Contemporary approaches to gastrointestinal stromal tumor: surgical considerations

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Greetings from
COLUMBUS
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The Ohio State University Health Care System

James Cancer Hospital
University Hospital
Ross Heart Hospital
University East Hospital
OSU Eye and Ear Institute
OSU Surgicenter
Brain and Spine Institute

320 faculty surgeons
>41,000 operations annually

To be discussed:

General considerations

Use of neoadjuvant therapies in primary GIST

Specific surgical issues

Use of adjuvant therapies in primary GIST

Treatment of recurrent/metastatic GIST

General considerations

~ 1-2% of all GI malignancies:

Stomach	50-70%
Small intestine	25-35%
Colo-rectum	5-10%
Esophagus	<5%

Those who do not know history are doomed to repeat it!

Prognostic Factors Influencing Survival in Gastrointestinal Leiomyosarcomas

Implications for Surgical Management and Staging

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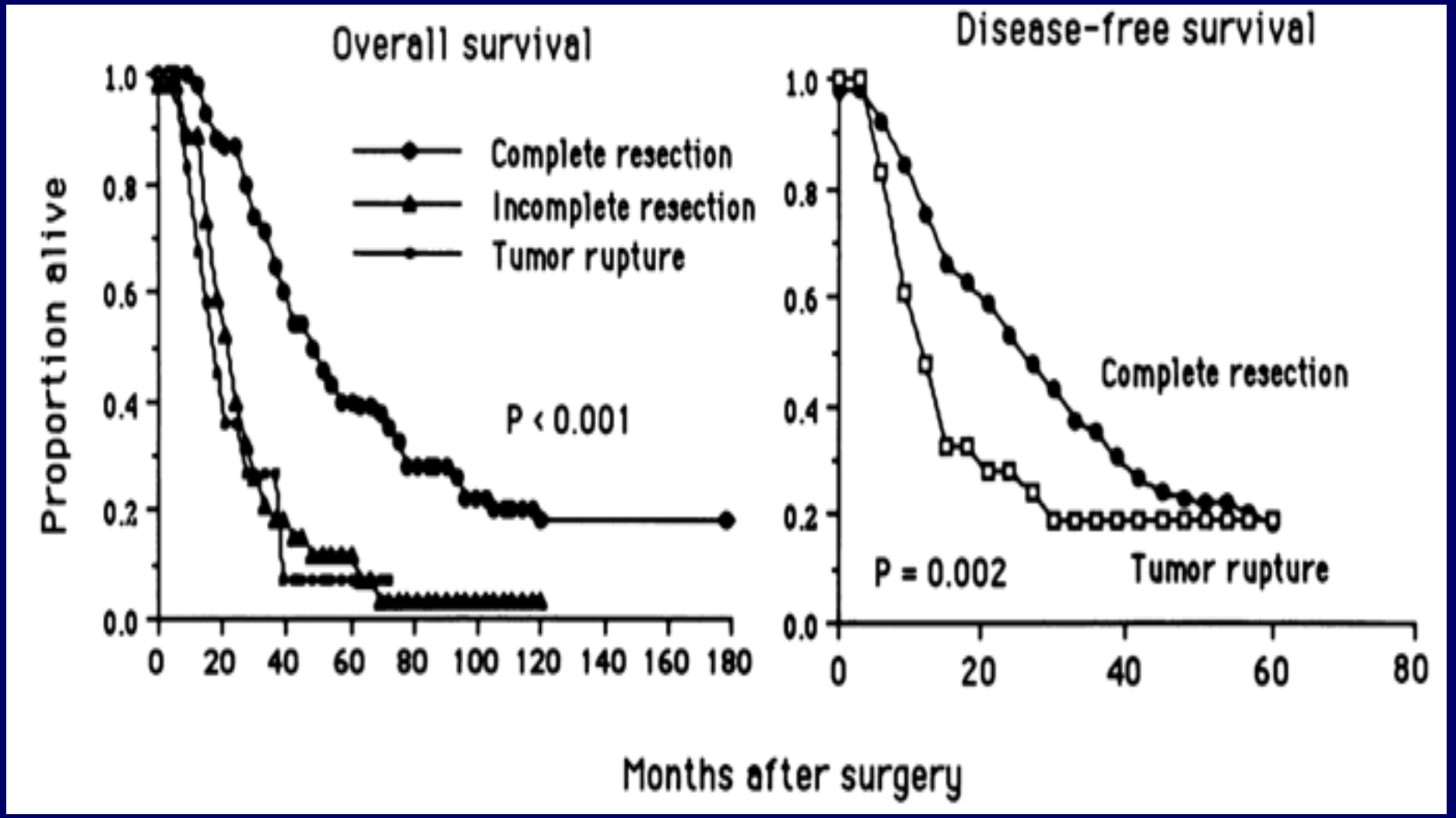
Ann Surg 215:68-77; 1991

