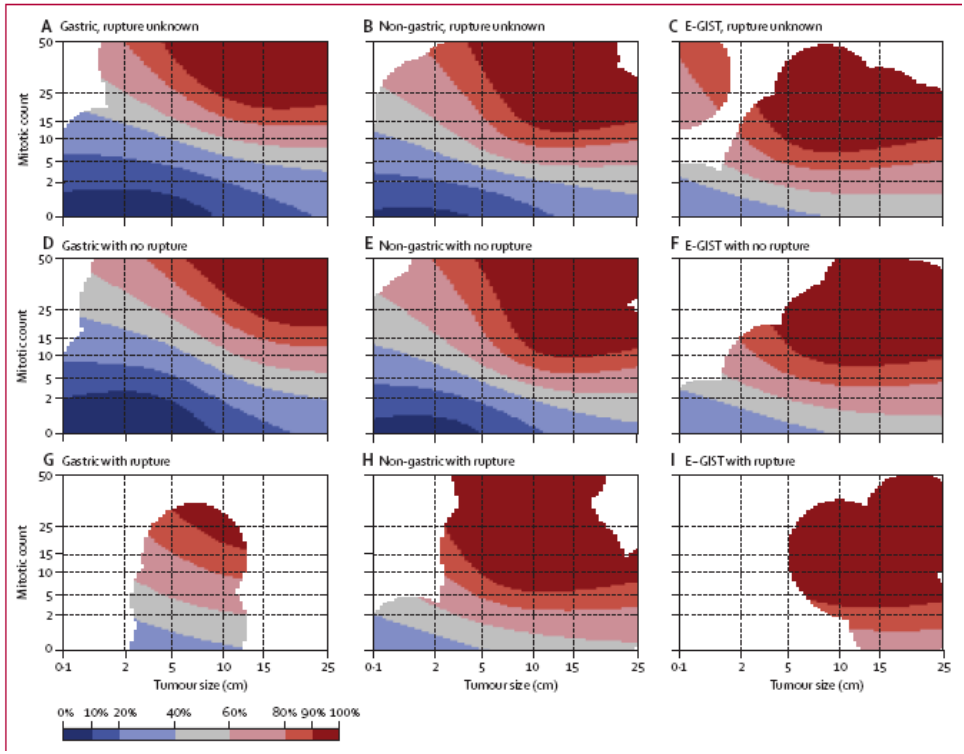


Joensuu, JAMA 2012

Adjuvant setting

- Given large proportion of pts being overtreated:
  - Need for improved prognostic classification

- Standard prognosticators:
  - Tumor size
  - Mitotic rate
  - Location
  - Tumor rupture
  - (Mutational status?)



Joensuu, Lancet Oncol 2012

1485PD

UNIKLINIK KÖLN

Gastrointestinal stromal tumors of the stomach with *KIT* exon 9 mutations mostly present with a favorable prognosis

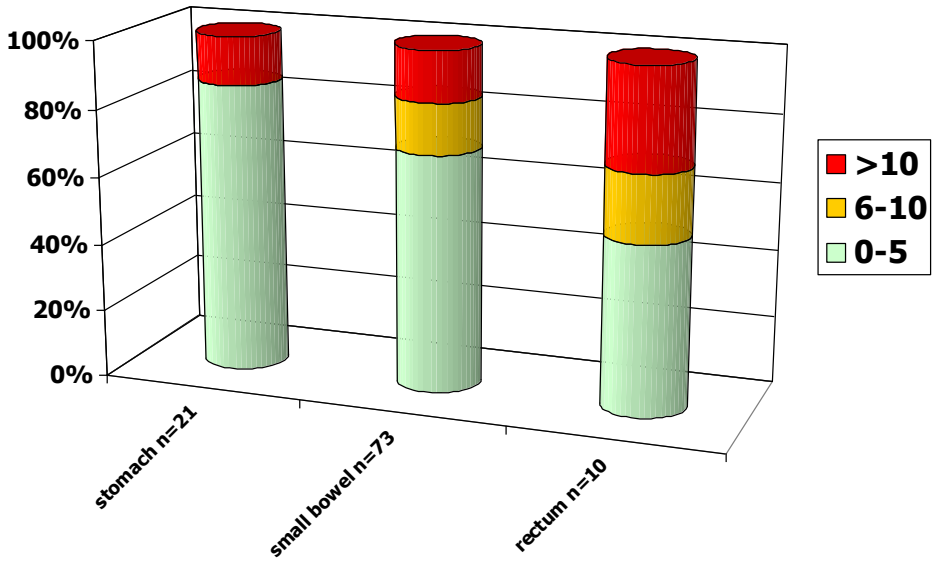
Eva Wardelmann, Heike Löser, Wiebke Jeske, Sabine Merkelbach-Bruse, Peter Hohenberger, Peter Reichardt, Sebastian Bauer, Reinhard Büttner, Sebastian Huss, Hans-Ulrich Schildhaus

Tumor aggressiveness of *c-KIT* exon-9 mutated GIST affected by location?

