Gastro-intestinale Stromatumoren

Peter Hohenberger

Spez. Chirurgische Onkologie & Thoraxchirurgie
Chirurgische Universitätsklinik

Medizinische Fakultät Mannheim

Universität Heidelberg

Chairman, EORTC Soft Tissue and Bone Sarcoma Group

UMM
UNIVERSITÄTSMEDIZIN
MANNHEIM

EORTC
European Organization for Research and Treatment of Cancer
STBSG

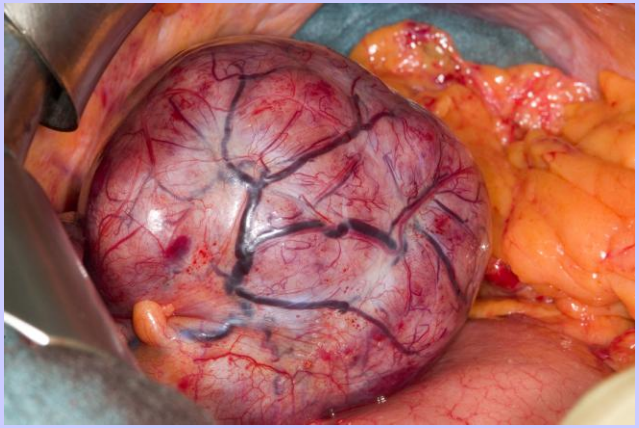
Pathologische Klassifizierung und neue Therapieansätze

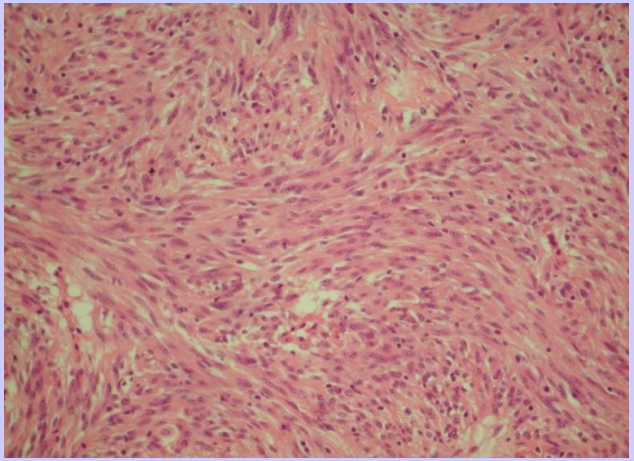
- Behandlungsprinzipien für Primärtumoren
- Indikation zur adjuvanten Therapie
- Indikation zur neoadjuvanten Therapie
- Wann ist eine Mutationsanalytik notwendig
- Plasmaspiegelbestimmung auch bei GIST ?

GIST - Klinische Präsentation

- Charakteristische Pathologie
  Früher: muskulärer Ursprung

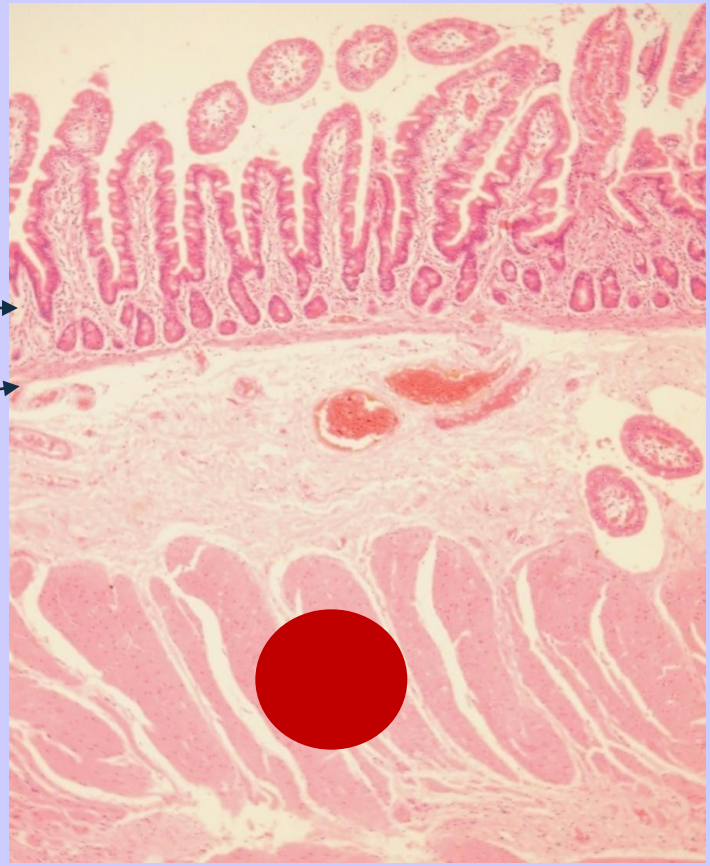
- Heute:
  - » nicht muskulär
  - » nicht neural
  - » “Stroma Tumoren”
    pacemaker Zellen Cajal





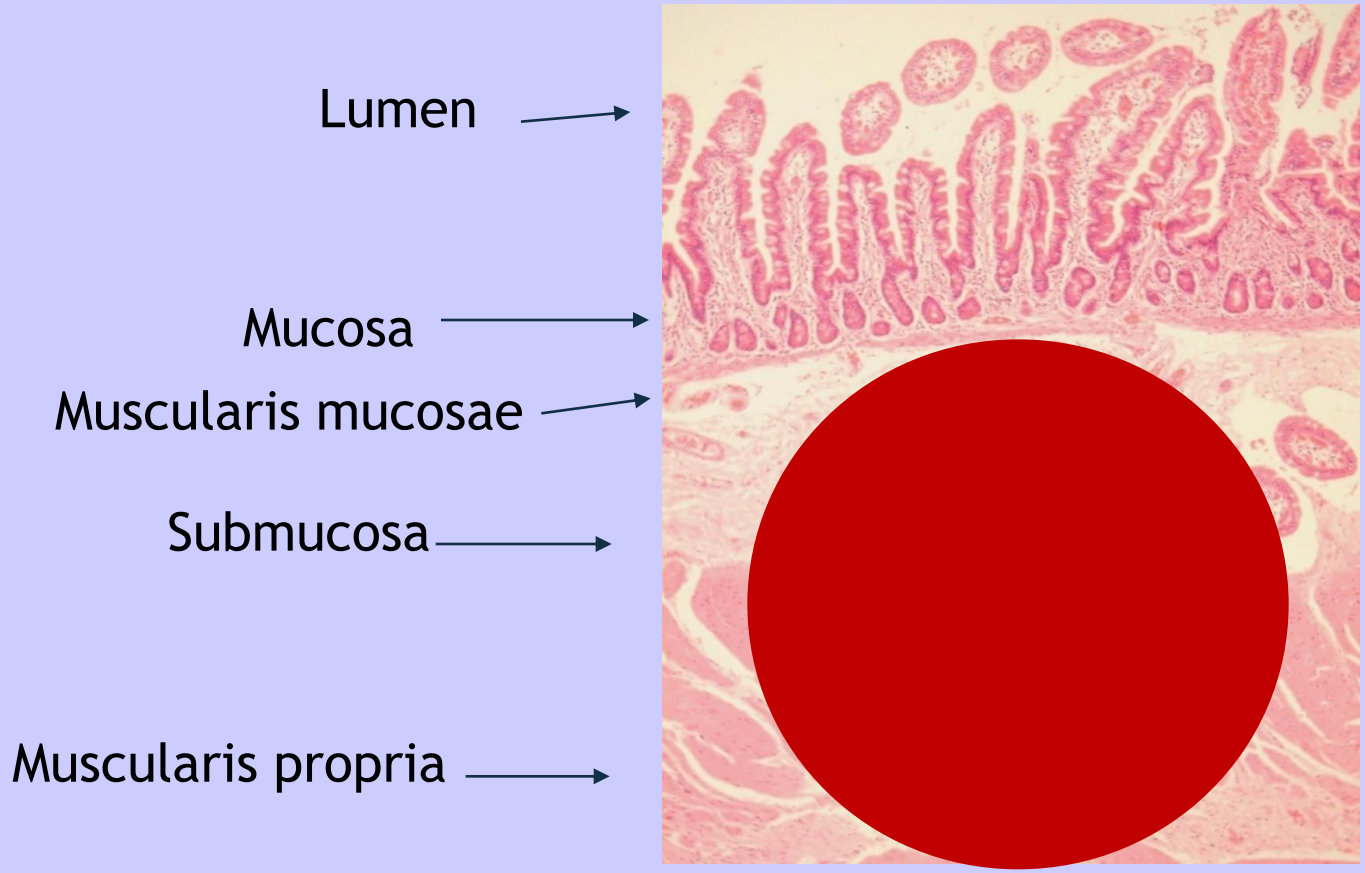
90% der mesenchymalen Tumoren des Darms sind GIST

GIST - Ursprung Cajal Zellen ?



Courtesy: R.Feakins, London

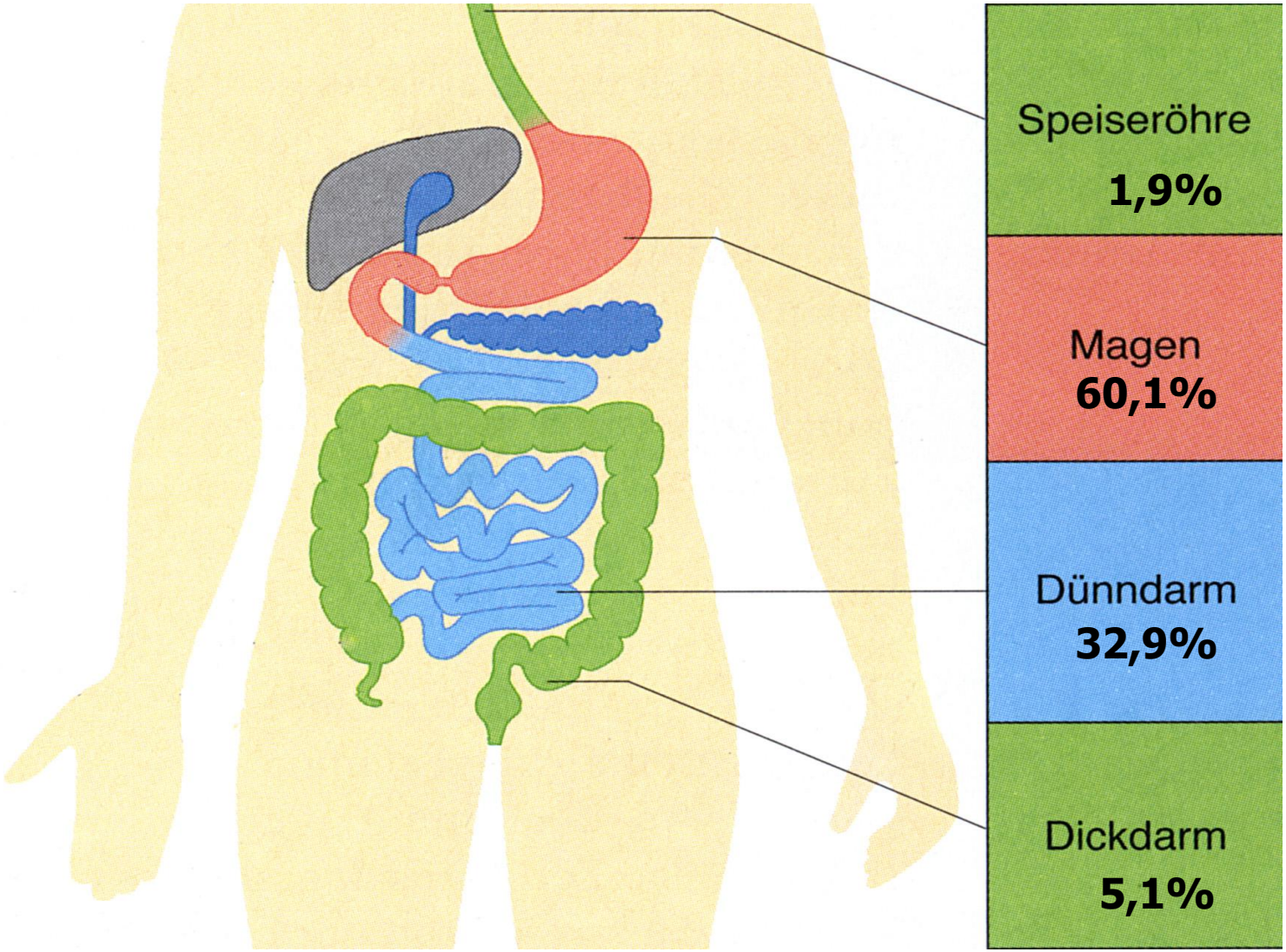
GIST - Ursprung Cajal Zellen



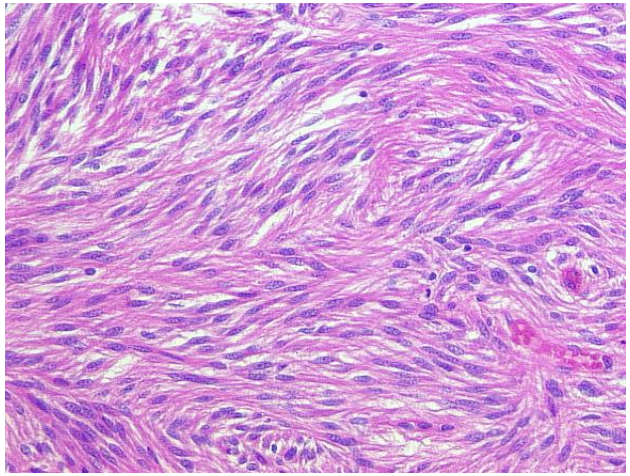
Courtesy: R.Feakins, London

Biopsie oft nicht zielführend

Lokalisation gastrointestinaler Stromatumoren (n=316)