OS/DFS ~ 20% at five years; circa 1991



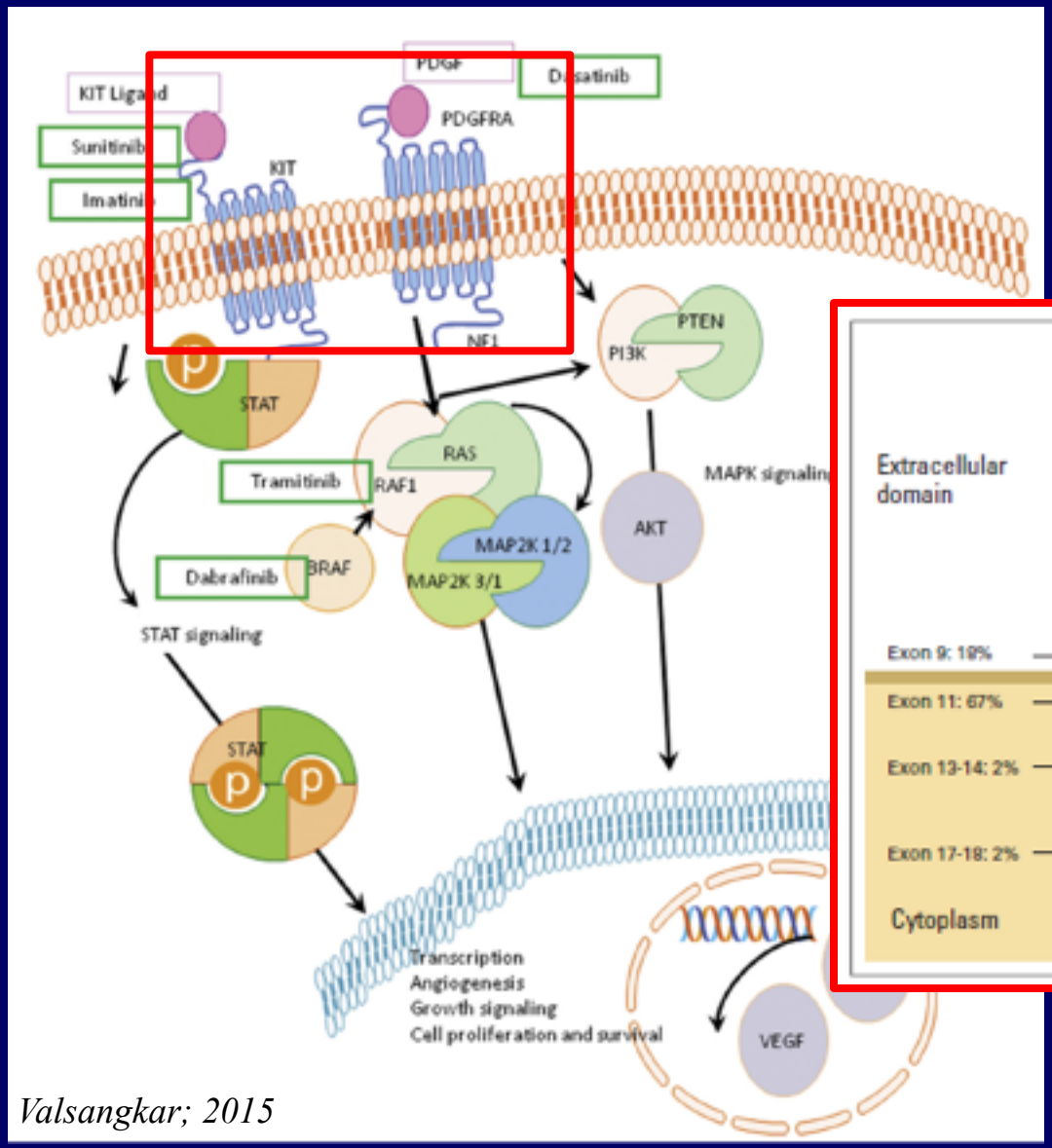
Ng, Pollock, et al. Ann Surg; 1991

Key GIST landmarks

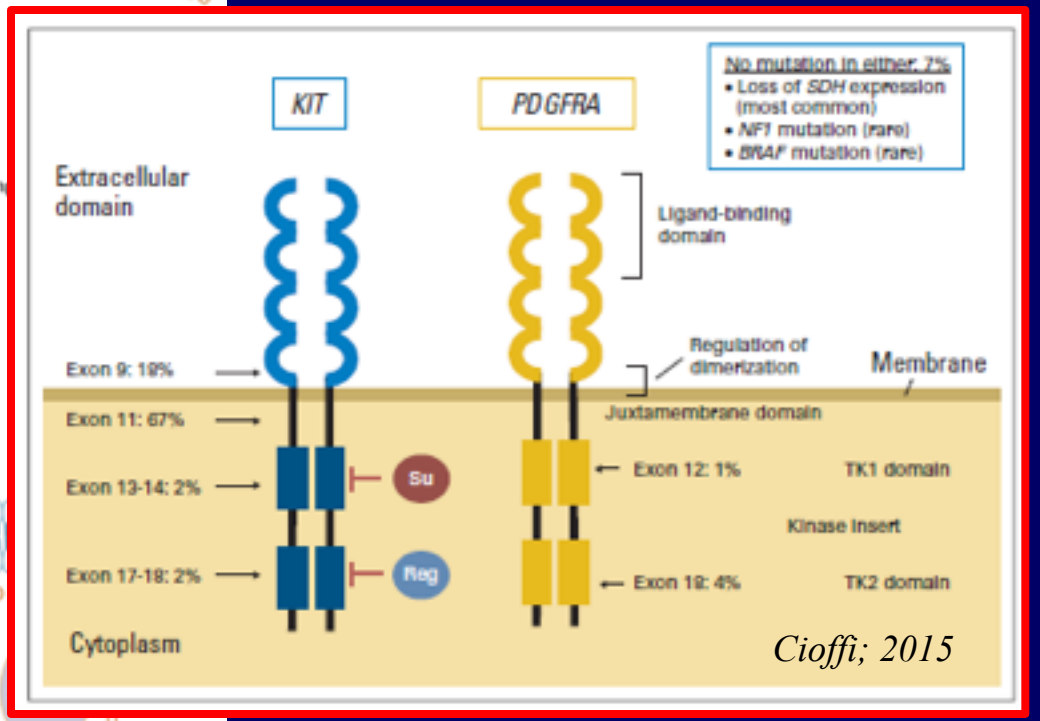
1998 Hirota identifies kit mutations in GIST and that GIST arises from interstitial cells of Cajal