1485PD

- 95 GIST with exon 9 mutation
- Size and mitotic index for tumors located in:
  - Stomach
  - Small bowel
  - Rectum
- Small bowel and rectal GIST have:
  - Larger size
  - Higher mitotic index

tumor diameter (cm)	stomach	small bowel	rectum
mean (SD)	**4.2 (4.3)**	**6.6 (3.4)**	**5.5 (2.1)**
Median	**2.5**	**6.0**	**5.0**



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Risk assessment in *KIT* exon 9 mutated GIST (acc. to Miettinen 2006)

	no risk very low risk low risk	moderate risk	high risk	total
Stomach	16	1	4	21
Small bowel	22	11	31	64
rectum	4	2	4	10
total	42	14	39	95

- The proportion of exon 9-mutated, low risk-GIST is significantly higher in the stomach (76.2%) than in the small bowel (34.4%) and rectum (40%).

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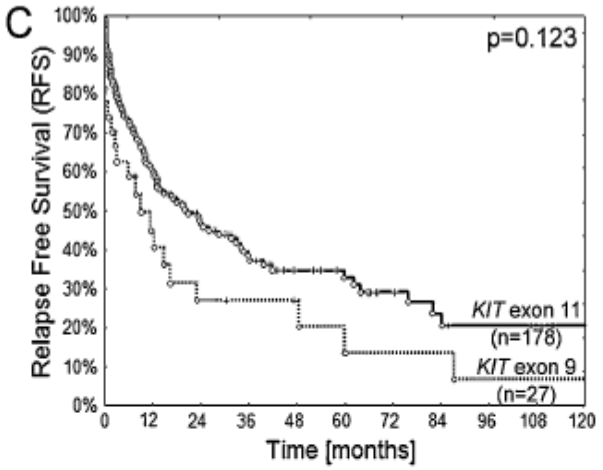
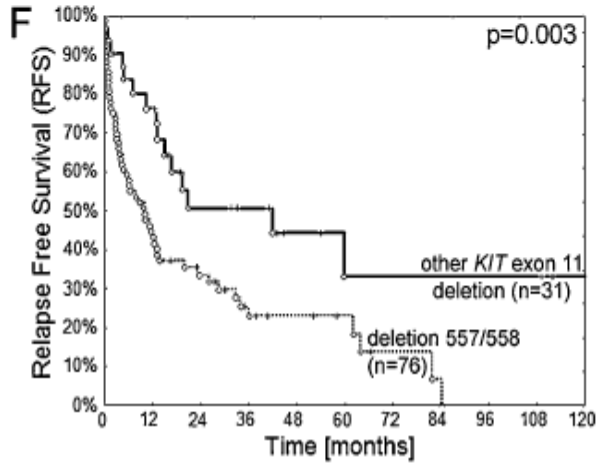
Conclusions

- Underlying mechanism?:
  - Different expression of co-factors needed for c-kit function (ie ETV1) by different miRNAs or methylation status?
  - Earlier presentation in case of gastric tumors vs rectum/small bowell?

- Collaborative effort to establish role of mutation status in prognostic models and role in adjuvant setting





Wozniak, Ann Oncol 2012

What to do with small gastric submucosal tumors?

Watchful waiting vs invasive procedures

- Gastric submucosal lesions:
  - Myogenic tumor (leiomyomas, LMS)
  - Neurogenic tumors (Schwannomas, neurofibromas)
  - GIST

Gastric small submucosal lesions

- Guidelines
  - Lesions ≥2 cm:
    - Excision (preceded by biopsy)
  - Lesions < 2 cm:
    - biopsy can be difficult, excision only way to get a diagnosis
    - Most lesions: low risk GIST or lesion of unknown significance
    - Standard approach:
      - Endoscopic ultrasound assessment
      - Annual follow-up
    - Excision when tumour increases in size or becomes symptomatic

Clinical significance of surgery for gastric submucosal tumors with size enlargement during watchful waiting; Miyazaki Y et al (1485PD)

- Objective: outcomes of surgery for lesions increasing in size during watchful waiting

- Retrospective series, asymptomatic, no biopsy:
  - 23 pts (out of ?)
  - Median tumor size:
    - Base-line: 2.0 cm (0.8-4.0)
    - At resection: 3.2 cm (2.0-7.0)
  - Median waiting period: 63 months (8-181)

Surgical procedure partial gastrectomy (laparoscopic/open) proximal gastrectomy (laparoscopic/open)	 18/4 0/1
Operation time (min)	110 (49-247)
Blood loss (ml)	20 (0-230)
Major operative/postoperative complications Data were presented as median (range).	0

Schwannoma		2
GIST		21
	Miettinen Risk Stratification	
	None	2
	Very low	13
	Low	1
	Moderate	**5**

Conclusions

- Majority of pts underwent laparoscopic partial gastrectomy
- Difficult to put into perspective: also lesions > 2 cm
- But 5/21 pts: moderate risk GIST: candidates for adjuvant imatinib?
  - What if these cases were resected earlier?
- High need for prospective, large series in pts with asymptomatic lesions < 2 cm to assess:
  - Proportion of pts with increasing tumor size
  - Proportion of pts with unfavorable outcome

Choose your battles wisely!