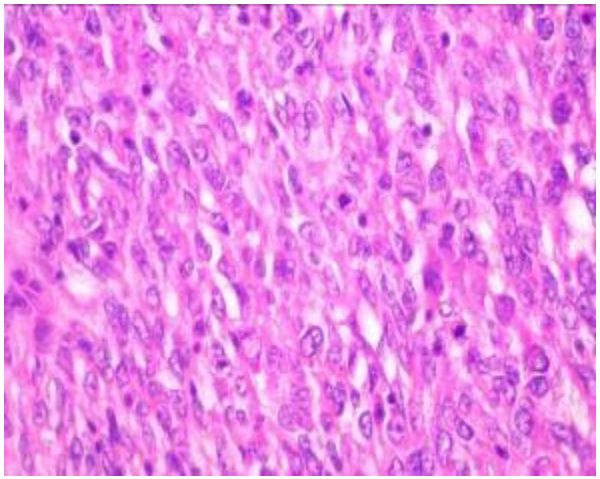


GIST: Mikroskopische Subtypen



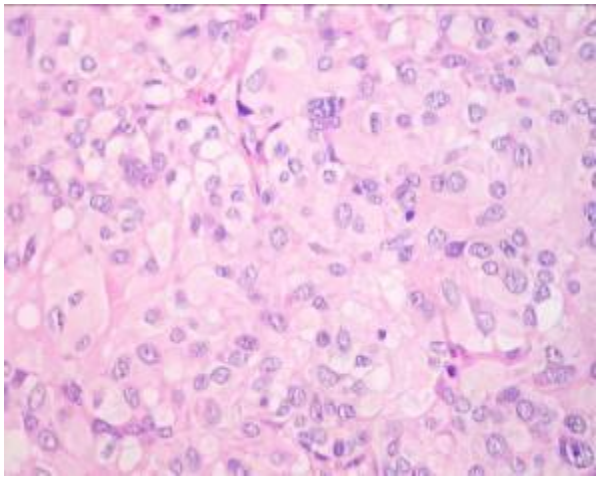
spindelzellig

n=220
70,1%



gemischt

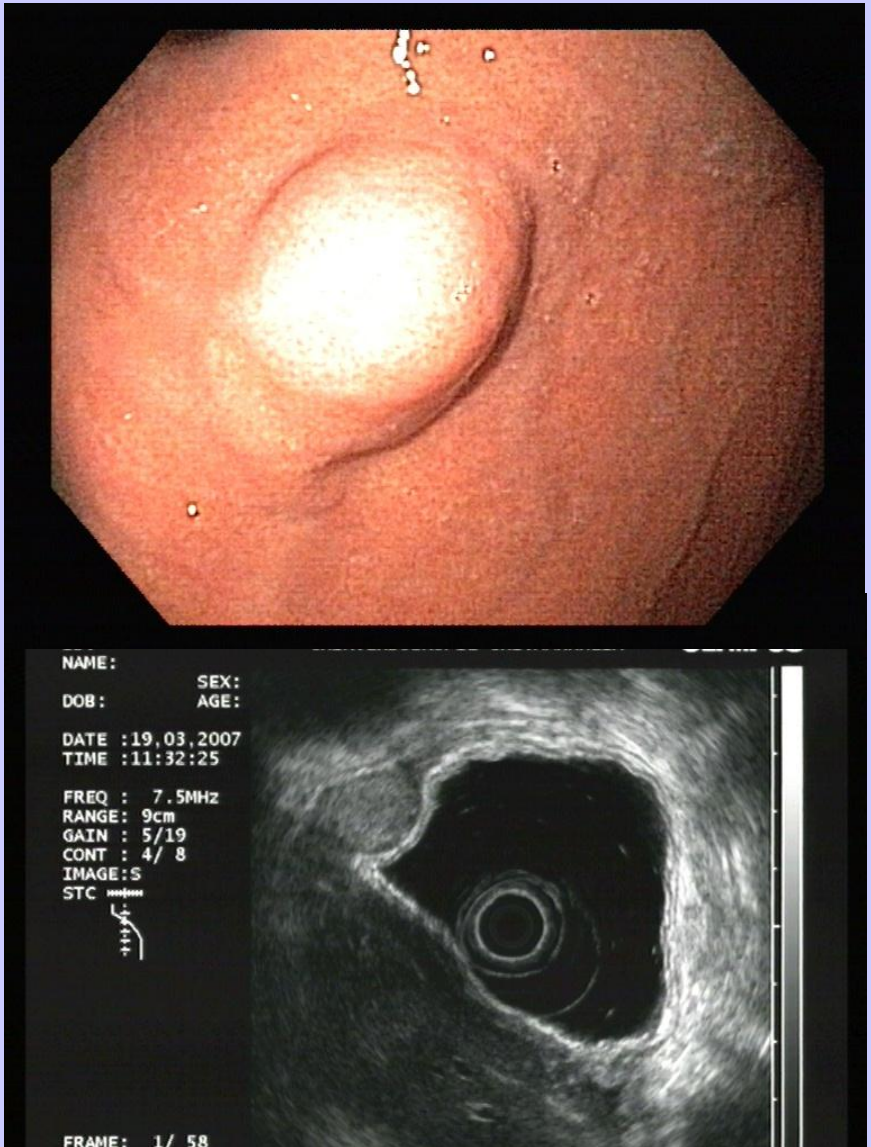
n=66
21,0%

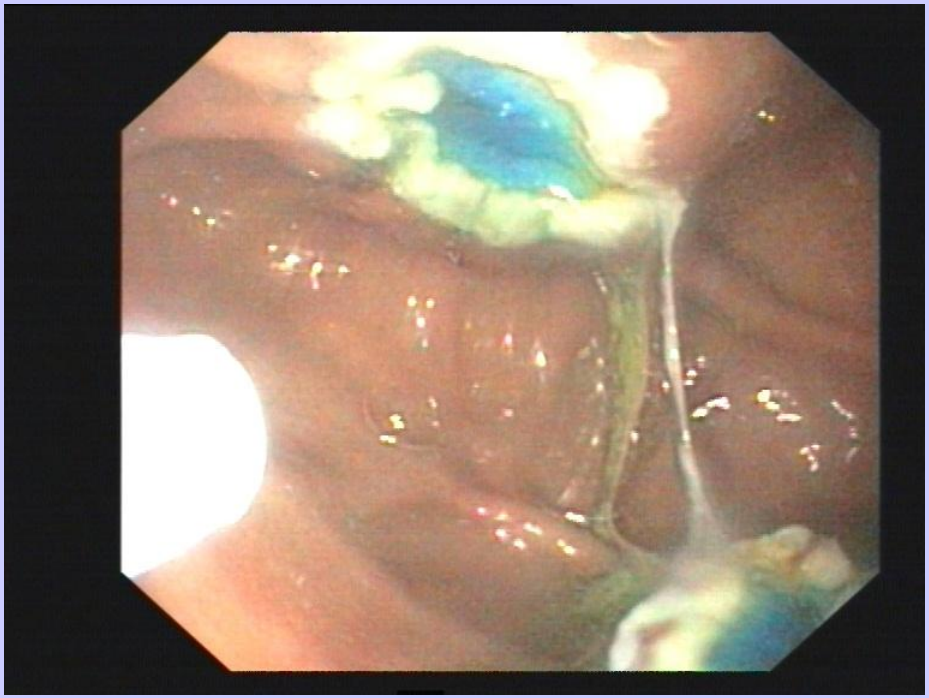


epitheloidzellig

n=28
8,9%

Sehr kleine GIST – endoskopische Resektion absolute Ausnahme !





Prinzipien chirurgischer Therapie

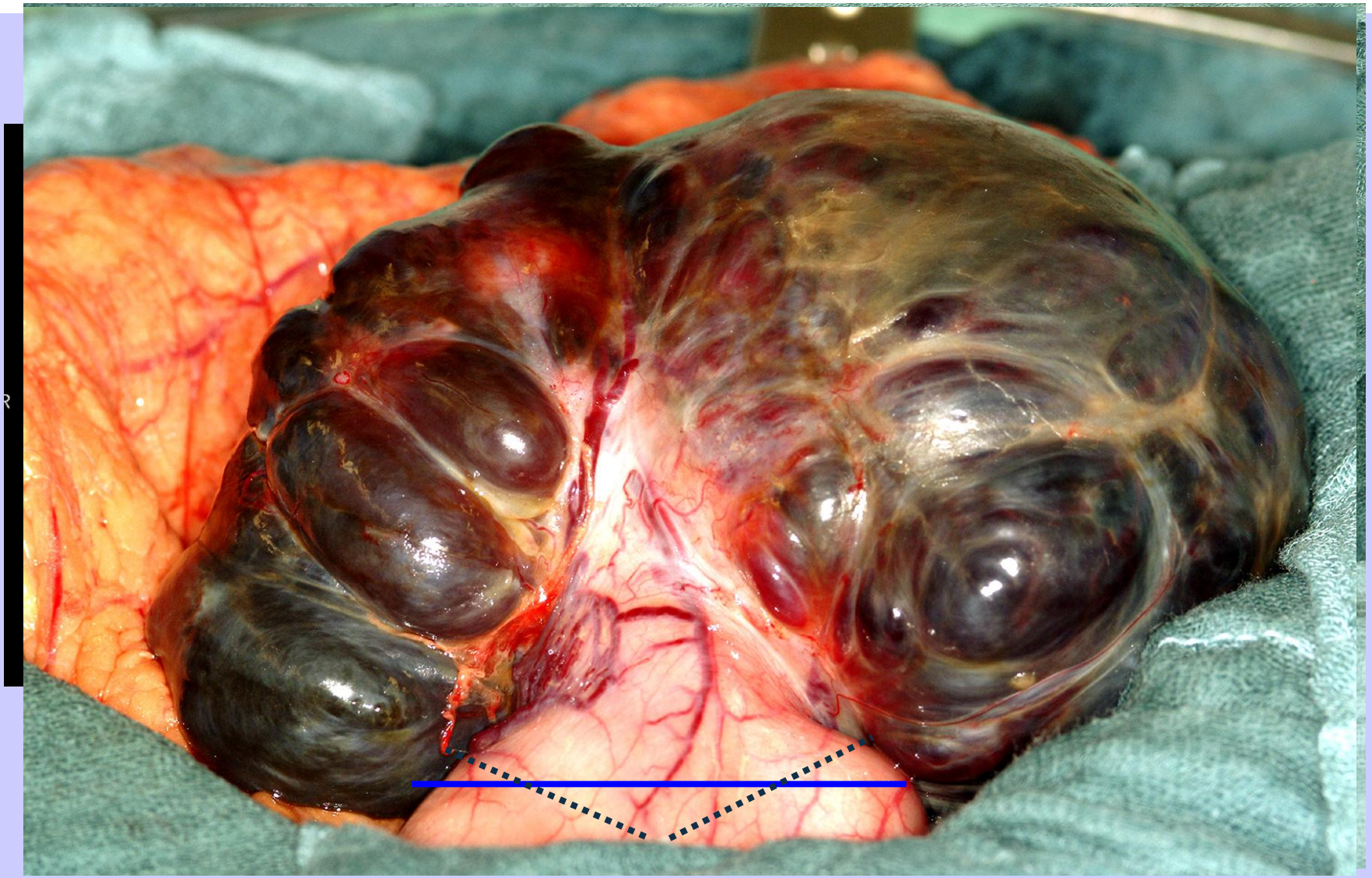
- Jeder GIST ist potentiell maligne
- OP-Prinzipien wie bei Krebsoperation
- Indikation zur OP : GIST > 2cm
- Komplette Resektion (R0)
- 1-2 cm Sicherheitsabstand
- Keine ausgedehnte Lymphknotendissektion

Prinzipien chirurgischer Therapie

- Endoskopisch : nein, Wachstum intramural
- Laparoskopisch : ja, wenn Prinzipien einer Krebsoperation eingehalten
- Problem der Lokalisation
- Tumorruptur
- Dissemination in der Bauchhöhle vermeiden

Resektionausmass: Dünndarm

Resektionsausmass am Magen



Was können wir aus chirurgischen Daten lernen ?
Tumor ruptur

Operative Therapie von Primärtumoren (n=486, MA/BN/B)

27 Pat. mit Tumorruptur / Perforation
3 pat. mit M1 disease + Perforation

18 primäre Tumorperforation
2 Tumorruptur nach stumpfen Bauchtrauma
4 Tumorruptur während Resektion

1 Patient rezidivfrei nach 82 Monaten !

4/5 Patienten unter adjuvanter Therapie rezidivfrei
alle anderen Patienten (18/19) entwickelten Metastasen

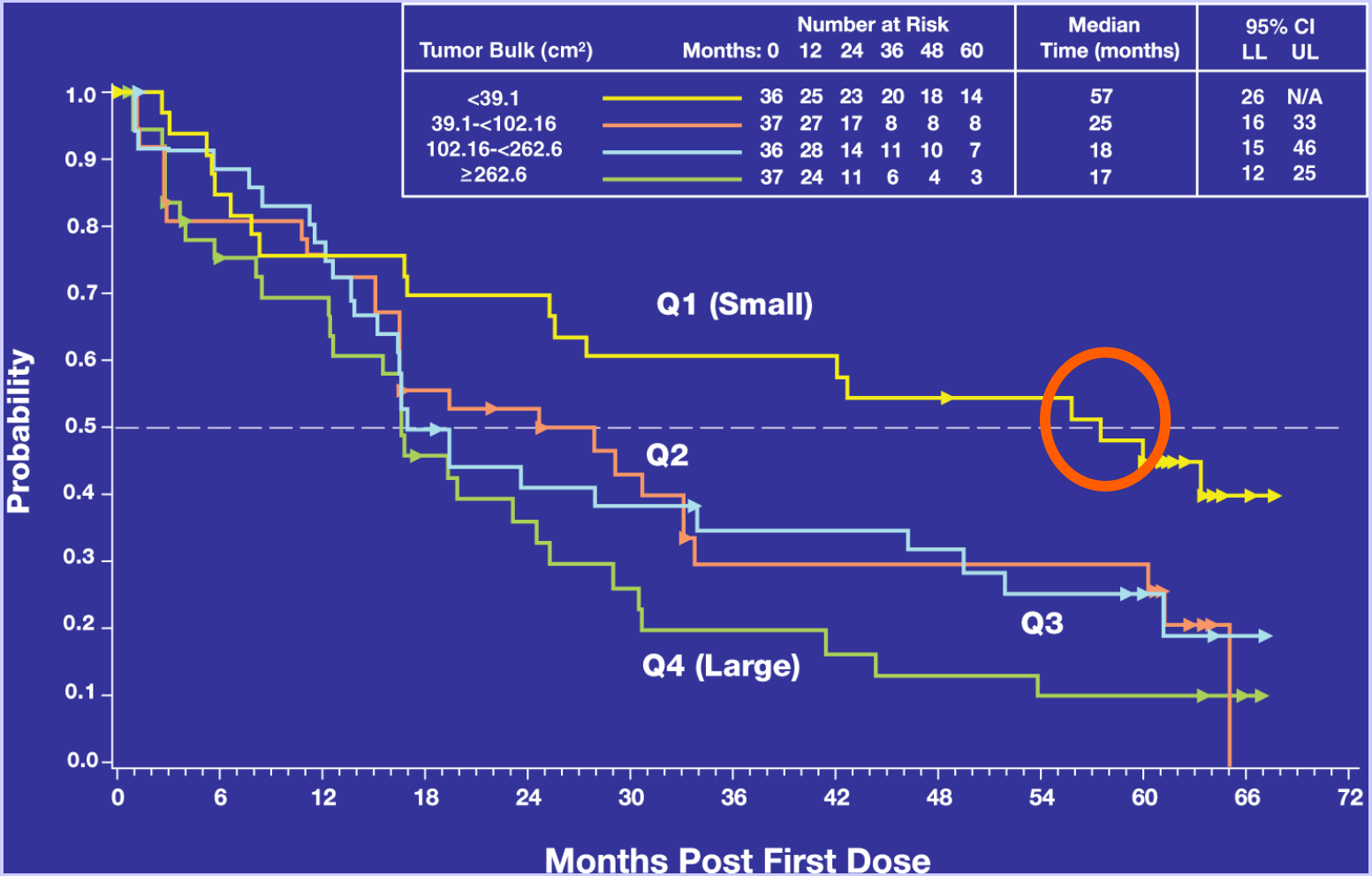
Medianes Zeitintervall bis zum Rezidiv : 22 Monate (range, 5-82)

Ann.Surg.Oncol 2009; 16,S1: A296

Omentale und peritoneale Metastasen

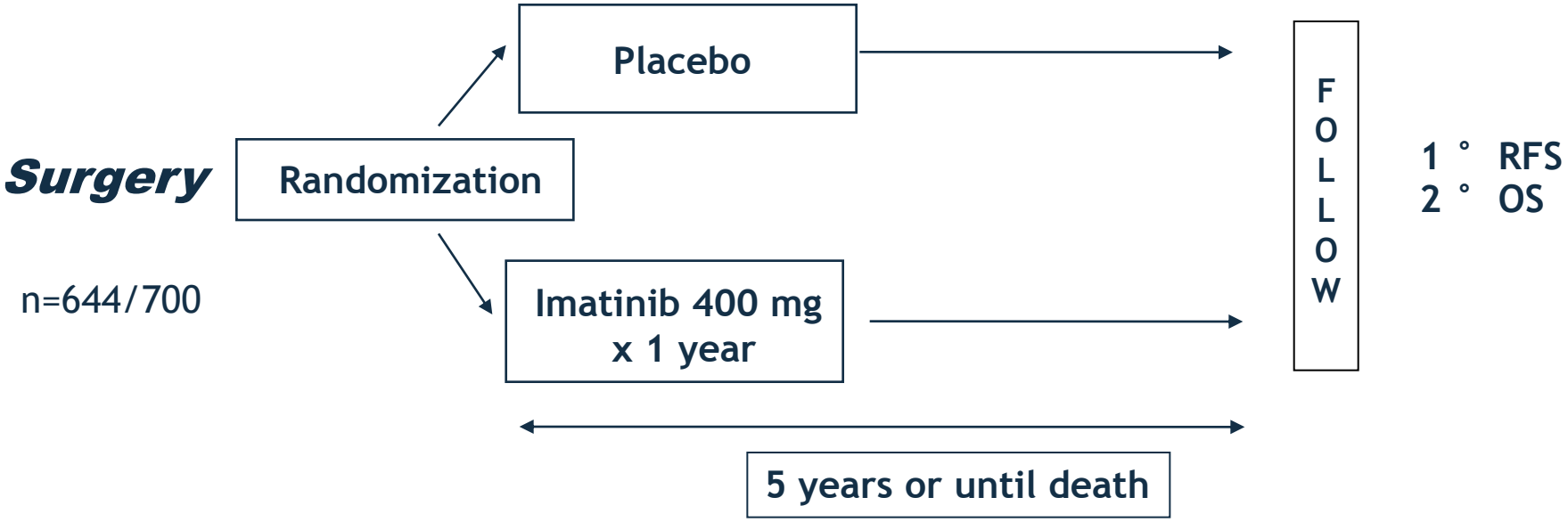
Adjuvante Therapie ?