2000 Joensuu treats first patient with imatinib

Underlying molecular considerations

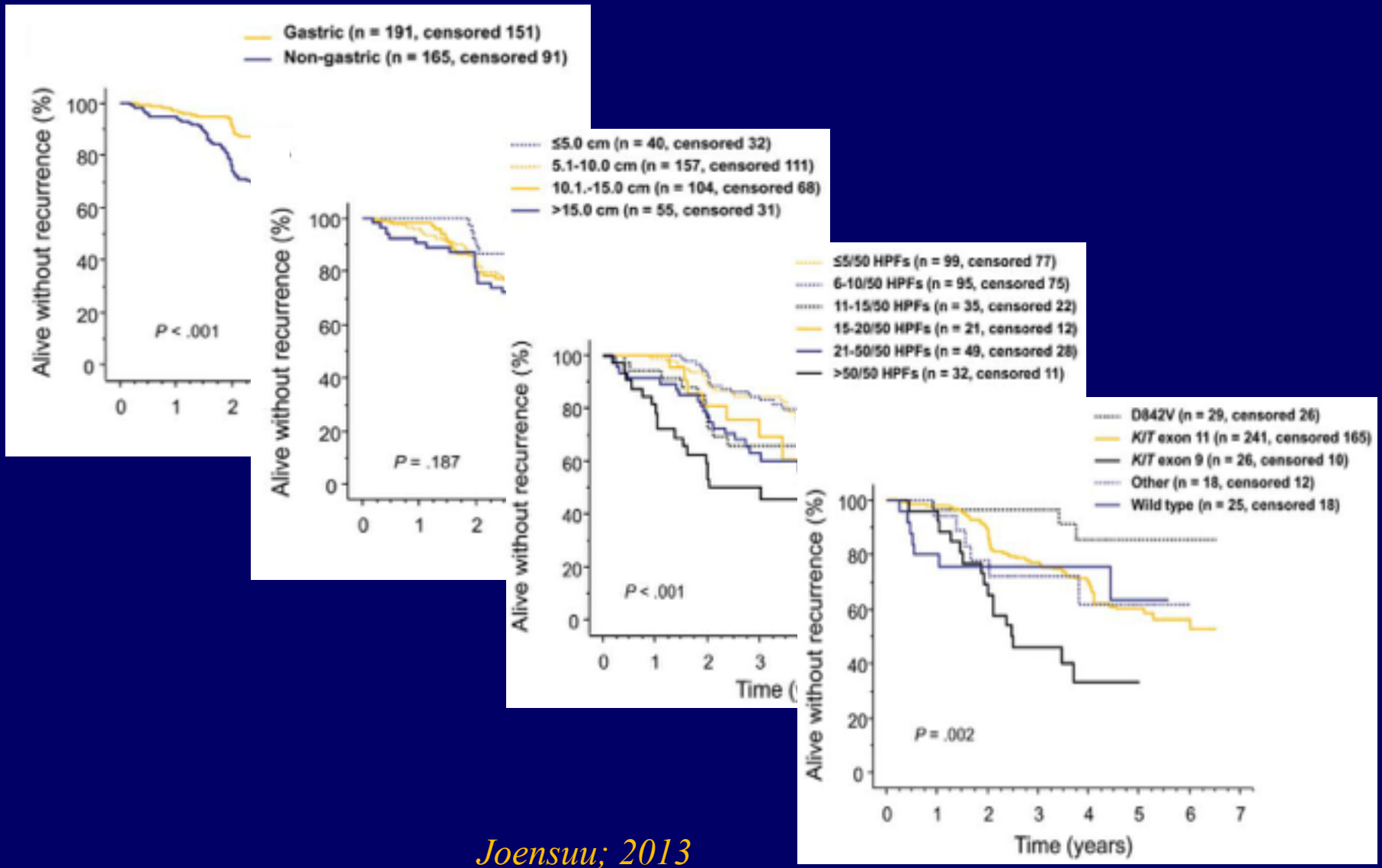


Valsangkar; 2015



Cioffi; 2015

GIST prognostic factors



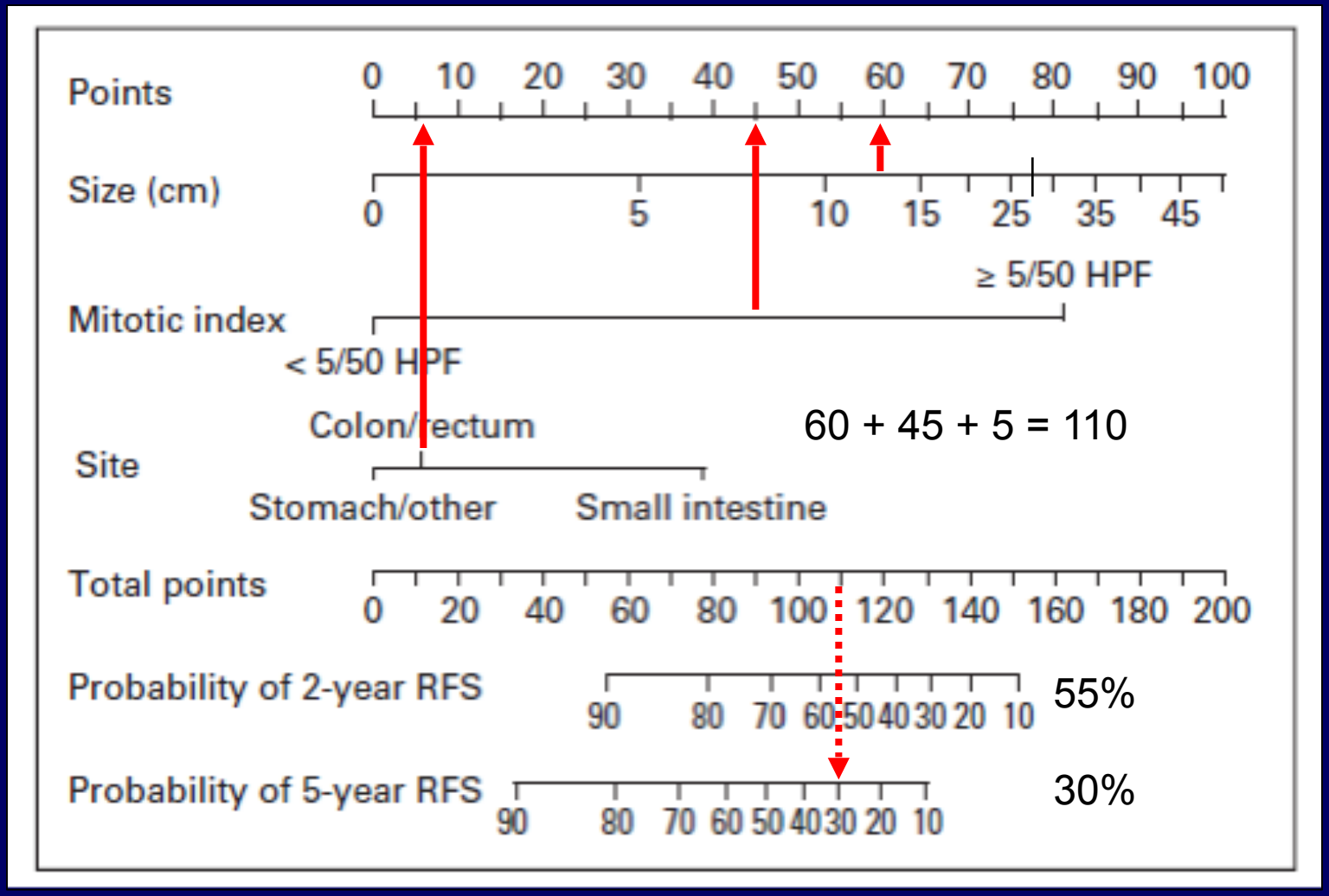
Joensuu; 2013

Risk stratification of primary GIST by mitotic index, size, and site

Tumor Parameters		Risk of Progressive Disease (%)			
Mitotic Index	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
< 5 per 50 hpf	< 2 cm	None (0%)	None (0%)	None (0%)	None (0%)
< 5 per 50 hpf	> 2 < 5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
< 5 per 50 hpf	> 5 < 10 cm	Low (3.6%)	Moderate (24%)	(Insuff. data)	(Insuff. data)
< 5 per 50 hpf	> 10 cm	Moderate (10%)	High (52%)	High (34%)	High (57%)
> 5 per 50 hpf	< 2 cm	None	High	(Insuff. data)	High (54%)
> 5 per 50 hpf	> 2 < 5 cm	Moderate (16%)	High (73%)	High (50%)	High (52%)
> 5 per 50 hpf	> 5 < 10 cm	High (55%)	High (85%)	(Insuff. data)	(Insuff. data)
> 5 per 50 hpf	> 10 cm	High (86%)	High (90%)	High (86%)	High (71%)

Demetri; 2007

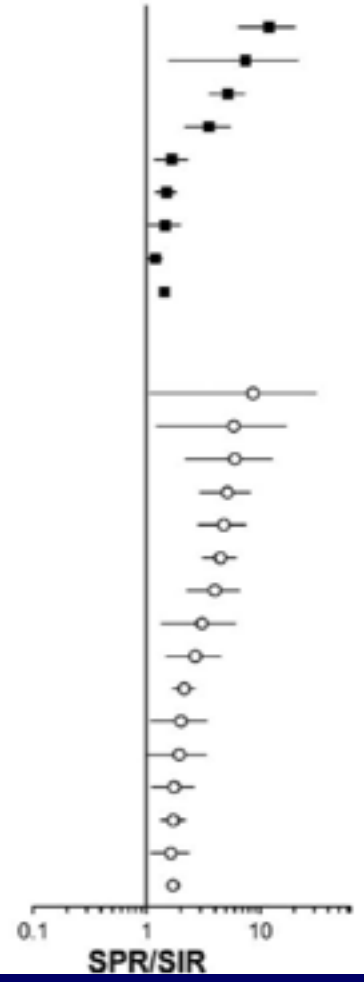
MSKCC nomogram for post-resection primary GIST RFS



Tap; 2014

Other malignancies are associated with GIST

Site	Observed	Expected	SPR/SIR (95% CI)
Cancers before GIST			
Esophageal adenocarcinoma	13	1.1	12.0 (6.40-20.6)
Bladder adenocarcinoma	3	0.4	7.51 (1.55-22.0)
Sarcoma	32	6.1	5.24 (3.58-7.39)
Neuroendocrine	20	5.6	3.56 (2.17-5.50)
Non-Hodgkin lymphoma	34	20.2	1.69 (1.17-2.35)
Colorectal adenocarcinoma	81	53.7	1.51 (1.20-1.88)
Melanoma	38	25.9	1.46 (1.04-2.01)
Prostate adenocarcinoma	184	153.9	1.20 (1.03-1.38)
All sites	*703*	*488*	*1.44 (1.33-1.55)*
Cancers after GIST			
Ovarian carcinoma	2	0.2	8.72 (1.06-31.5)
Small bowel adenocarcinoma	3	0.5	5.89 (1.22-17.2)
Other female GU*	6	1.0	6.00 (2.20-13.1)
Papillary thyroid cancer	16	3.1	5.16 (2.95-8.38)
Neuroendocrine	18	3.8	4.79 (2.84-7.56)
Renal cell carcinoma	35	7.8	4.46 (3.11-6.21)
Sarcoma	15	3.7	4.02 (2.25-6.64)
Hepatobiliary adenocarcinoma**	8	2.6	3.10 (1.34-6.10)
Gastric adenocarcinoma	14	5.2	2.70 (1.48-4.54)
Colorectal adenocarcinoma	71	32.8	2.16 (1.69-2.73)
Pancreatic adenocarcinoma	13	6.4	2.03 (1.08-3.47)
Uterine adenocarcinoma	12	6.1	1.96 (1.01-3.43)
Non-Hodgkin lymphoma	22	12.5	1.76 (1.11-2.67)
Non-small cell lung cancer	61	35.1	1.74 (1.33-2.23)
Bladder transitional cell carcinoma	27	16.4	1.65 (1.09-2.40)
All sites	*505*	*304*	*1.66 (1.52-1.81)*



Murphy; 2015

To be discussed:

General considerations

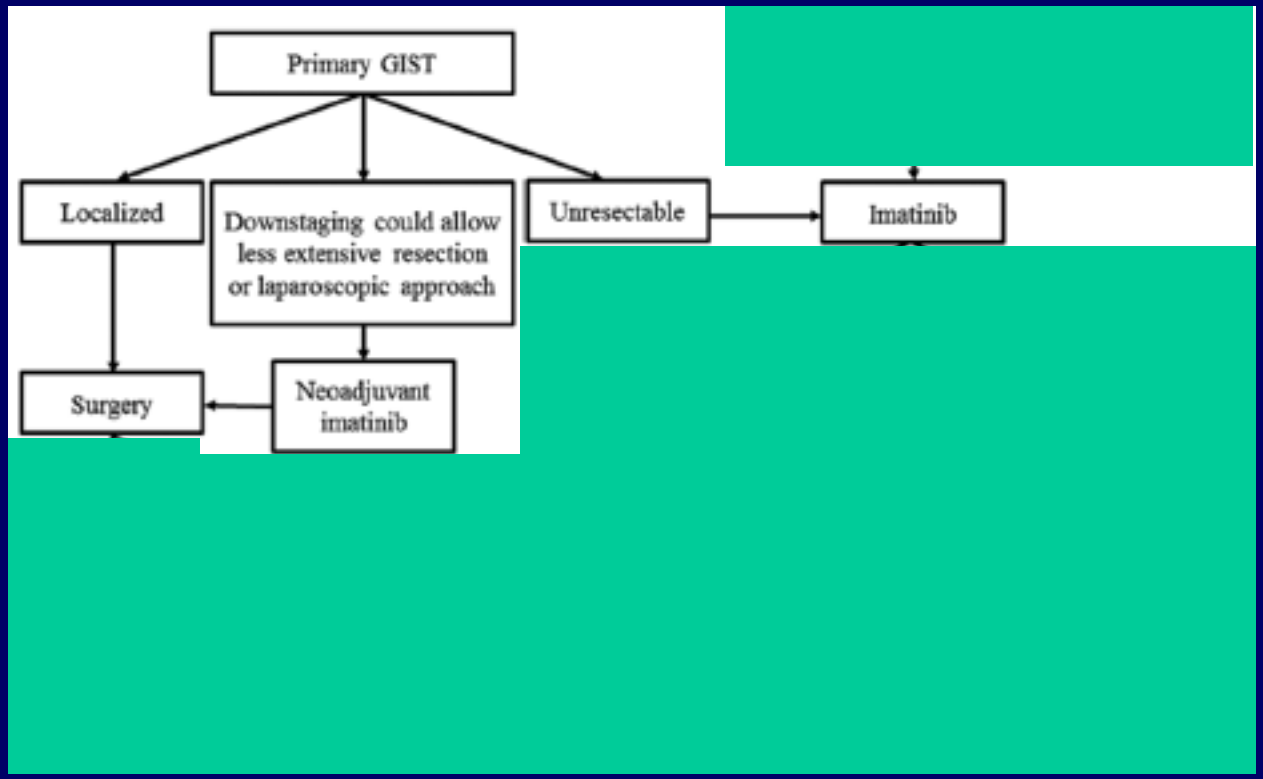
Use of neoadjuvant therapies in primary GIST