Progressionsfreie Zeit vs. Tumorlast



Blanke C, et al. *JCO*. 2008;26(4):626-632.

ACOSOG Z9001 (Closed in April 2007)



Objectives:

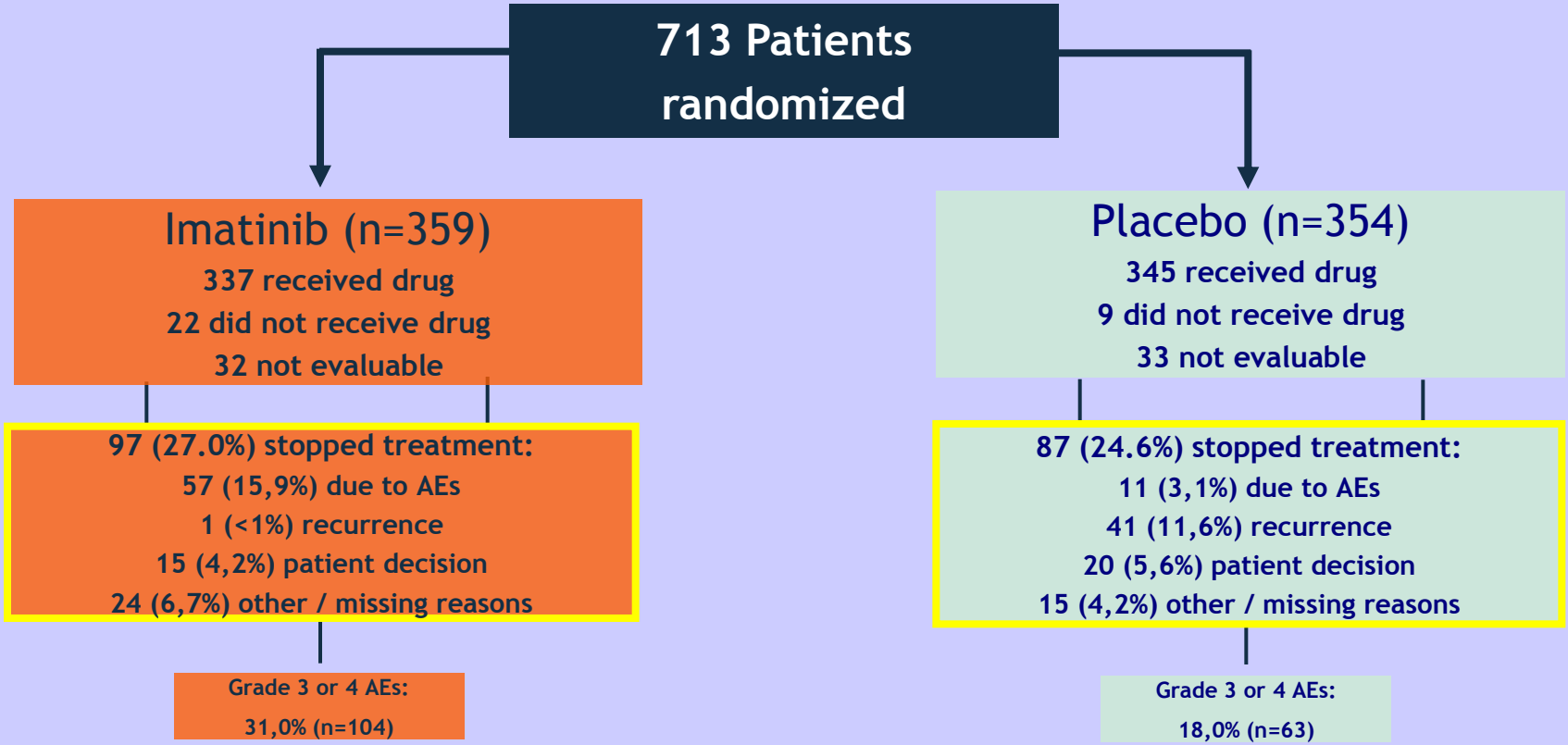
- Primary: Relapse free survival
- Secondary: Overall survival

Inclusion criteria:

- KIT-positive GIST
- > 3 cm
- Completely resected

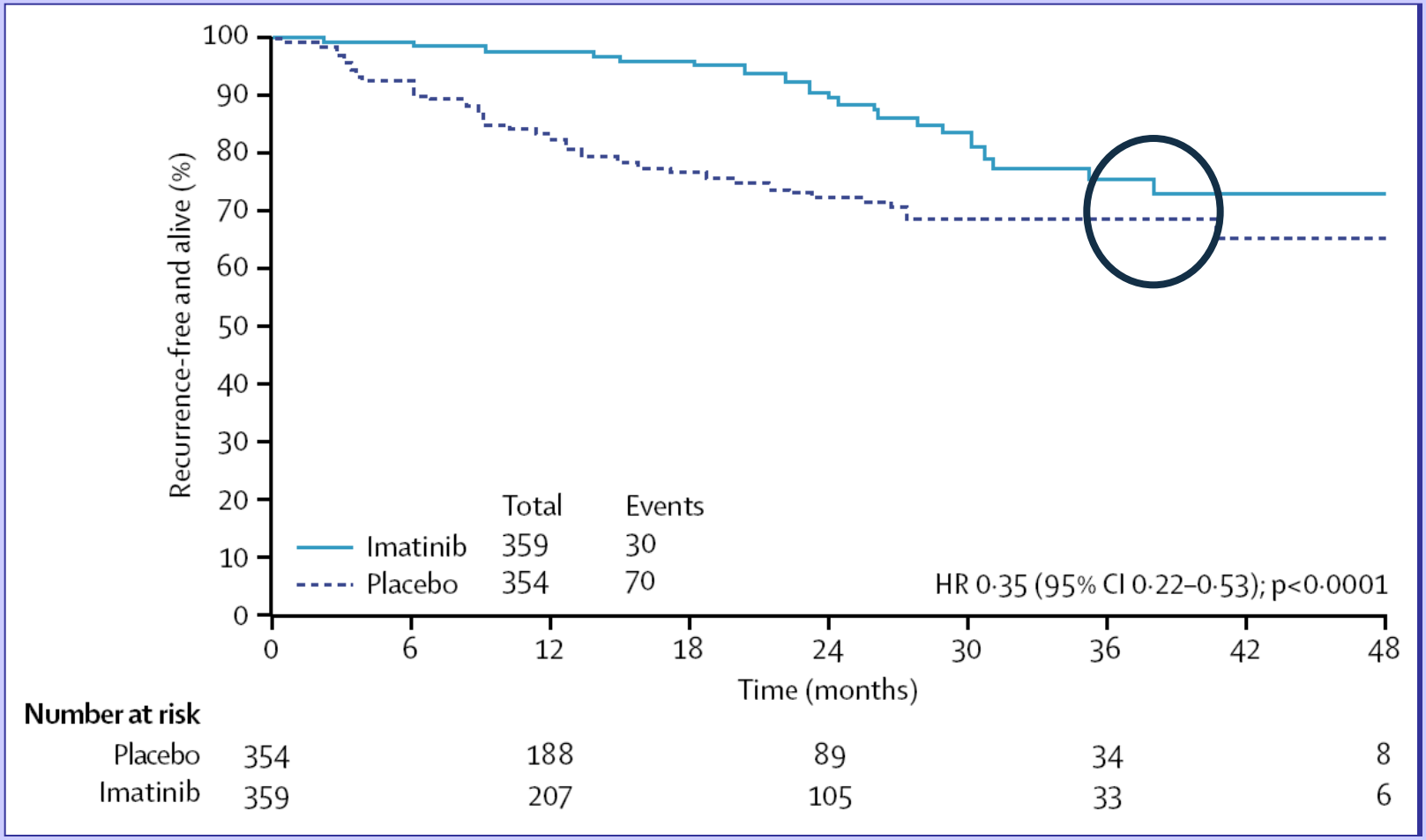
DeMatteo et al. *Lancet*. 2009;373:1097-1104.

Treatment / Compliance



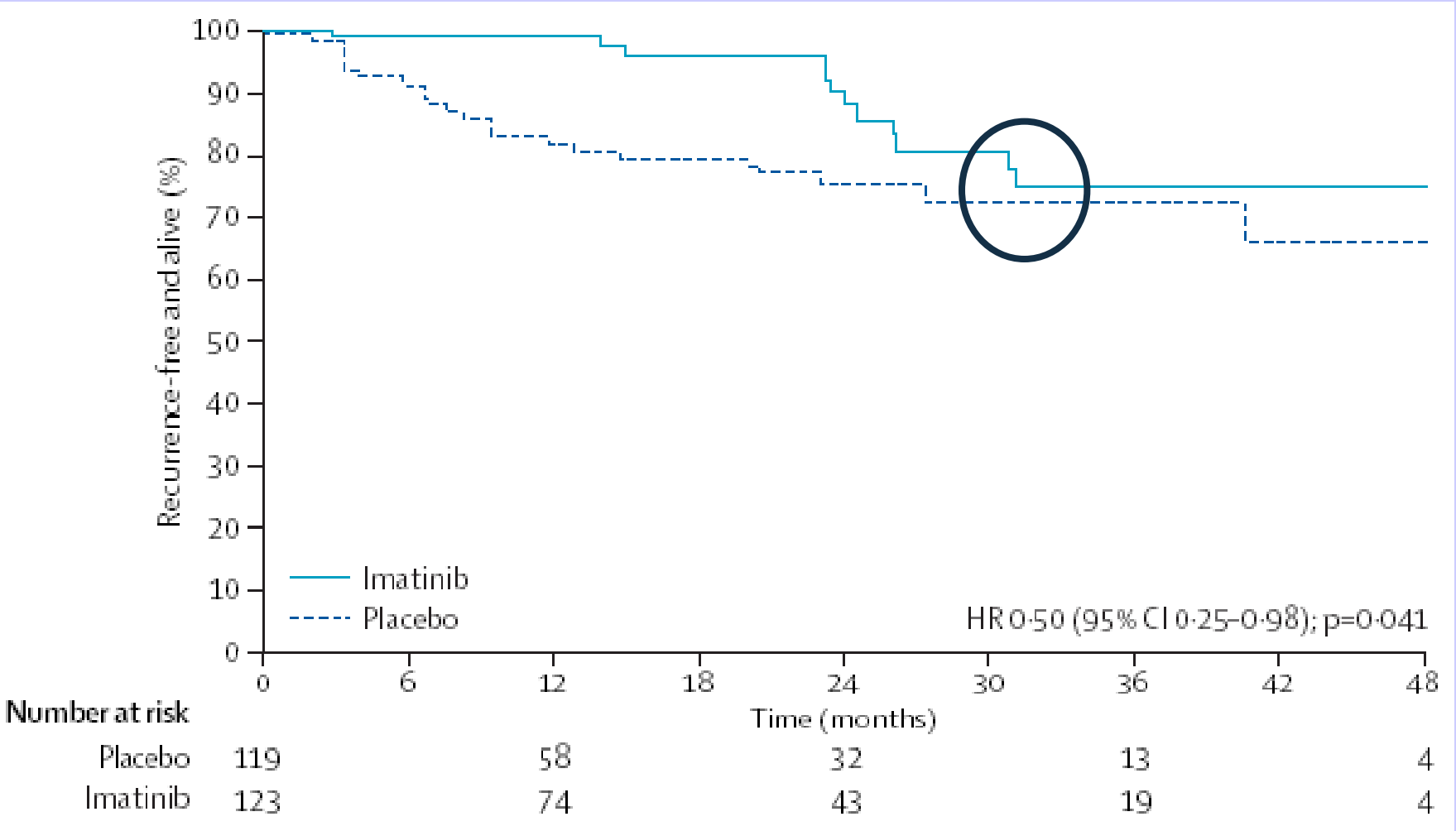
DeMatteo et al. *Lancet*. 2009;373:1097-1104.

Z9001: Recurrence-Free Survival



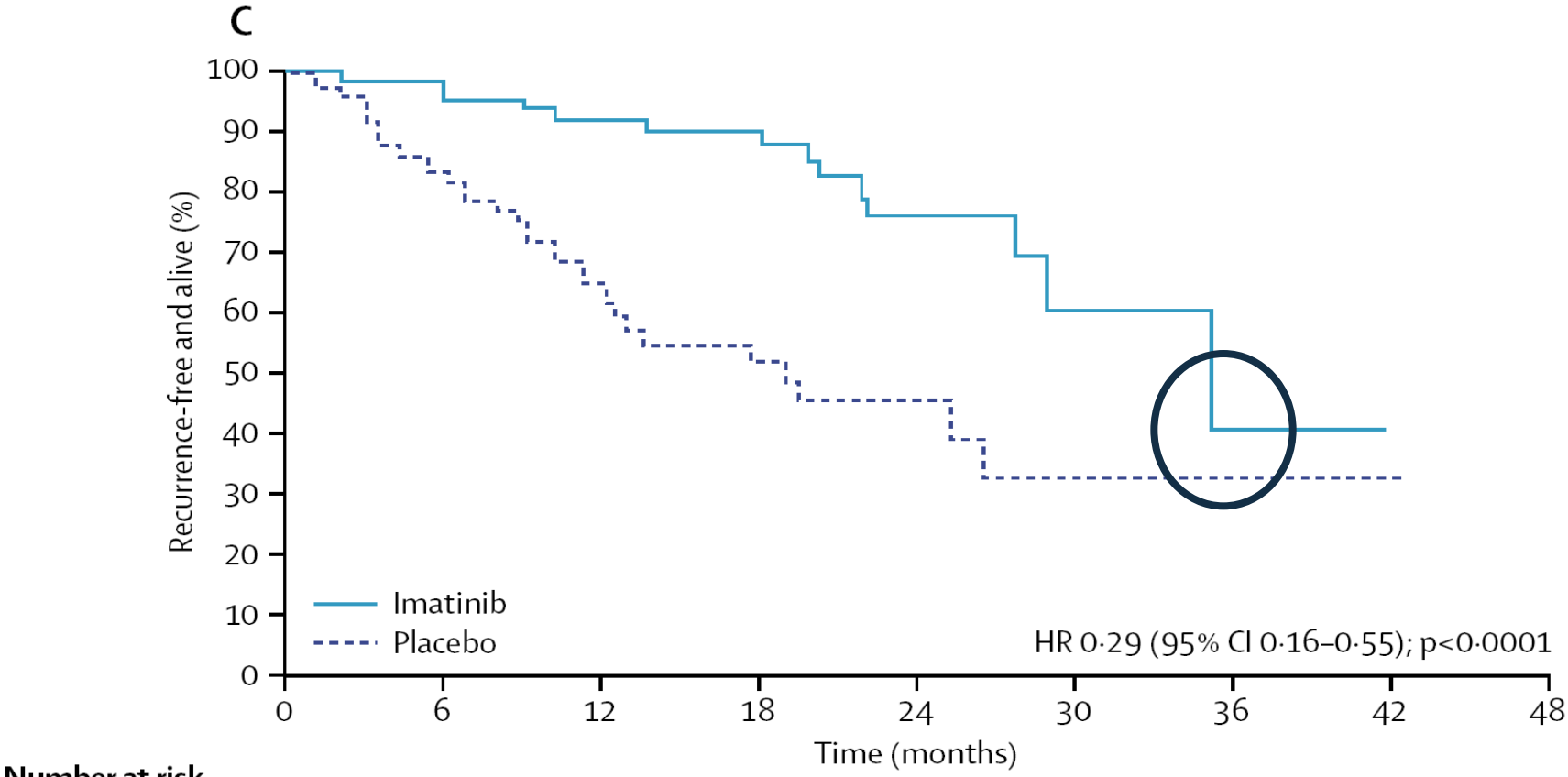
DeMatteo et al. *Lancet*. 2009;373:1097-1104.

Recurrence-Free Survival: Tumors > 6 cm and < 10 cm



DeMatteo et al. *Lancet*. 2009;373:1097-1104.

Z9001: Recurrence-Free Survival: > 10 cm

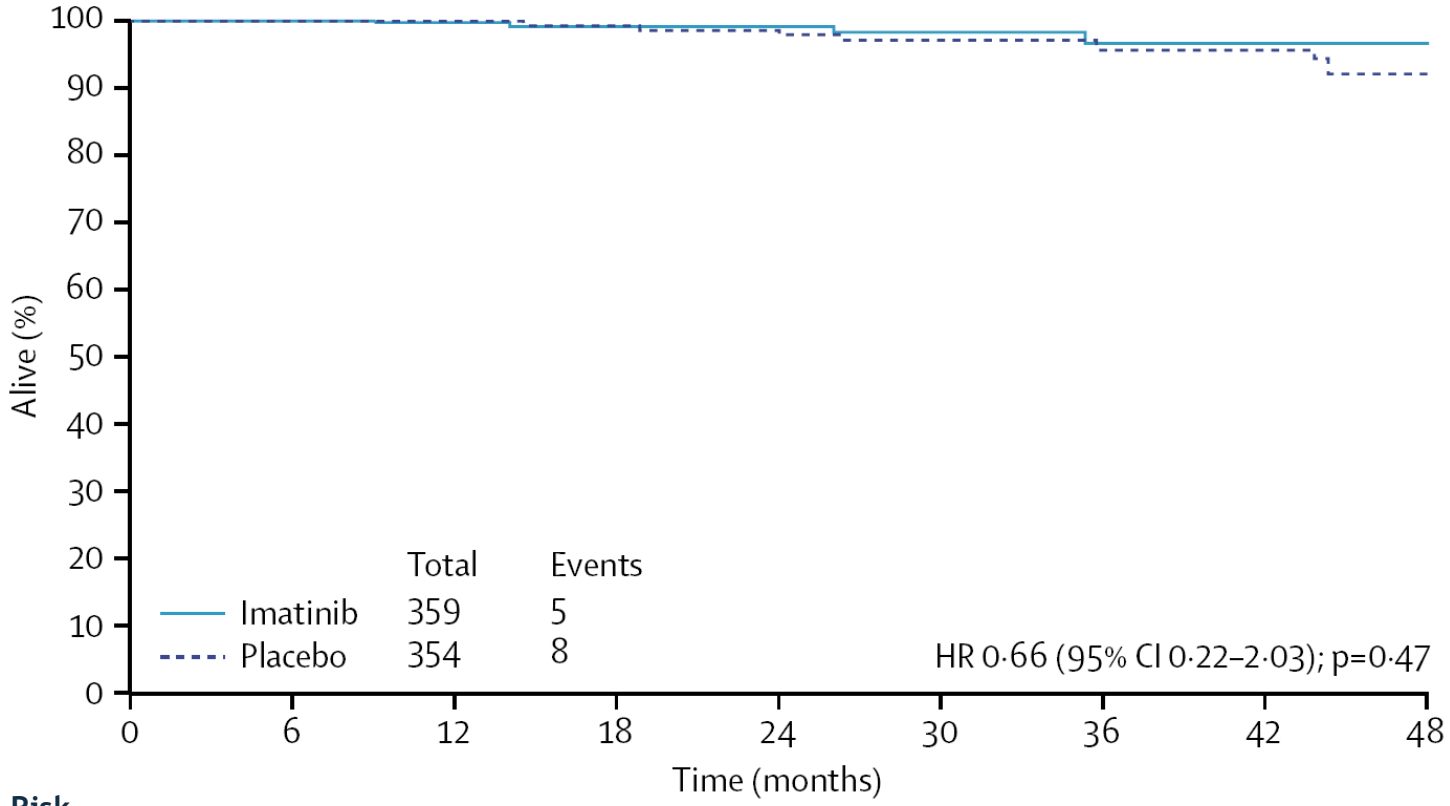


Number at risk

Placebo	86	35	10	1	0
Imatinib	93	51	21	2	0

DeMatteo et al. *Lancet*. 2009;373:1097-1104.

Z9001: Overall Survival



Number at Risk

Placebo	354	241	151	58	15
Imatinib	359	226	137	51	15

DeMatteo et al. *Lancet*. 2009;373:1097-1104.

Recently completed trials of adjuvant imatinib in GIST

SSG XVIII-AIO:

- Trial description
  - 12 months versus 36 months of Imatinib
- Objectives
  - Primary: relapse-free survival
- Inclusion criteria
  - High-risk GIST
  - (initially M1)
- Patient numbers
  - 400 randomized

EORTC 62024:

- Trial description
  - 24 months of imatinib versus control
- Objectives
  - **New primary: Time to imatinib failure**
- Inclusion criteria
  - Intermediate-risk or high-risk GIST
- Patient numbers
  - 906 randomized

Press Release: Basel, April 12, 2007

MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG

Positiv … e to
patien…

- …
- …
- …
- … or

- Glivec is indicated for the adjuvant treatment of adult patients after resection
of KIT (CD117) positive GIST
larger than 3 cm

CHMP Recommendation March 19, 2009

European Medicines Agency
Evaluation of Medicines for Human Use

- Glivec is indicated for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117) positive GIST
- Patients who have a low or very low risk should not be treated

Glivec is indicated for

- the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.

GIST-Klassifikation nach Fletcher 2002

Risiko eines aggressiven klinischen Verhaltens

sehr niedrig	< 2 cm	≤5/50 HPFs
niedrig	2-5 cm	≤5/50 HPFs
mittel	≤ 5 cm	6-10/50 HPFs
	5-10 cm	≤5/50 HPFs
hoch	**> 5 cm**	**>5/50 HPFs**
	> 10 cm	**jede Mitosezahl**
	jede Grösse	**>10/50 HPFs**

Metastasenrisiko bei intestinalen und gastralen GIST

(nach Miettinen und Lasota, Sem Diagn Pathol 2006)

Gruppe	Größe	Mitosenzahl	Risiko			
			Magen	**Jej./Ileum**	**Duodenum**	**Rektum**
1	≤ 2 cm	≤5/50 HPFs	ø	ø	ø	ø
2	> 2-5 cm	≤5/50 HPFs	sehr niedrig	niedrig	niedrig	niedrig
3a	> 5-10 cm	≤5/50 HPFs	niedrig	moderat	hoch	hoch
3b	> 10 cm	≤5/50 HPFs	moderat	hoch		
4	≤ 2 cm	>5/50 HPFs	ø*	hoch*	-	hoch
5	> 2-5 cm	>5/50 HPFs	moderat	hoch	hoch	hoch
6a	> 5-10 cm	>5/50 HPFs	hoch	hoch	hoch	hoch
6b	> 10 cm	>5/50 HPFs	hoch	hoch		

* Sehr geringe Fallzahl; - keine Fälle

Mitotic Index	Size	Gastric	Jejunum/ Ileum	Duodenum	Rectum
≤ 5 per 50HPF	≤ 2cm	0%	0%	0%	0%
	>2 - ≤ 5cm	1.9%	4.3%	8.3%	8.5%
	>5 - ≤ 10cm	3.6%			
	> 10cm				
> 5 per 50HPF	≤ 2cm				
	>2 - ≤ 5cm				
	>5 - ≤ 10cm				
	> 10cm				

Very low risk

Low risk

Mitotic Index	Size	Gastric	Jejunum/ Ileum	Duodenum	Rectum
≤ 5 per 50HPF	≤ 2cm				
	>2 - ≤ 5cm				
	>5 - ≤ 10cm			34%	57%
	> 10cm		52%		
> 5 per 50HPF	≤ 2cm		50%	No data	54%
	>2 - ≤ 5cm		73%	50%	52%
	>5 - ≤ 10cm	55%	85%	86%	71%
	> 10cm	86%	90%		

High risk

Mitotic Index	Size	Gastric	Jejunum/ Ileum	Duodenum	Rectum
≤ 5 per 50HPF	≤ 2cm				
	>2 - ≤ 5cm				
	>5 - ≤ 10cm		24%		
	> 10cm	12%			
> 5 per 50HPF	≤ 2cm			No data	
	>2 - ≤ 5cm	16%			
	>5 - ≤ 10cm				
	> 10cm				

Intermediate risk

Discussion required

Mitotic Index	Size	Gastric	Jejunum/ Ileum	Duodenum	Rectum
≤ 5 per 50HPF	≤ 2cm	0%	0%	0%	0%
	>2 - ≤ 5cm	1.9%	4.3%	8.3%	8.5%
	>5 - ≤ 10cm	3.6%	24%	34%	57%
	> 10cm	12%	52%		
> 5 per 50HPF	≤ 2cm	0%	50%	No data	54%
	>2 - ≤ 5cm	16%	73%	50%	52%
	>5 - ≤ 10cm	55%	85%	86%	71%
	> 10cm	86%	90%		

Very low risk | Intermediate risk

Low risk | High risk

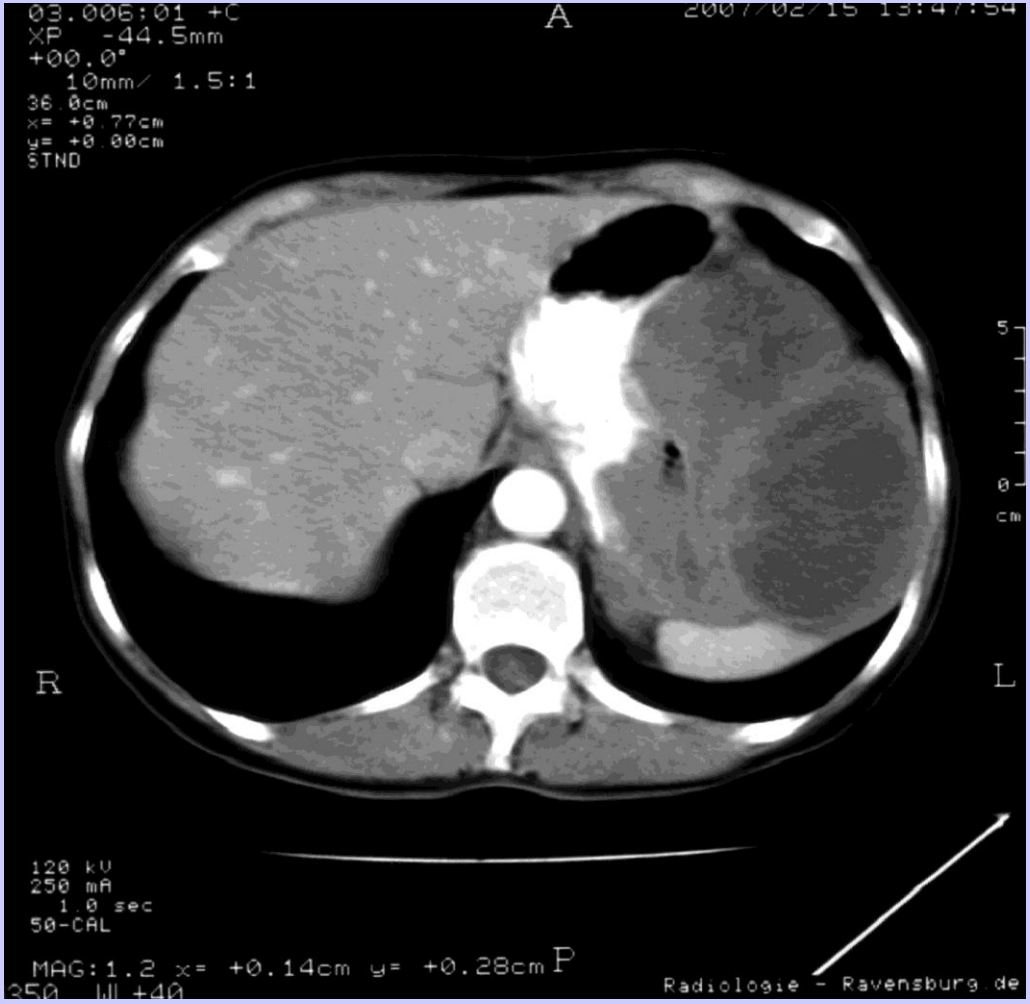
Praktischer Vorschlag

- **Indikation:** Patienten mit hohem Risiko
  - nach Fletcher, Miettinen oder Joensuu
- **Keine Indikation:** Patienten mit ‘low’ / ‘very low’ Risiko
  - nach Fletcher, Miettinen or Joensuu
- Diskussion mit dem Patienten mit ‘intermediate risk’
- **Indikation bei Patienten mit Tumorruptur**
- **Imatinib unwirksam bei NF-1, KIT exon 17 Mutation, D842V PDGFRa Mutation**
- **Mutations-analyse bei Hoch-Risiko Patienten Pflicht**