Specific surgical issues

Use of adjuvant therapies in primary GIST

Treatment of recurrent/metastatic GIST

Approach to primary GIST



Fairweather; 2015

Neoadjuvant approaches to primary GIST

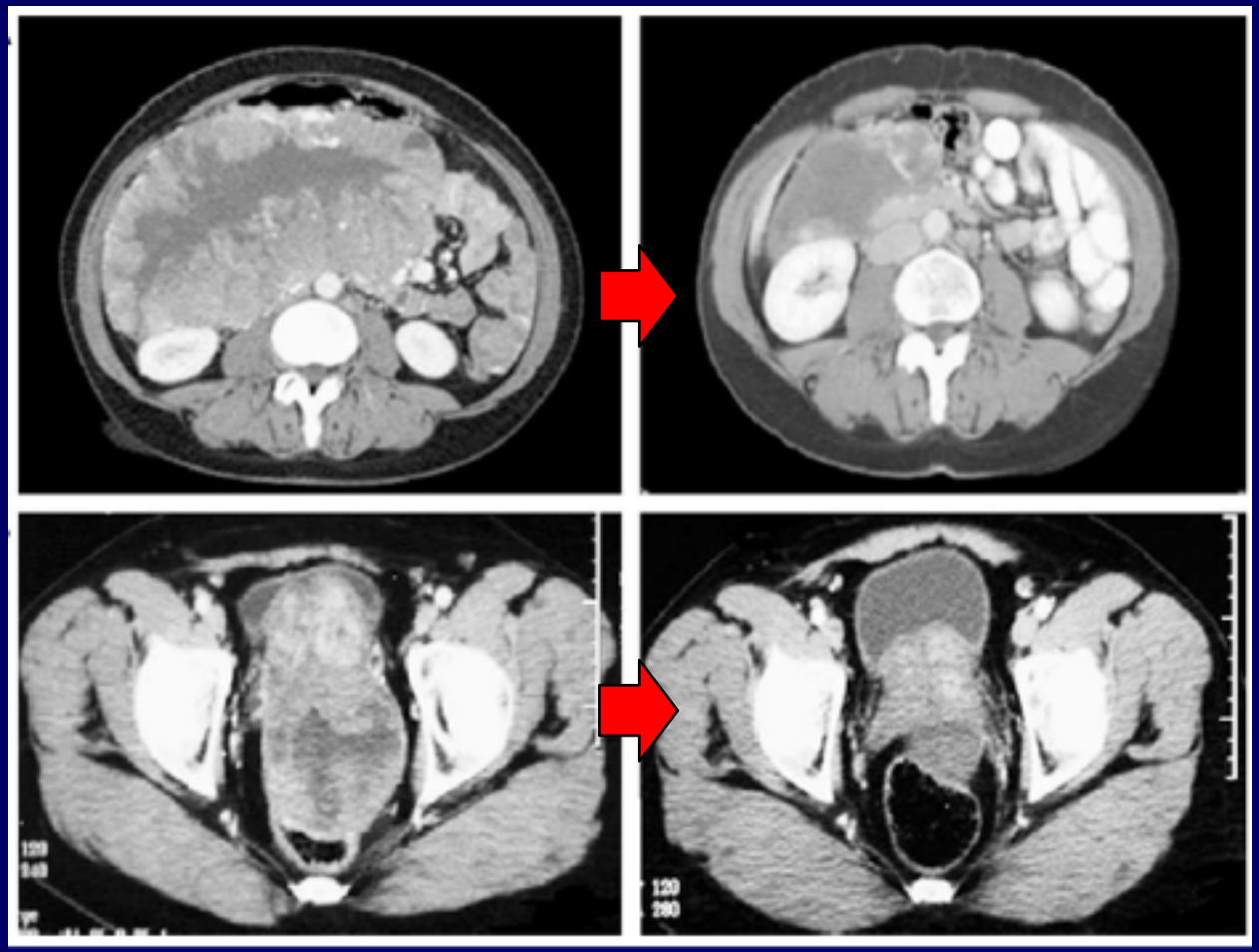
Three large phase II clinical trials: preoperative imatinib
significantly improves outcomes in patients with unfavorable GIST
(RTOG 0132; MD Anderson; German Apollon study)

No phase III trials with control arm evaluating neoadjuvant imatinib;
long term survival benefit of neoadjuvant approaches uncertain

Localized GIST: resect if can be done w/o extensive resection. Otherwise imatinib until no further cytoreduction seen on two successive scans or progression despite dose escalation

Best imatinib responses by 28 weeks; plateau at 34 weeks (Tirumani; 2014)

Neoadjuvant approaches to primary GIST



Baseline After neoadjuvant imatinib

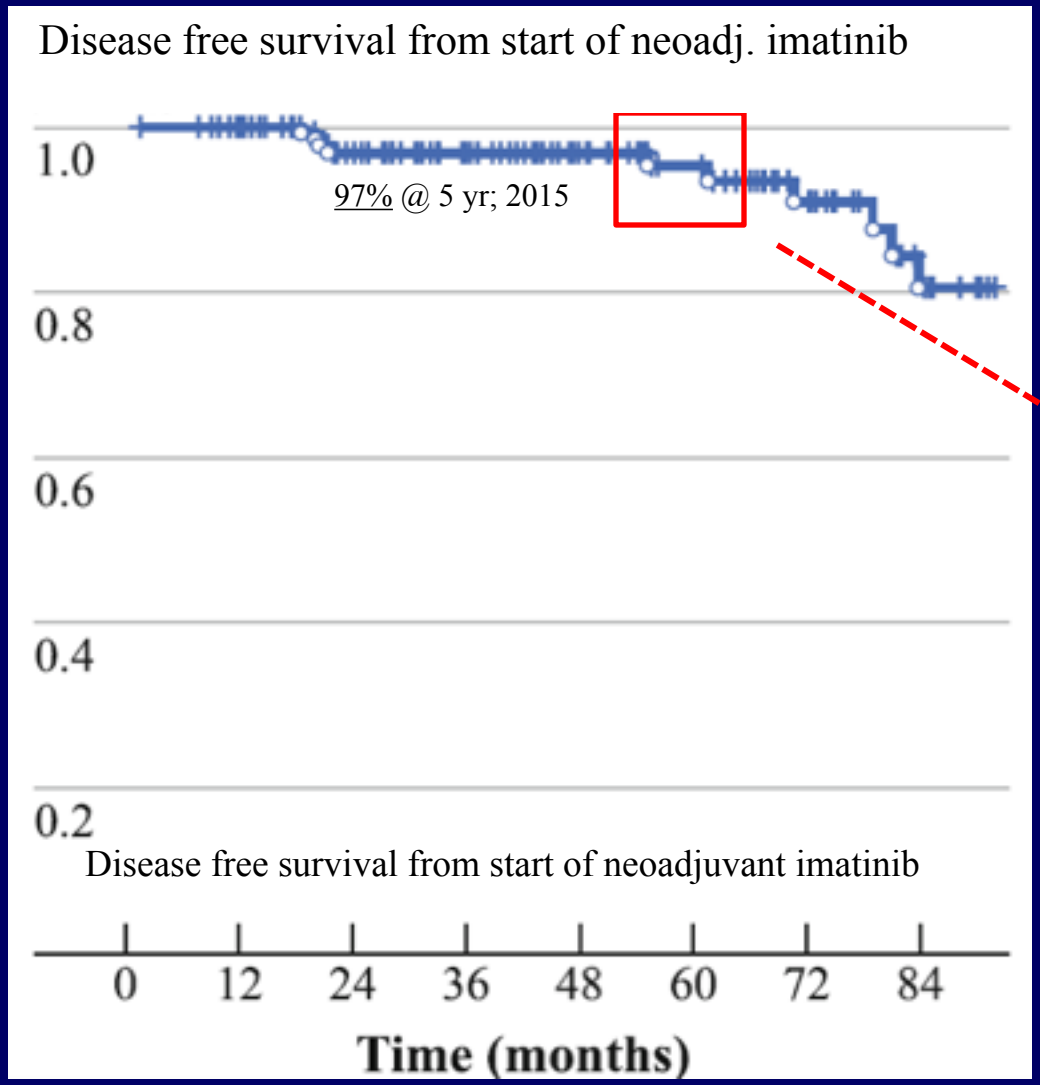
Fiore; 2009

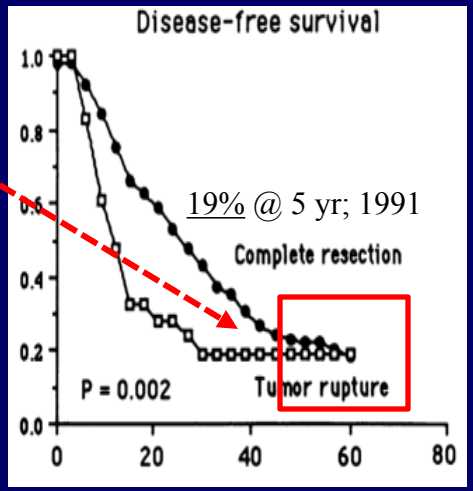
Relationship between kinase genotype, imatinib response, and outcome for advanced GIST patients

	B2222 Phase II	EORTC-Australasian Phase III	SWOG S0033 Phase III
Objective response (recist criteria)			
KIT exon 11	83%	70%	67%
KIT exon 9	48%	35%	40%
No mutation	0%	25%	39%
Progressive disease			
KIT exon 11	4.7%	3.2%	NR
KIT exon 9	17.4%	17.2%	NR
No mutation	55.6%	19.2%	NR

Demetri; 2007

Neoadjuvant approaches to primary GIST





Rutkowski; 2013

Surgical outcomes in neoadjuvant-treated GISTs

Incidence of R0/R1 resections in GIST patients treated neoadjuvantly :

- Stable disease: 78% achieved R0/R1 margins
- Limited disease progression: 25% achieved R0/R1 margins
- Generalized disease progression: 7% achieved R0/R1 margins