Neoadjuvante Therapie

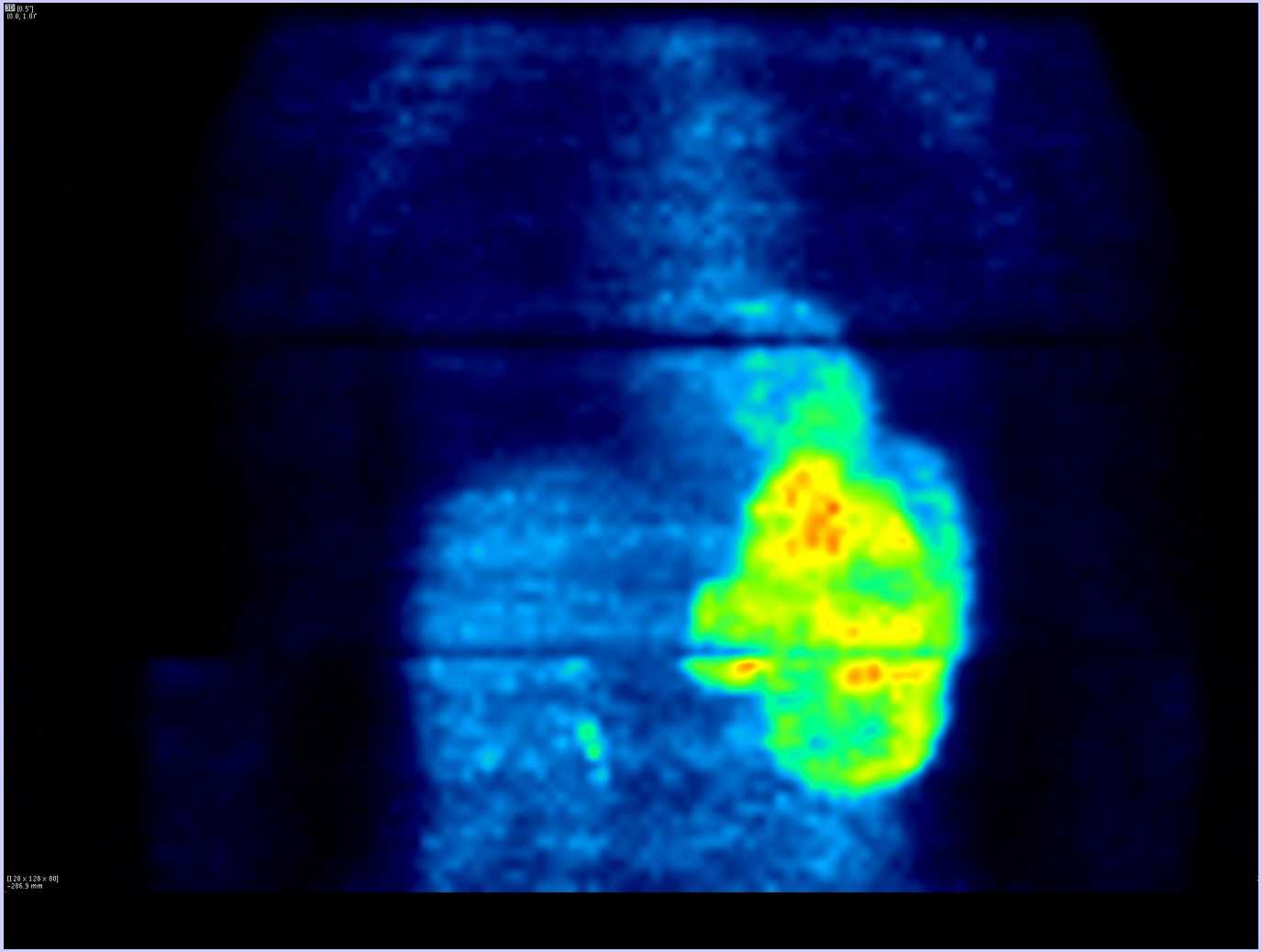
Multiviscerale Resektion notwendig : Magen, Milz+ Zwerchfell

Geplant : totale Gastrektomie, Pankreas, Splenektomie + Zwerchfellresektion

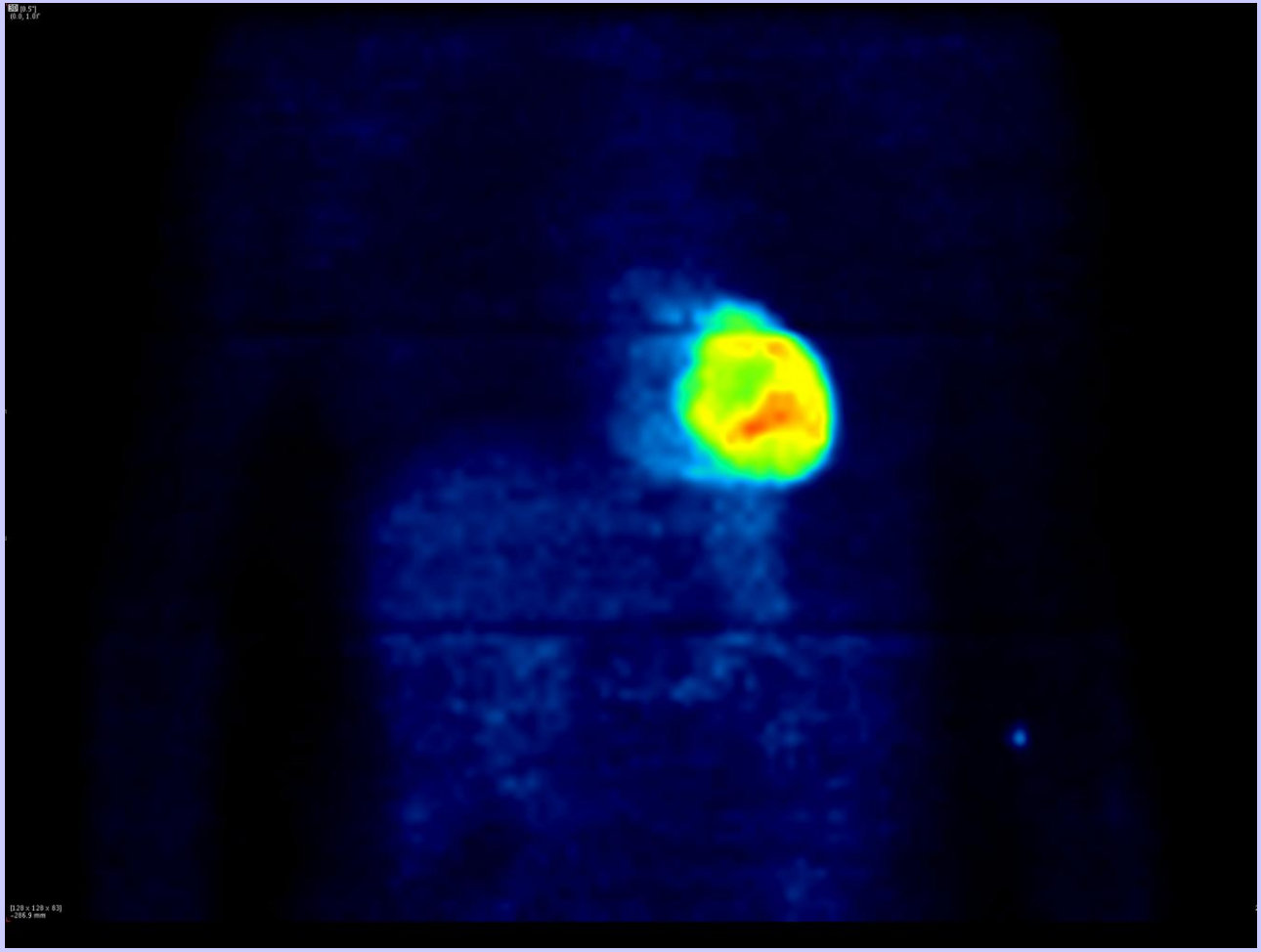


Nach 6 Monaten imatinib 400 mg

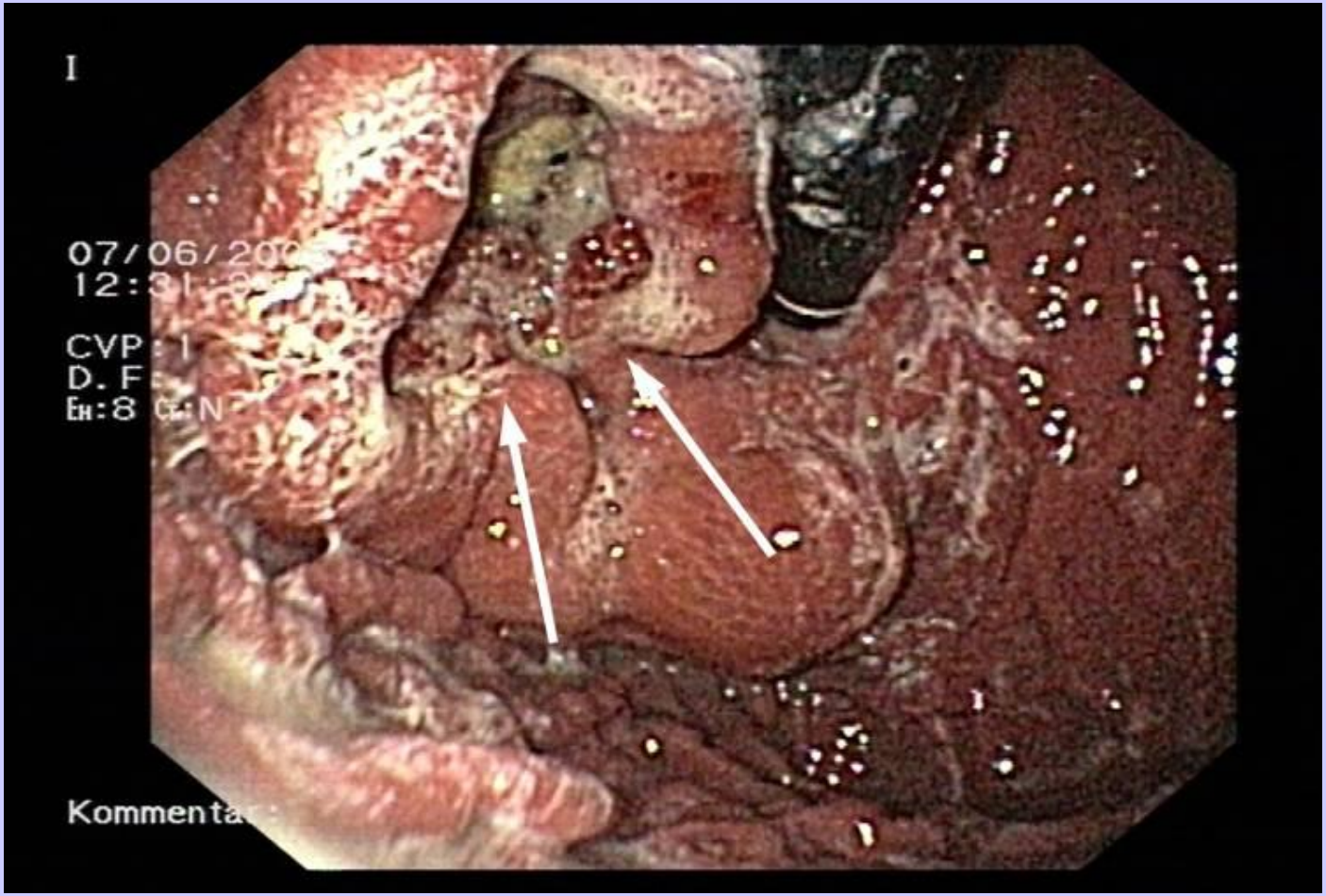
PET prior to therapy



PET after imatinib



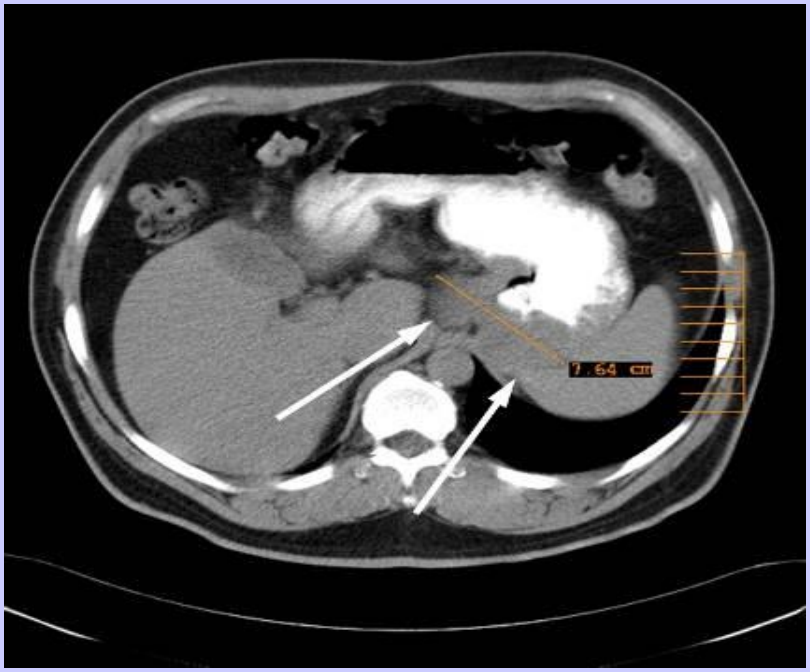
GIST des AEG

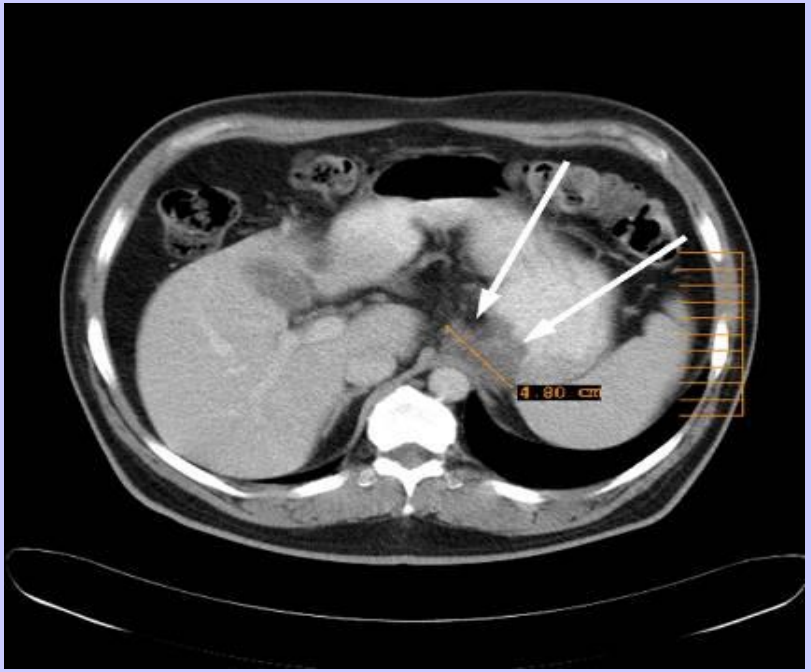


Staiger World J Surg Oncol 2008; 4: 37

GIST des AEG

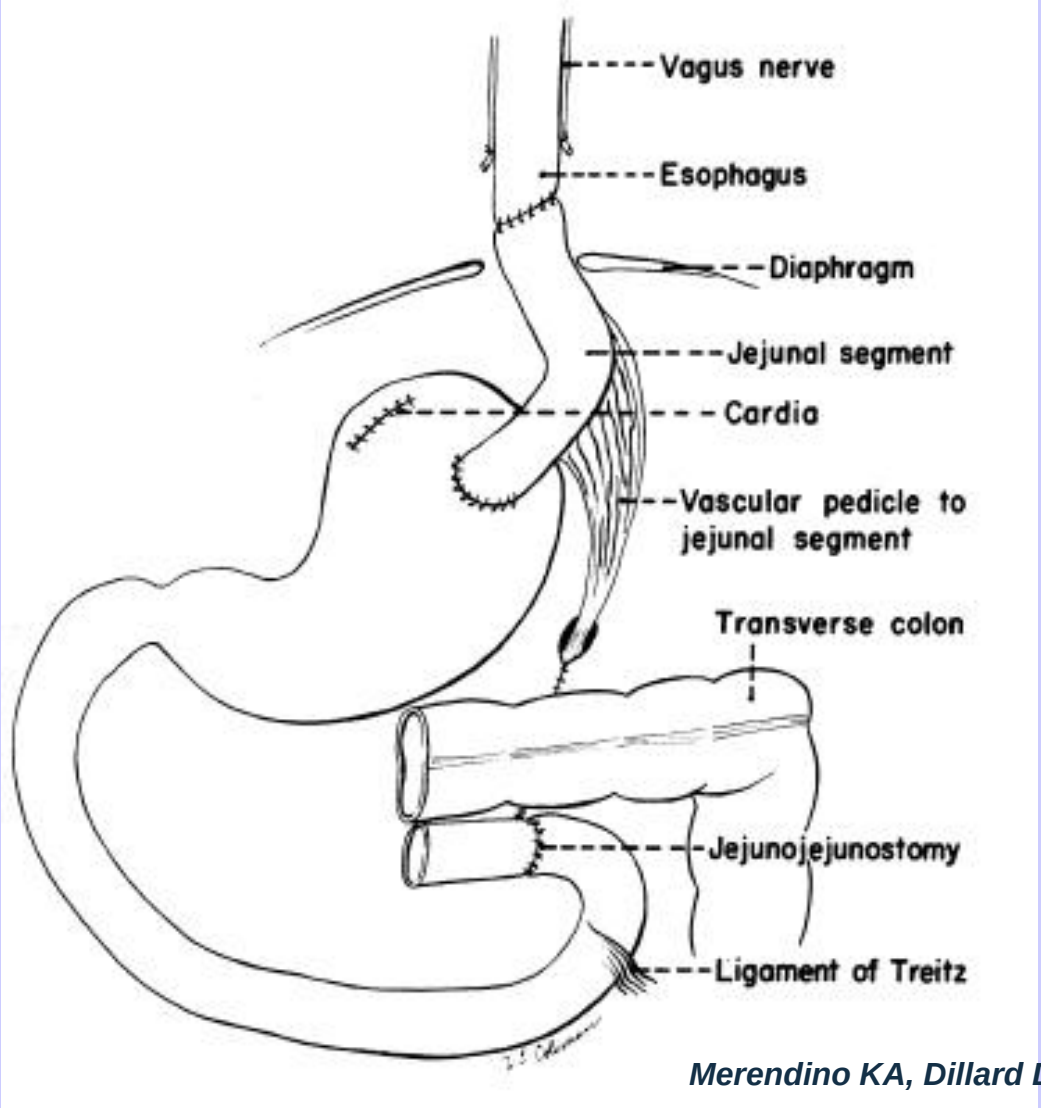
after 6 months imatinib





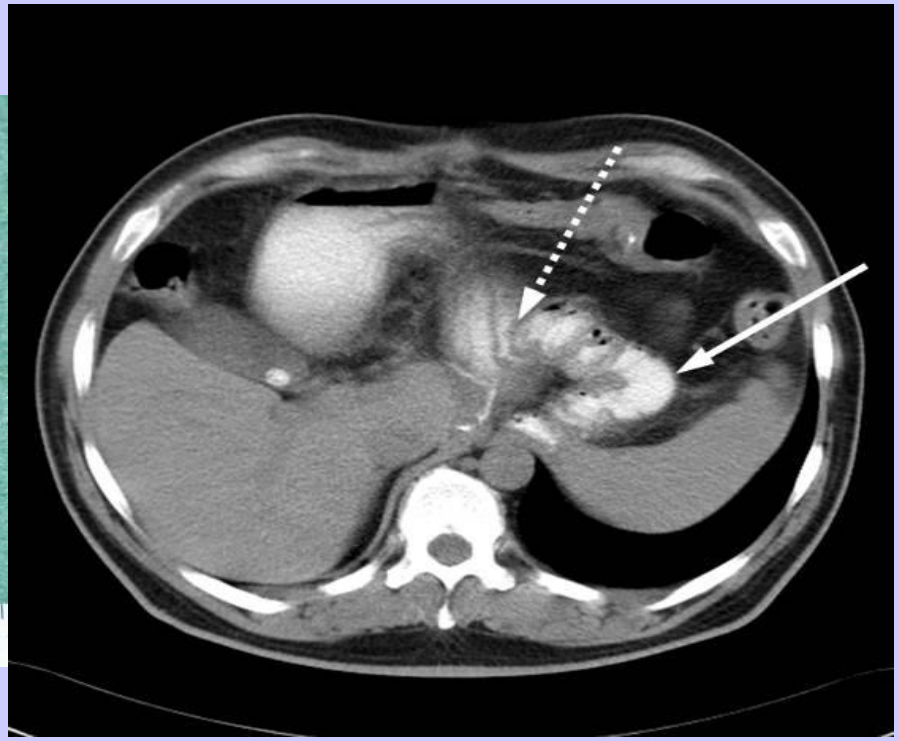
Staiger World J Surg Oncol 2008; 4: 37

Merendin - Rekonstruction



Merendino KA, Dillard DH. Ann Surg. 1955; 142: 486-506

Specimen and postop. situation



Staiger World J Surg Oncol 2008; 4: 37

Neoadjuvant studies of imatinib

Trial	N	Phase	Regimen	Setting	Primary End Point	Status[a]
RTOG S-0132[1]	63	2	Imatinib 600 mg/d	Neoadjuvant/ adjuvant	PFS	Enrollment completed
MDACC ID03-0023[2]	48[b]	2	Imatinib 300 mg twice daily	Neoadjuvant/a djuvant	DFS	Recruiting
Apollon CSTI571 BDE43	46	2	Imatinib 400 mg/d	Neoadjuvant	DFS	Recruiting

DFS, disease-free survival; EORTC, European Organisation for Research and Treatment of Cancer; GSS, GIST-specific survival; MDACC, M.D. Anderson Cancer Center; OS, overall survival; RFS, recurrence-free survival; RTOG, Radiation Therapy Oncology Group; SSG, Scandinavian Sarcoma Group.

1. ClinicalTrials.gov. Accessed July 31, 2008.

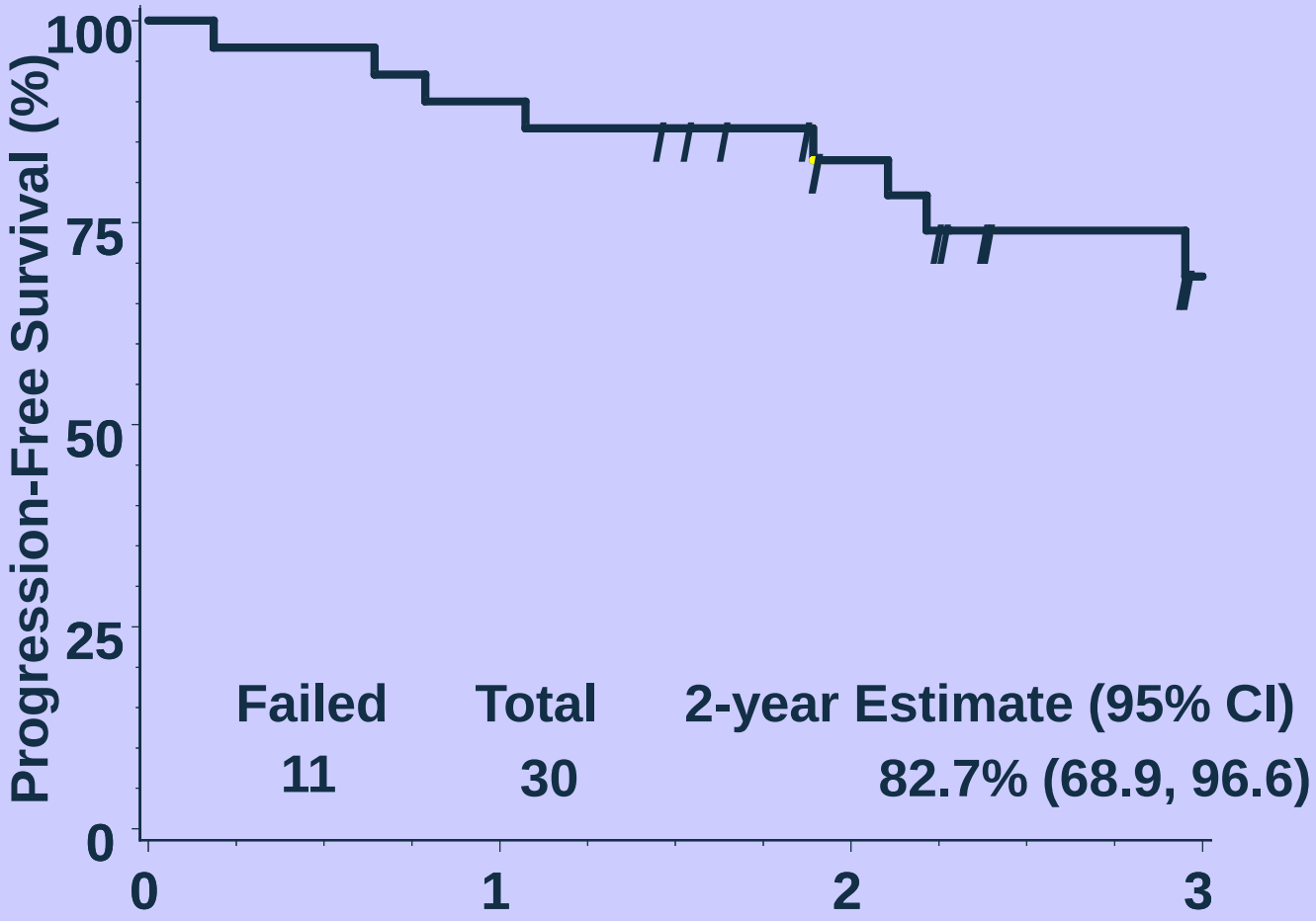
2. Trent J. http://utm-ext01a.mdacc.tmc.edu/dept/prot/clinicaltrialswp.nsf/index/id03-0023.

RTOG 0132: neoadjuvant imatinib for primary GIST

- 30 patients
- Median tumor size 9 cm (5-25 cm)
- GE junction, duodenal, rectal
- R0 resection 77%
- Median follow-up 3 years

Eisenberg et al. J Surg Oncol. 2009; 99(1):42-7.