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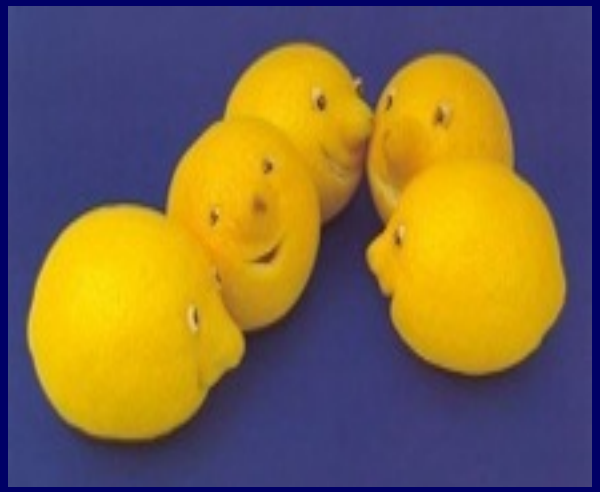
Surgical strategies for primary GIST management

Before surgery:

- ✓ Comprehensively understand the natural history of GIST
- ✓ Develop multi-disciplinary treatment plan prior to surgical intervention
- ✓ Thoroughly review plan, options, and strategy with patient and family
- ✓ Recruit other needed surgical specialists

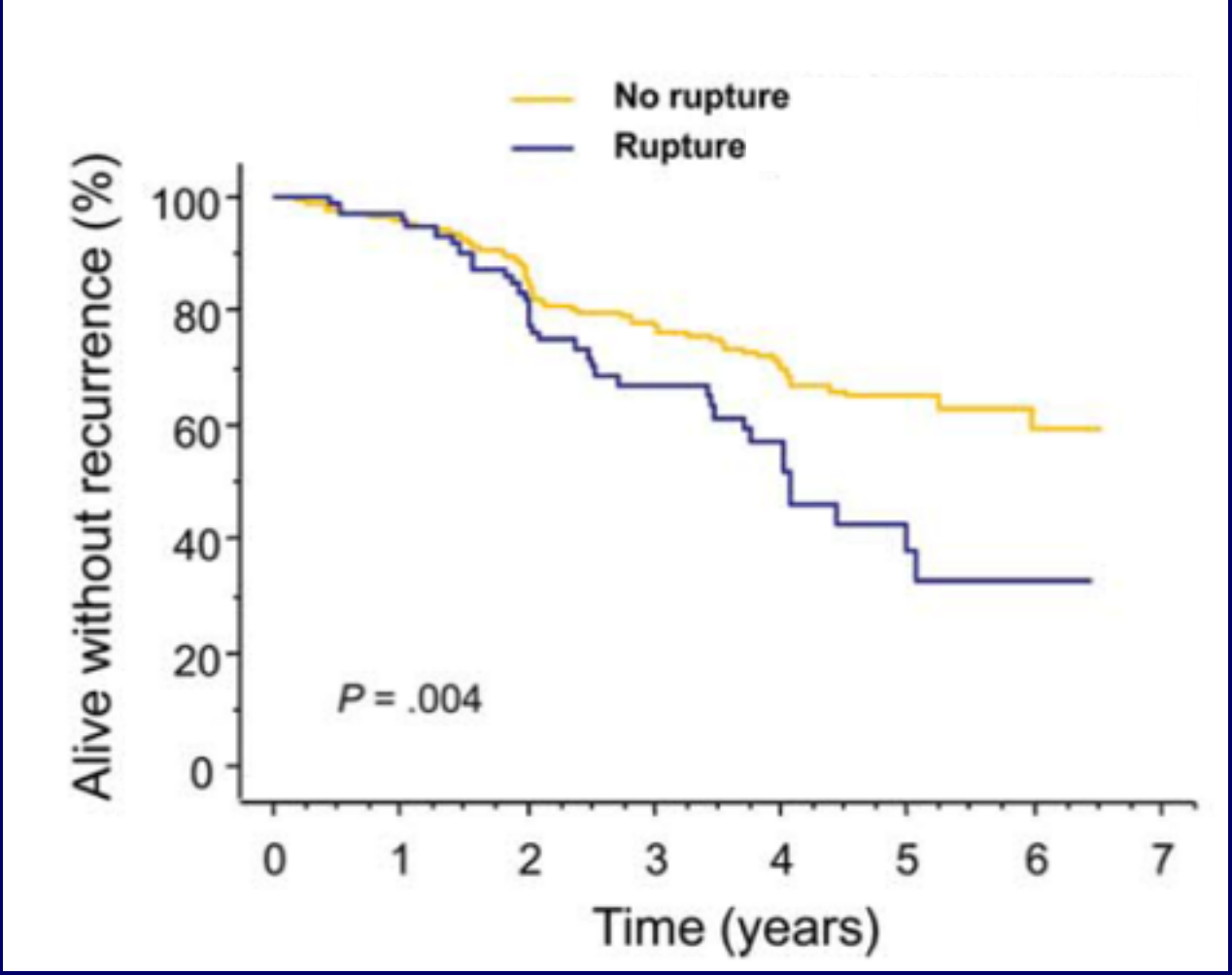


Surgical strategies for primary GIST management

During surgery:

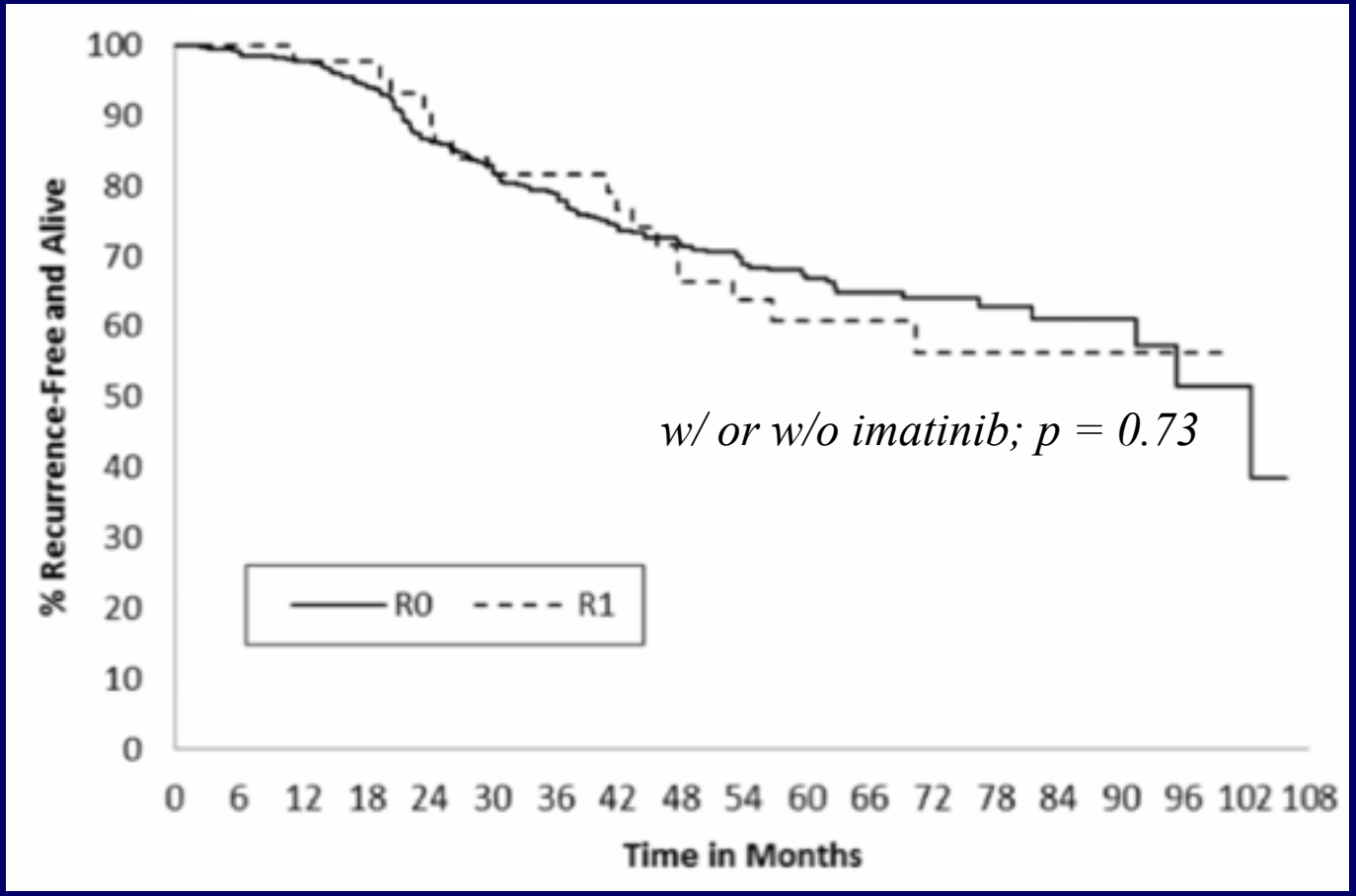
- ✓Incision for exposure; explore entire abdomen and pelvis
- ✓Identify/control critical anatomy; delineate margins
- ✓En bloc resect all gross tumor w/ adherent structures; intact pseudo-capsule; avoid intra-op bleeding or rupture
- ✓Lymphadenectomy not needed; contiguous organ invasion rare; frozen sections usually not useful
- ✓Segmental resection usually sufficient to achieve R0/R1 margins
- ✓Reoperation to convert R1 to R0 does not decreases recurrence