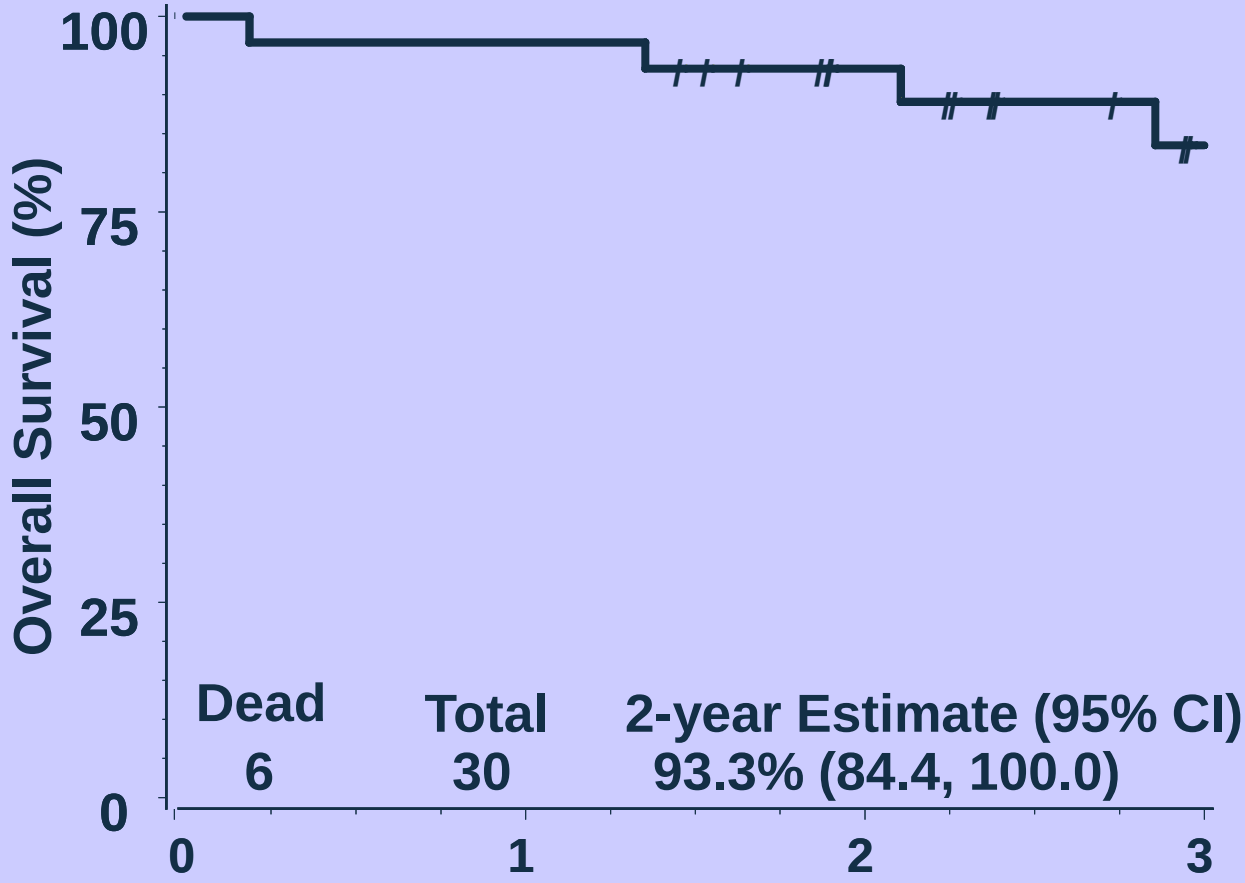
RTOG 0132: PFS



Patients at Risk				
Primary	30	27	19	10

Eisenberg, J Surg Oncol. 2009; 99(1):42-7

RTOG 0132: Overall Survival, Primary GIST

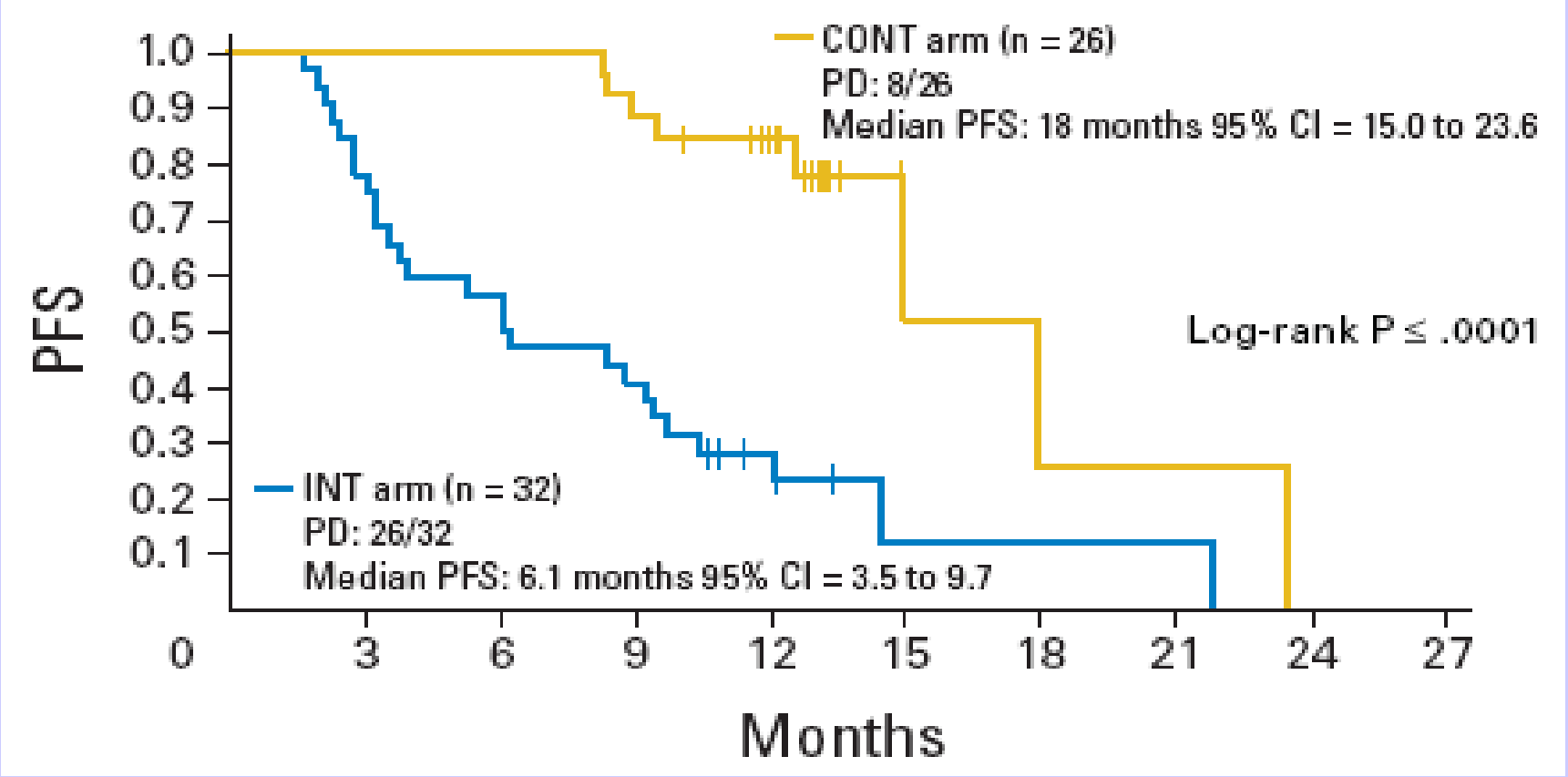


Patients at Risk				
Primary	30	29	22	13

Eisenberg et al. J Surg Oncol. 2009; 99(1):42-7.

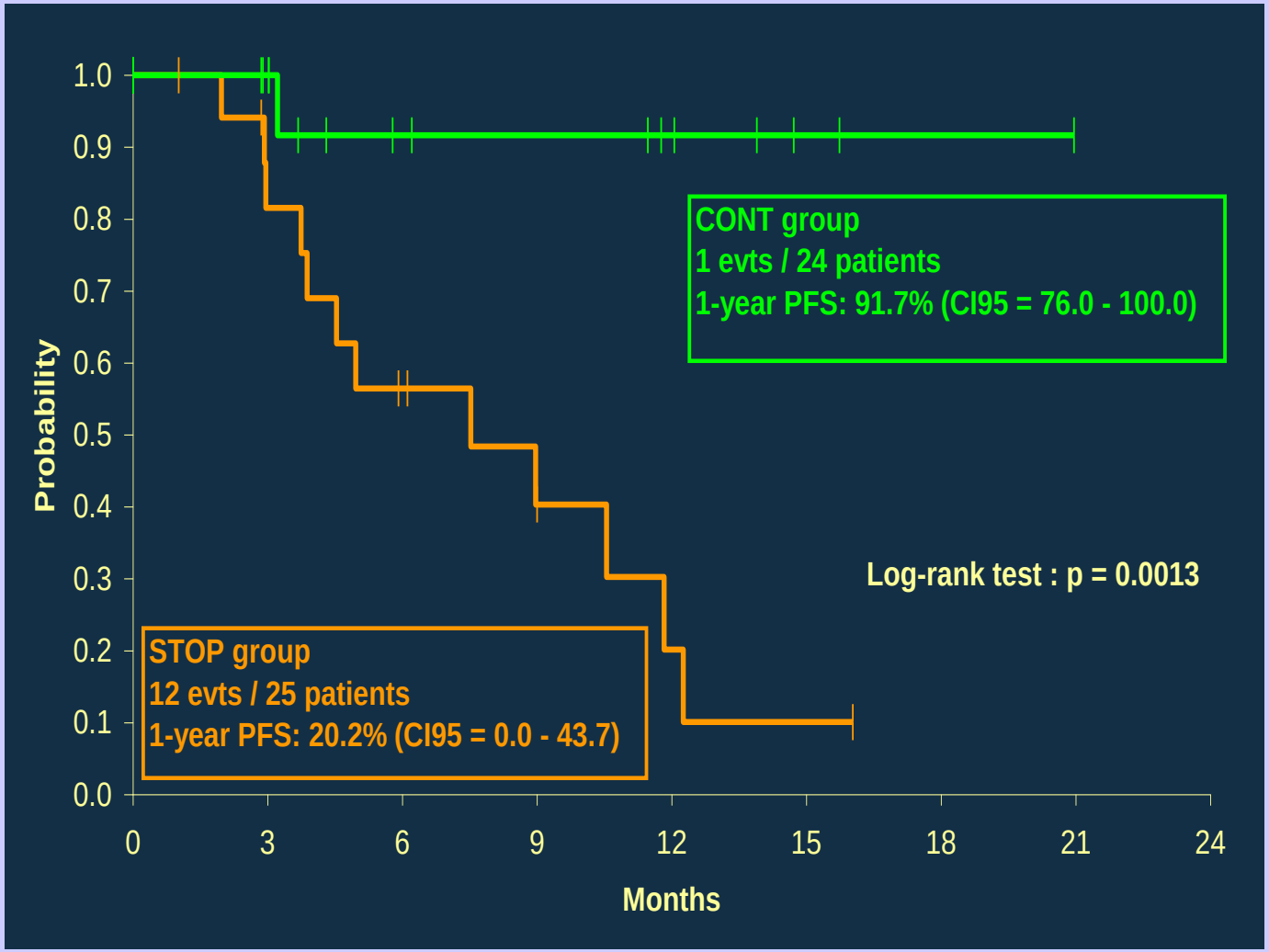
Systemische Therapie bei M1

Therapiestop nach 1 Jahr



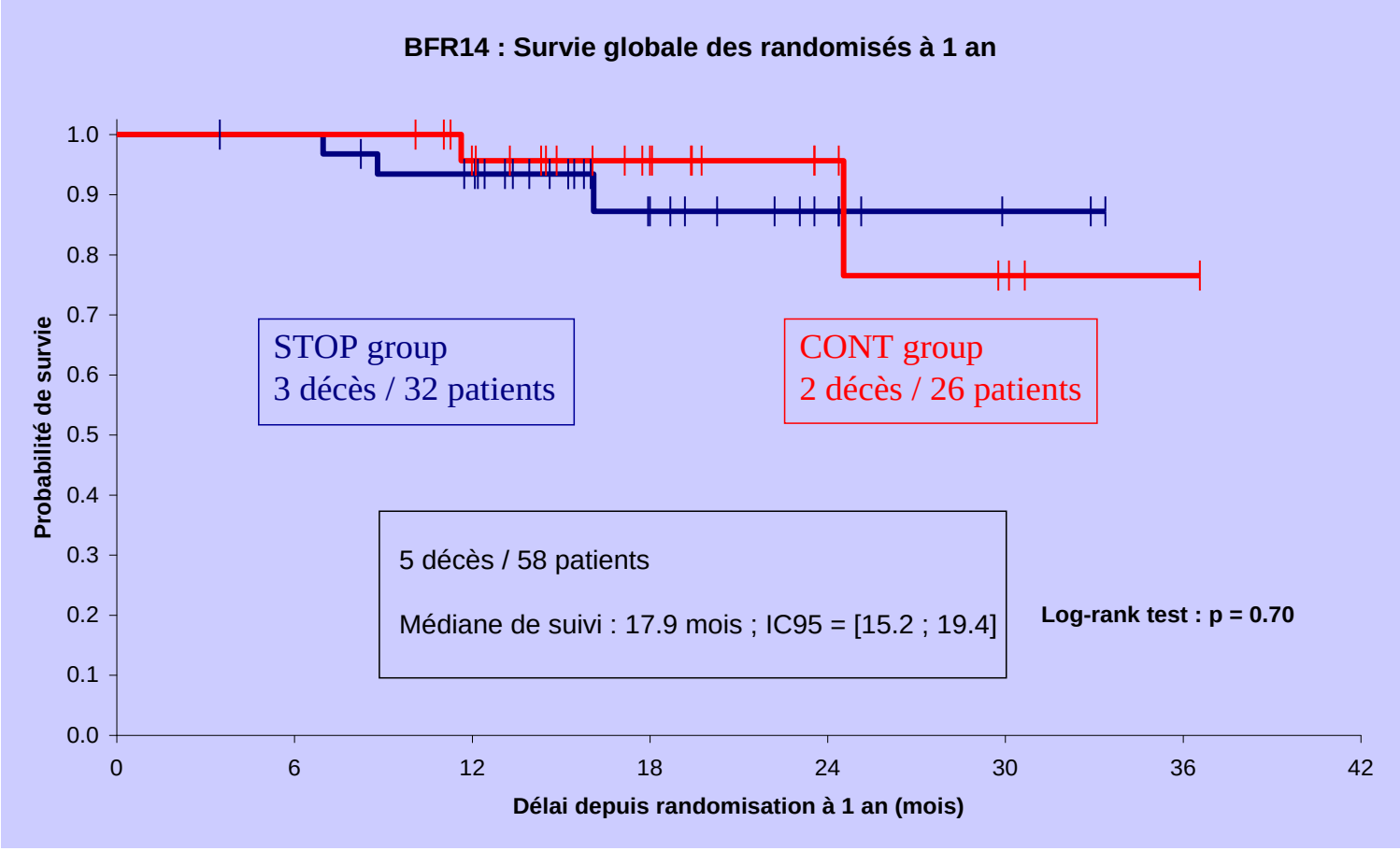
Blay JY et al. J Clin Oncol. 2007;25(9):1107-1113.

Therapiestop nach 3 Jahren

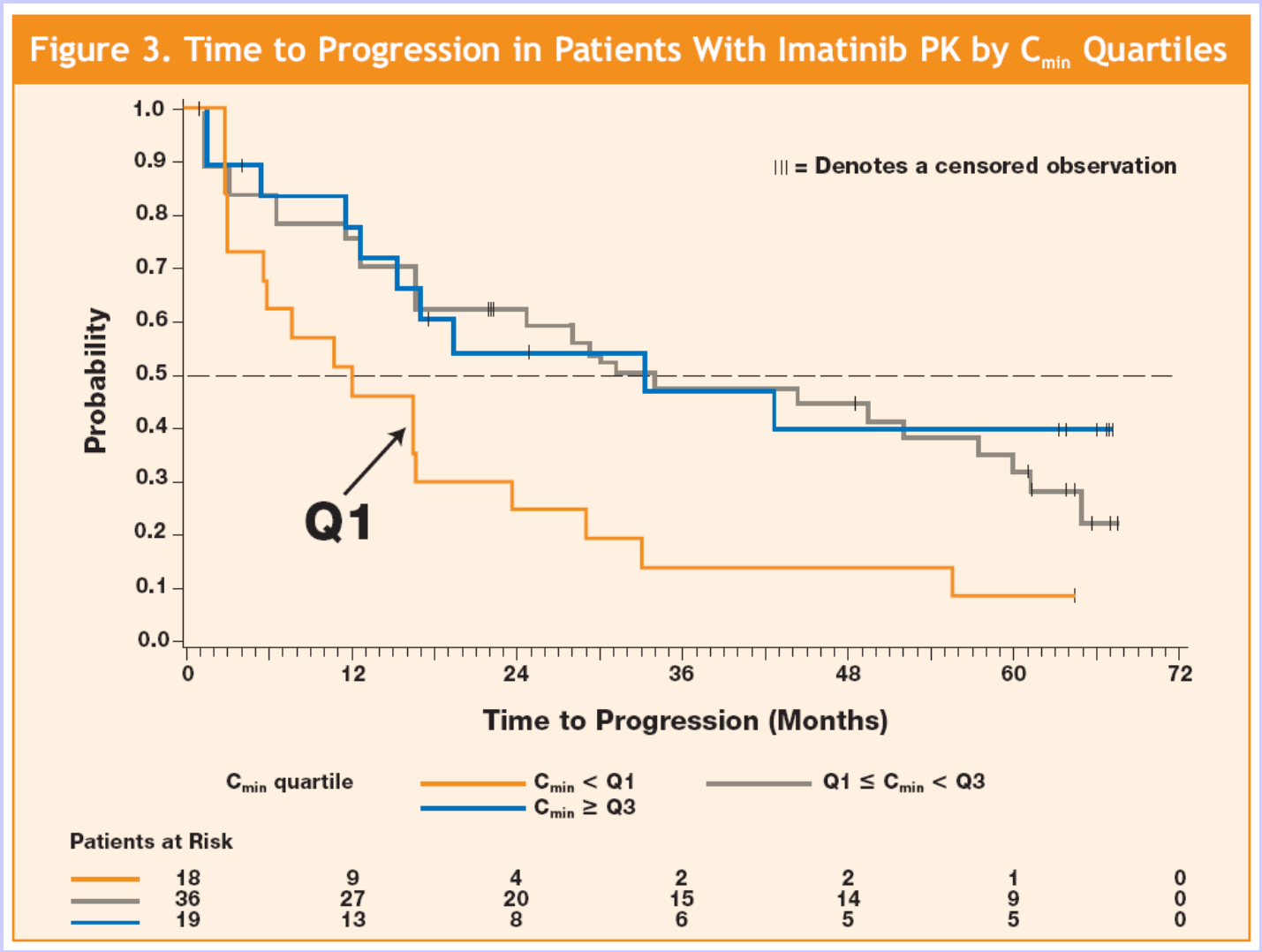


Le Cesne et al., ASCO 2007, # 10005

No survival disadvantage after stop



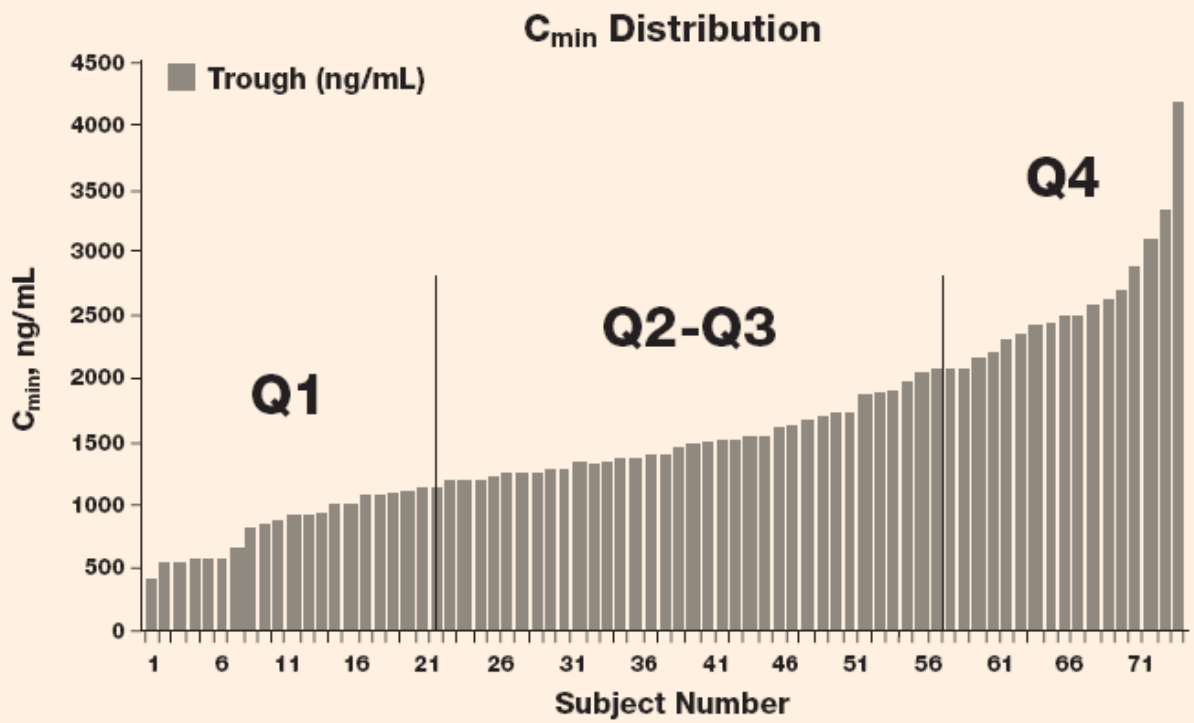
Imatinib-Plasmaspiegel korrelieren mit dem klinischen Benefit von Patienten mit inoperablem/metastasiertem GIST