Surgical strategy: avoid intra-operative GIST rupture



Joensuu; 2013

Surgical strategy: R0 and R1 RFS equivalent



McCarter; 2012

MIS: high R0/R1 and low recurrence rates

Summary of Retrospective Studies Investigating Outcomes of Laparoscopic Resection of Gastrointestinal Stromal Tumors (GIST)

Author	N	Mean tumor size (cm)	Conversion rate (%)	Complication rate (%)	R0/R1 resection rate (%)	Mean follow-up (months)	Recurrence rate (%)
Novitsky [29]	50	4.4	0	8	100	36	8
Otani [30]	35	4.3	0	2.9	100	53	2.9
Sexton [32]	63	3.8	1.6	16.4	98.4	15	4.8
Karakousis [33]	40	3.6	22.5	14	97.5	28	2.5
De Vogelaere [34]	31	4.4	0	3.2	100	52	0
Honda [35]	78	3.5	1.3	9	100	45.3	1.3

Fairweather; 2015

Surgical strategy: factors favoring MIS vs open approach to GIST

Logistic analysis examining preoperative factors associated with receipt of minimally invasive versus open surgery

	Univariate analysis			Multivariate analysis		
	OR	95 % CI	*p* value	OR	95 % CI	*p* value
Age	1.00	0.98–1.01	0.61	–	–	–
Male gender	0.54	0.36–0.81	0.003	0.89	0.51–1.55	0.67
Size at diagnosis	0.76	0.69–0.83	<0.001	0.78	0.70–0.86	<0.001
Neoadjuvant TKI	0.24	0.08–0.73	0.01	1.14	0.30–4.33	0.85
Adjacent organ involvement	0.07	0.02–0.29	<0.001	0.14	0.01–1.40	0.09
BMI >30 kg/m^2	2.17	1.31–3.59	0.003	2.41	1.28–4.54	0.006

BMI body mass index, *TKI* tyrosine kinase inhibitor

Bischof; 2015

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Rationale for adjuvant therapy

50% recur by 10 years after R0/R1 primary GIST resection:

< 1 cm <1% recur

5-10 cm 50% recur

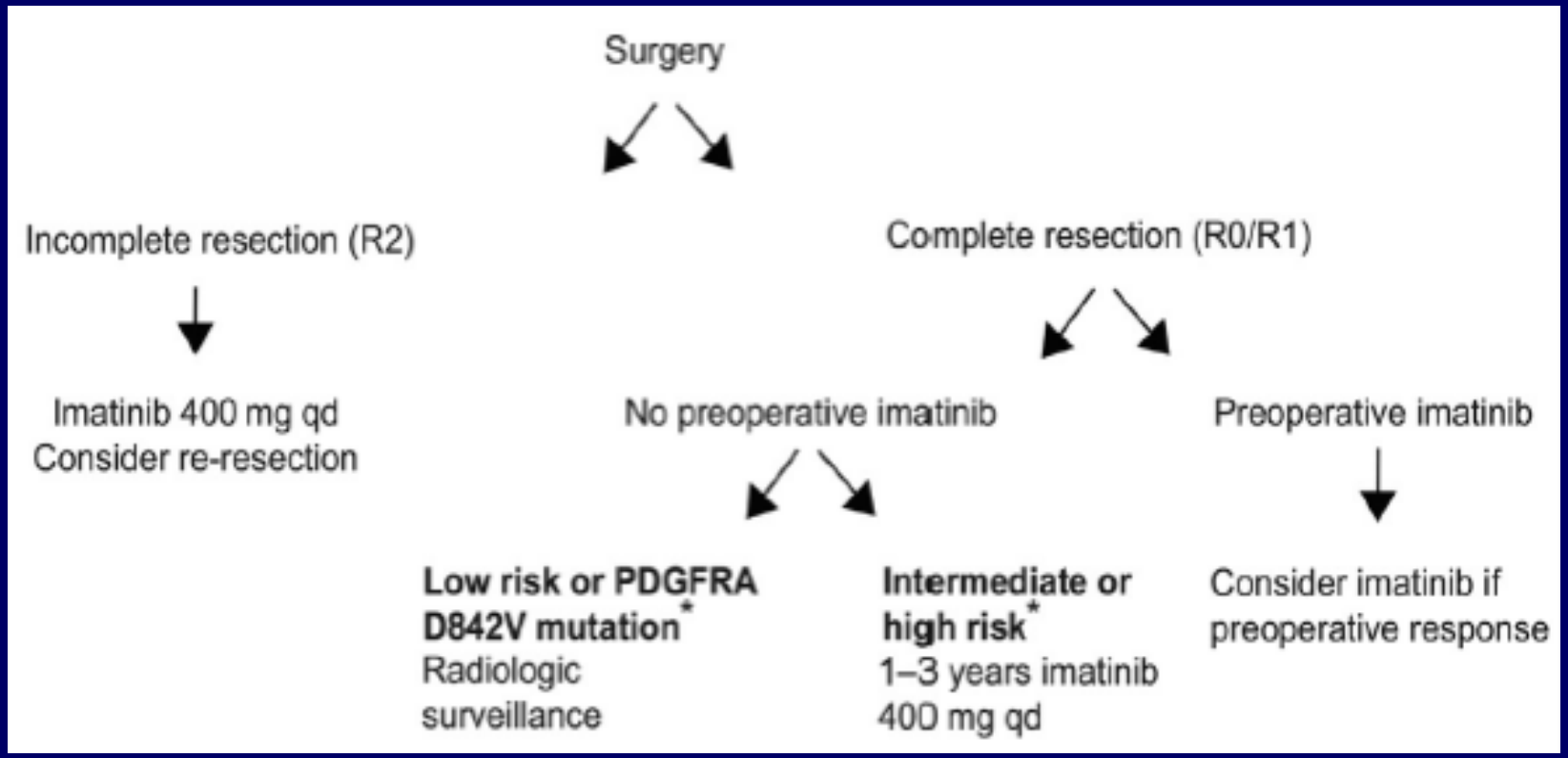
10-15 cm 70% recur

< 50 mitoses/hpf 25% recur

> 50 mitoses/hpf 70% recur

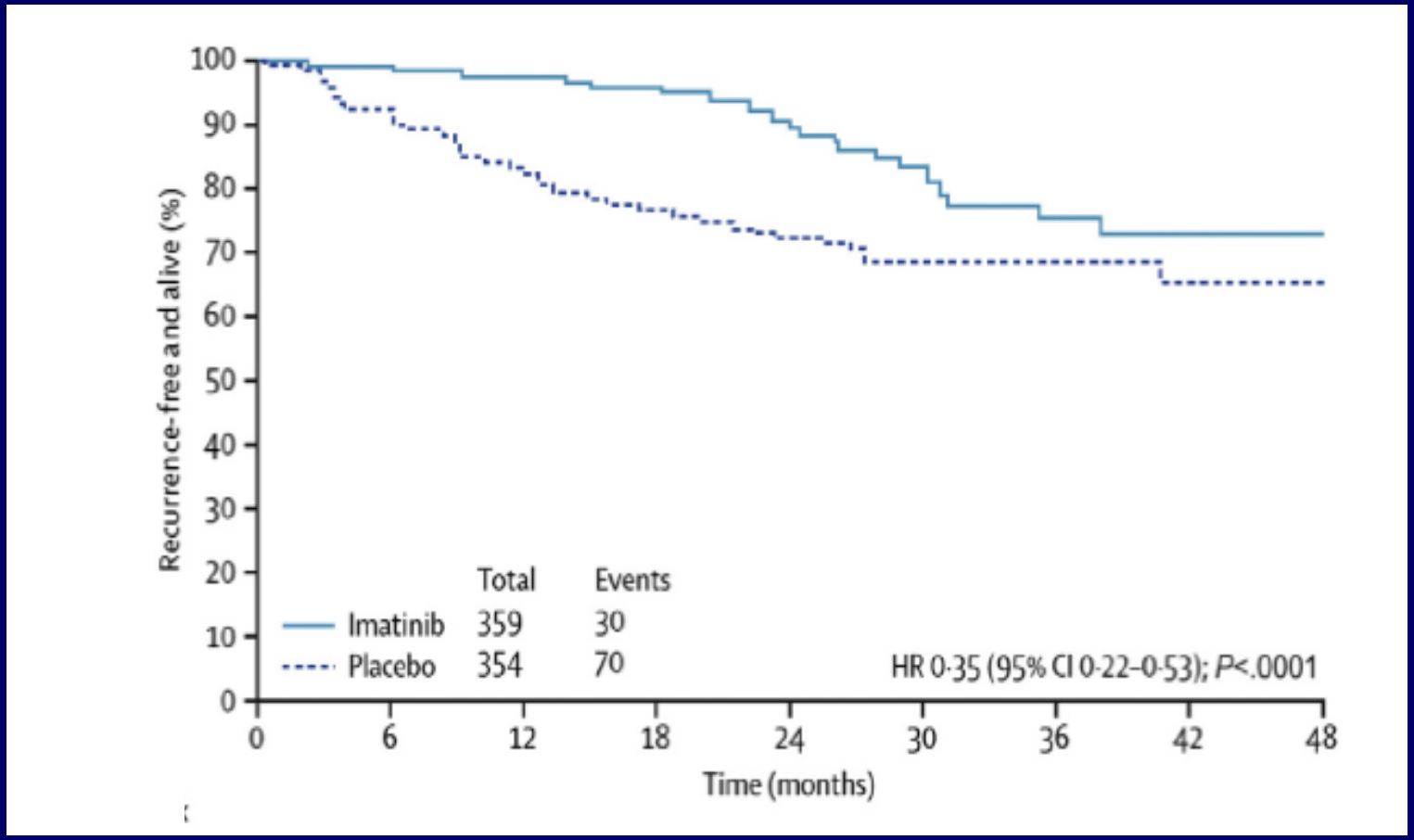
Recurrences: 2/3 hepatic; 1/2 intra-peritoneal

Approach to adjuvant therapy after surgery for primary GIST



Balachandran; 2014

ACOSOG Z9001: one year of adjuvant imatinib vs placebo for GIST > 3cm



Balachandran; 2014

ACOSOG Z9001

Phase III trial: no difference in OS but improved RFS

Patients with larger tumors, small bowel origin tumors, tumors w/ > 5 mitosis/hpf had decreased RFS (placebo control group)

No benefit seen with adjuvant imatinib in *kit* wild type GIST tumor patients

Other adjuvant trials

Scandinavian Sarcoma Group (SSG XVIII):

Phase III randomized trial; 1 vs 3 years adjuvant imatinib

1 year imatinib: 48% five year RFS

3 year imatinib: 66% five year RFS

Other adjuvant trials

EORTC 62024

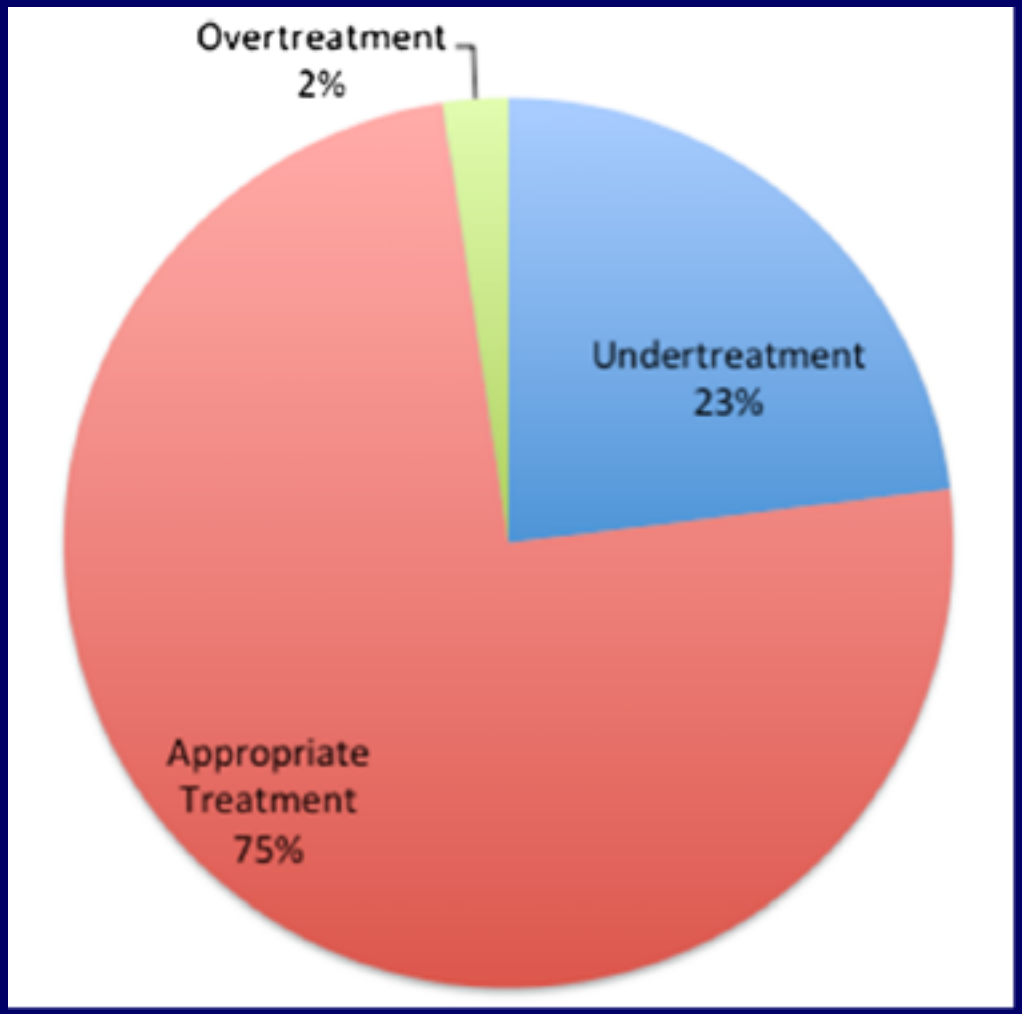
Phase III randomized; 2 year imatinib vs observation

At 3 and 5 years:

RFS (but not OS) improved in imatinib group

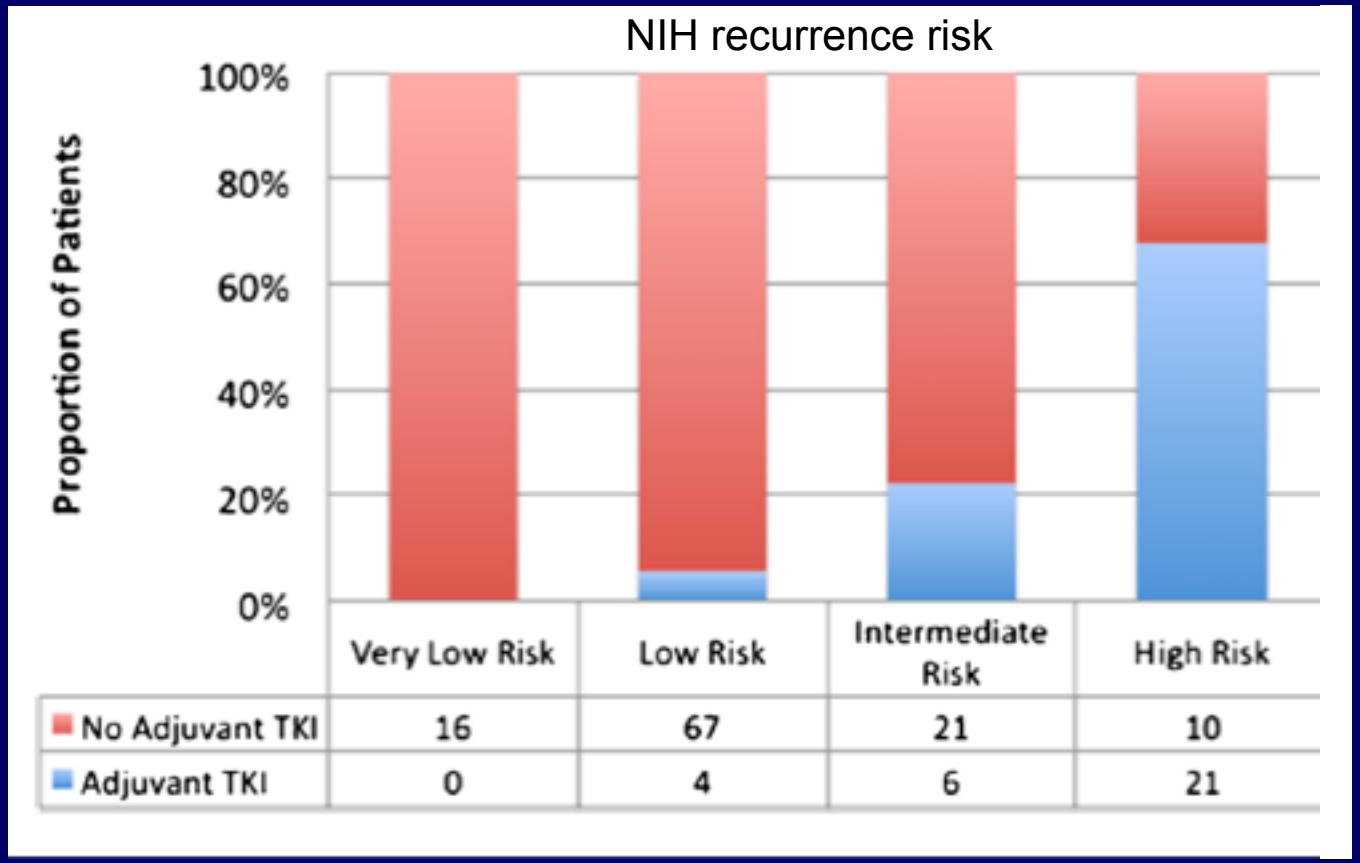
Current NCCN guideline: patients w/ intermediate/high risk of recurrence: adjuvant imatinib for at least 3 years

Compliance with GIST adjuvant treatment can be problematic (NCCN guidelines)



Bischof; 2014

Even NIH high risk patients frequently do not receive optimal adjuvant treatment



Bischof; 2014

How long should adjuvant treatment be continued?