Demetri et al., ASCO-GI 2008, # 3

Imatinib-Plasmaspiegel korrelieren mit dem klinischen Benefit von Patienten mit inoperablem/metastasiertem GIST

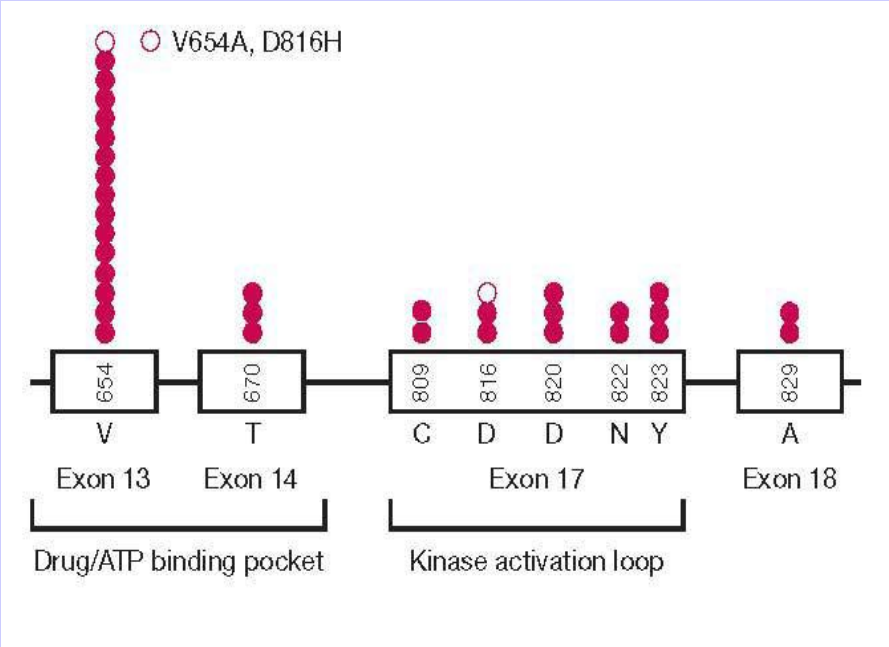
Figure 2. Imatinib C_{min} (Trough) Distribution: 400 mg and 600 mg Data Combined

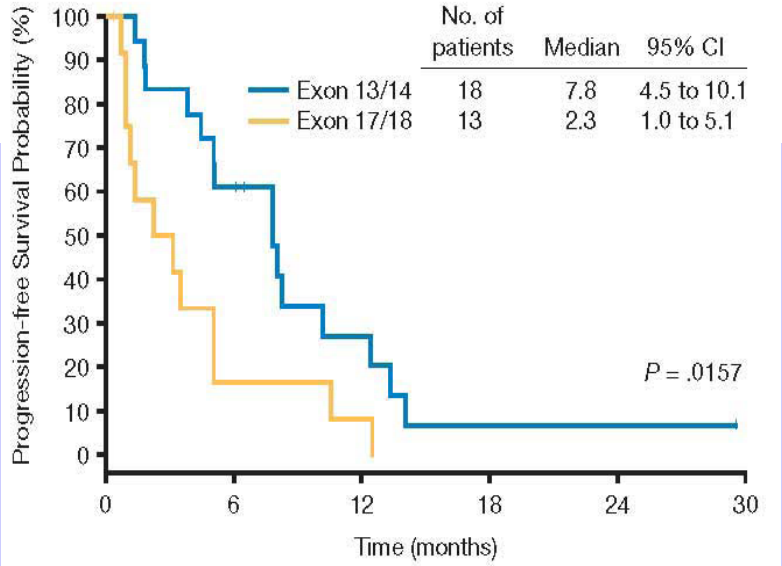


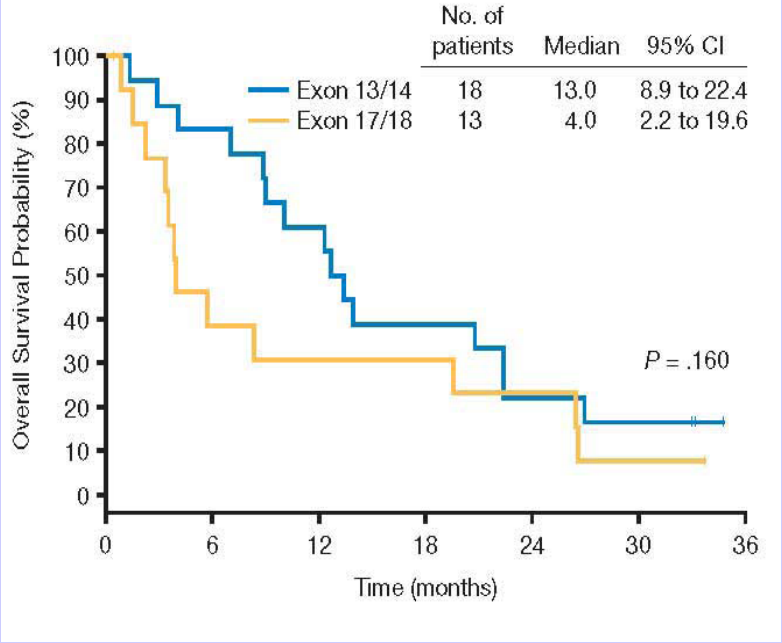
	Q1	Q2-3	Q4
400 mg (n = 34)	11	16	7
600 mg (n = 39)	7	20	12

Overall mean, 1570 ± 722 ng/mL. Range [410, 4180]. N = 73.

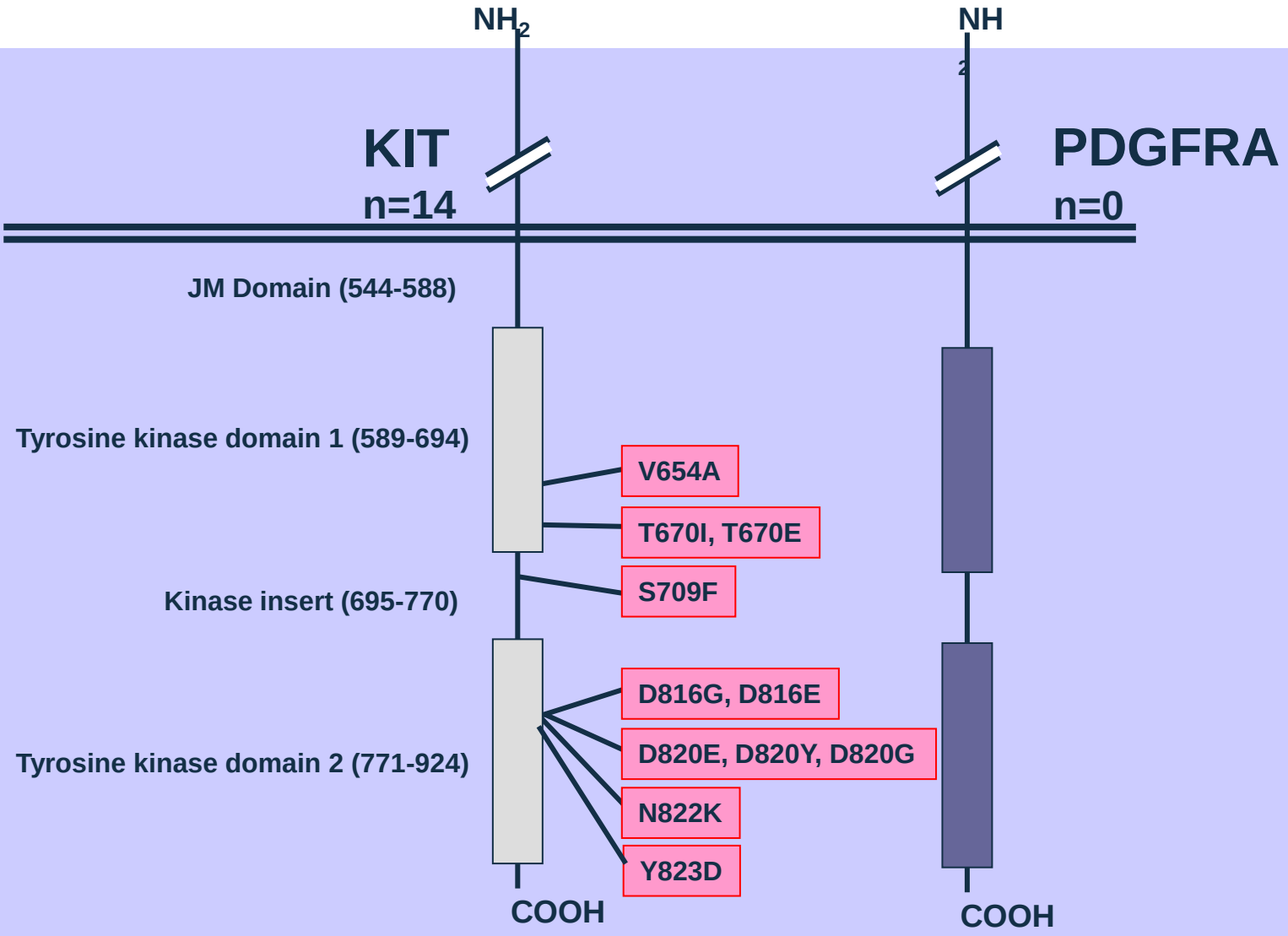
Ungünstige Konstellation







2ndary *KIT* mutations in GISTs under treatment with Glivec



Clin Cancer Res. 2006 15;12: 1743

Relevanz der Mutationsanalyse bei GIST

- Diagnose von schwach CD117-positiven oder CD117-negativen GIST
- prognostische Relevanz – spezifische Mutationstypen haben eine
  - bessere Prognose (PDGFRα Exon 18, Duplikation in KIT Exon 11) oder
  - schlechtere Prognose (Deletion in KIT Exon 11, Duplikation in KIT Exon 9)
- Prädiktion des Therapieansprechens: Exon 11 > Exon 9 > Exon 18 (Punktmutation)/Wildtyp
- Optimierung der Imatinibdosis

Schlussfolgerung:

- Analyse aller klinisch relevanten GISTs bei Primärdiagnose

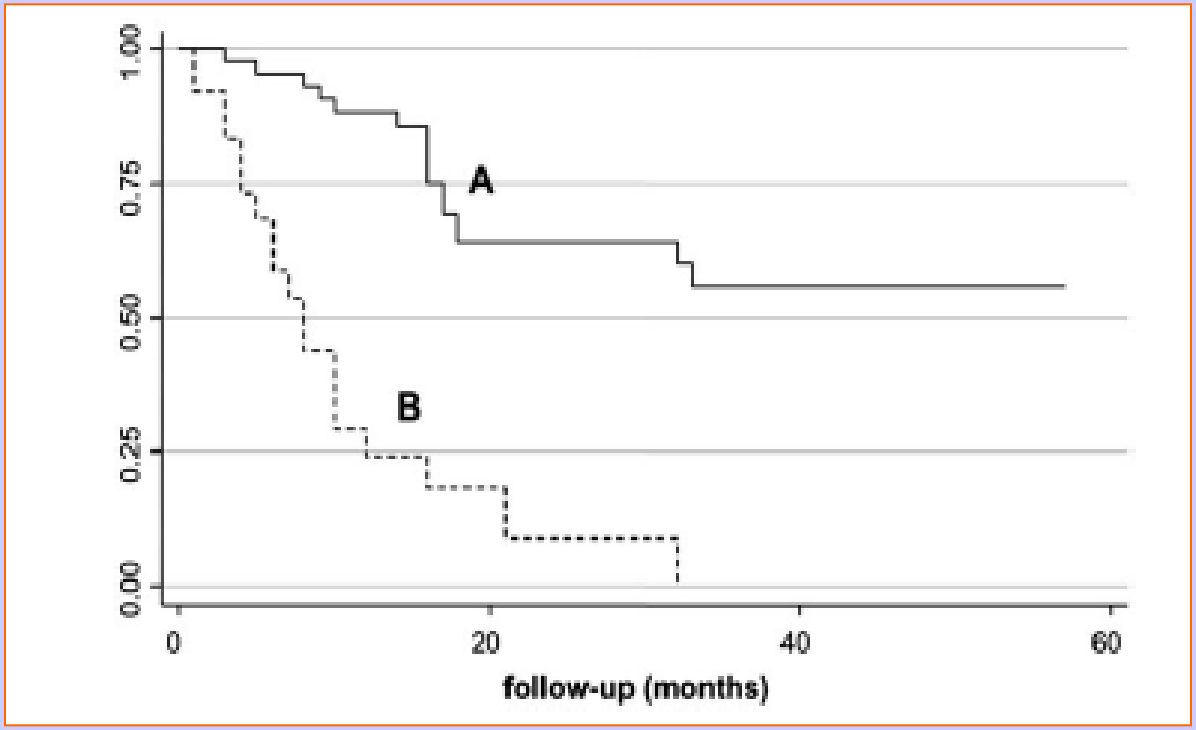
universitätsklinikumbonn

KO.SAR. Kompetenznetz SARKOME

Residualtumor (A) vs. Resektion bei Progress

80 patients Mannheim/Milano

Progression-free survival



Mussi C et al., Annals of Oncol 2009; July 23rd, 2009 ahead of print

A phase III randomized study evaluating surgery of residual disease in patients with metastatic gastro-intestinal stromal tumor responding to Imatinib mesylate.

Metastatic GIST in response on IM

Imatinib

Imatinib + **surgery** at best response (within 1 yr)

Follow for PFS & OS

Zusammenfassung

- Einhaltung chirurgischer Standards – Krebsoperation !
- Indikation zur adjuvanten Therapie :
  signifikantes Rezidivrisiko, Ruptur
- Multiviscerale Resektion von Primärtumoren ist nicht länger ‚Standard of care‘
- Mutationsanalytik für Patienten mit metastâsiertem GIST und ‚atypische‘ GIST für die adjuvante Therapie !
- Plasmaspiegel bei Patienten mit diskrepantem Ansprechen im Vgl. zur Mutationsanalytik indiziert.
- Randomisierte Studie zum Stellenwert der Operation bei Respondern in der M1 Situation