PERSIST 5 is an ongoing phase II trial testing 5 years of adjuvant imatinib therapy in patients at moderate to high risk of recurrence (NCT00867113)

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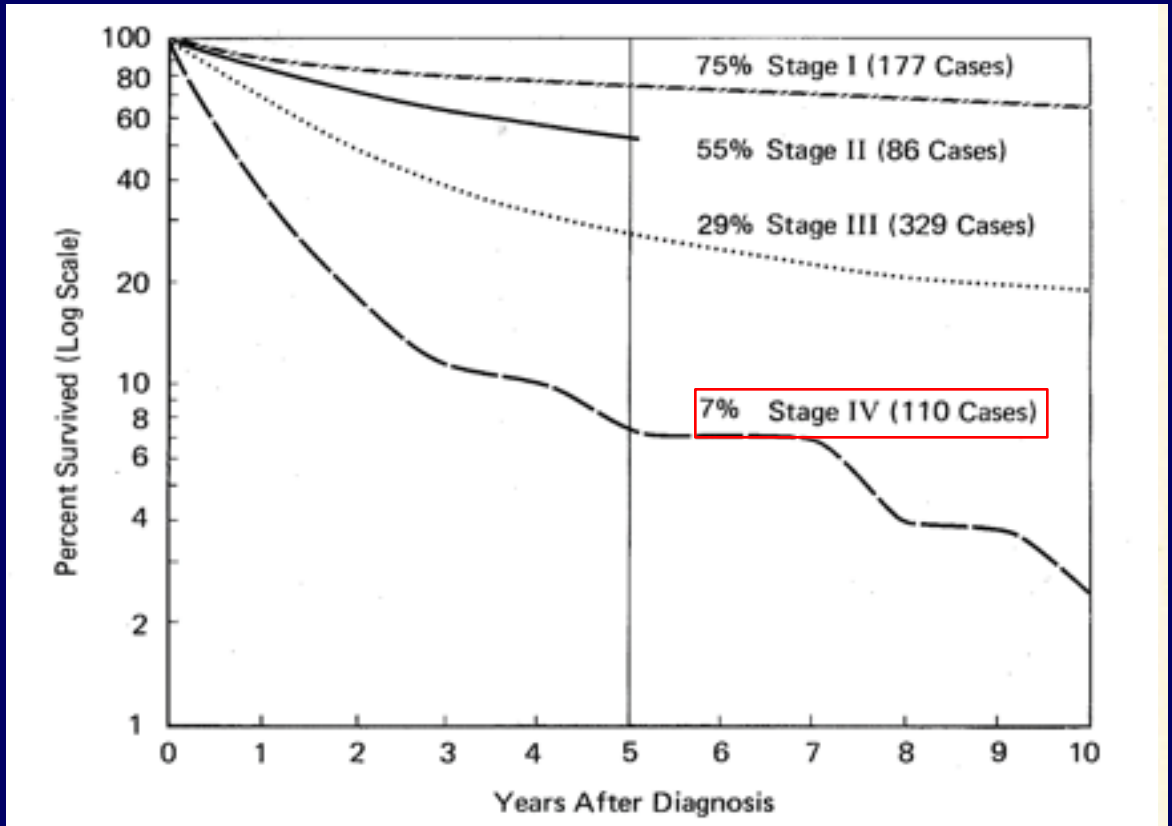
Historical experience: hepatic STS metastasectomy



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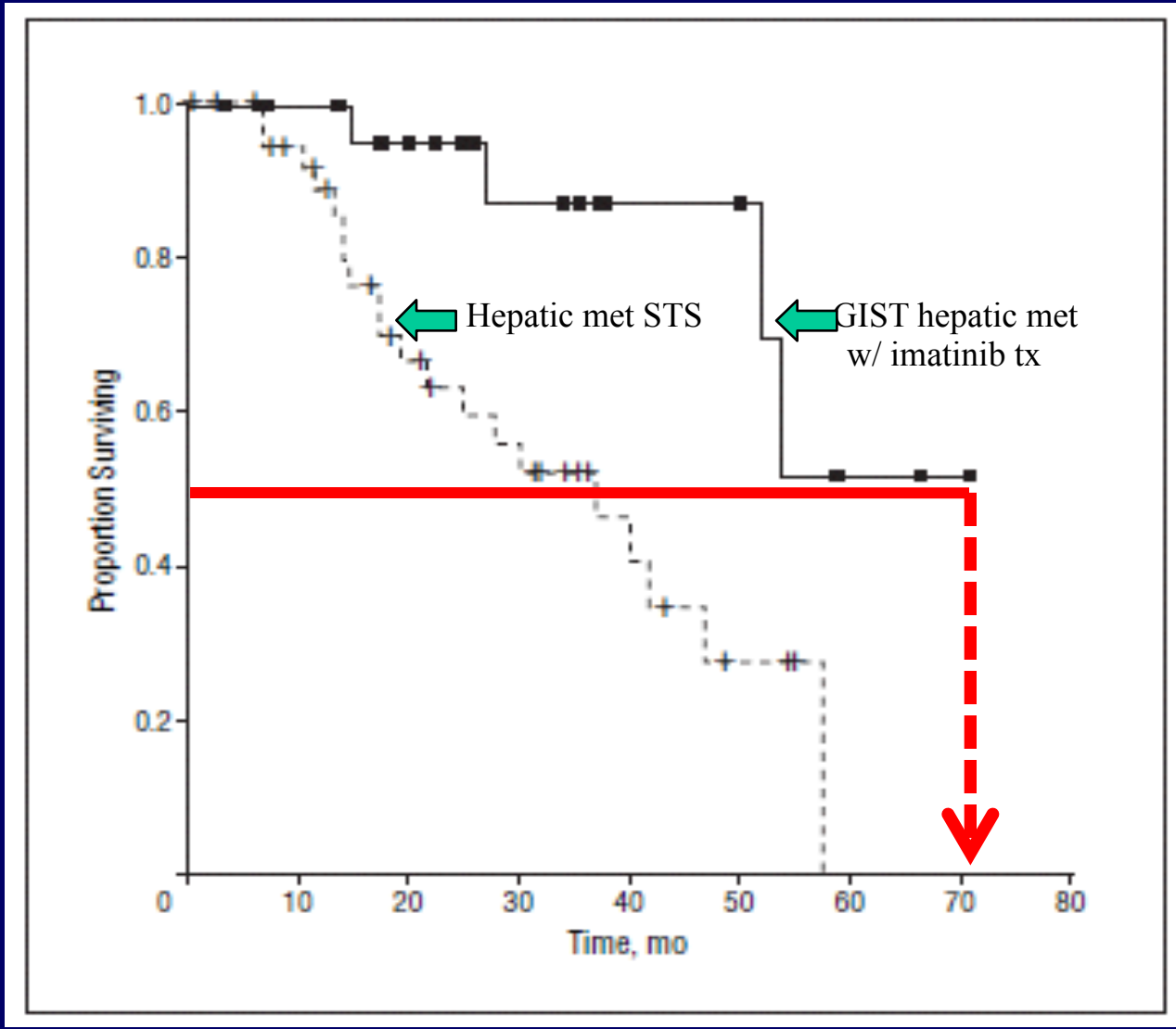
CANCER STAGING AND END RESULTS REPORTING
TASK FORCE ON SOFT TISSUE SARCOMA

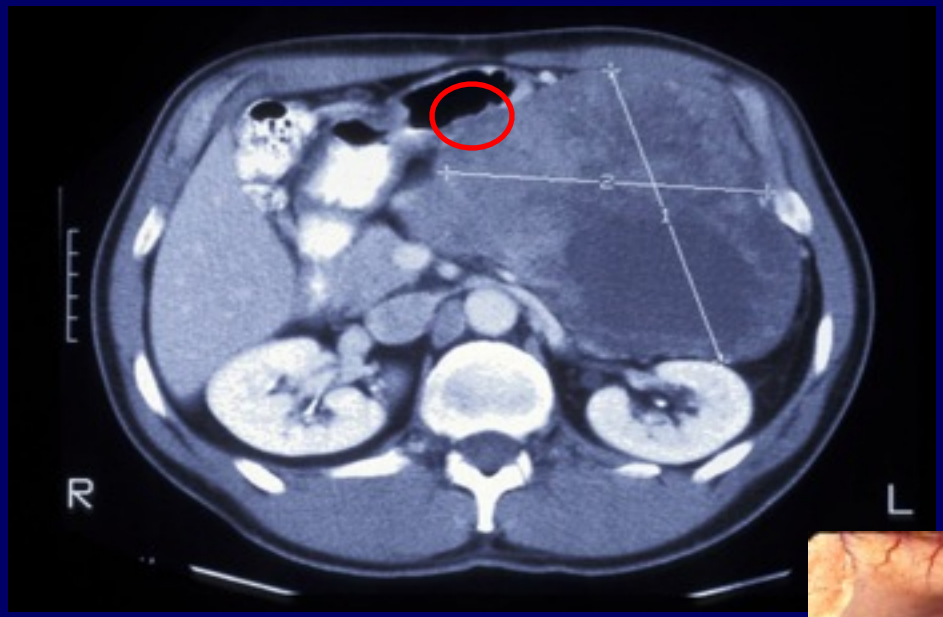
Reprinted from Manual for Staging of Cancer 1978

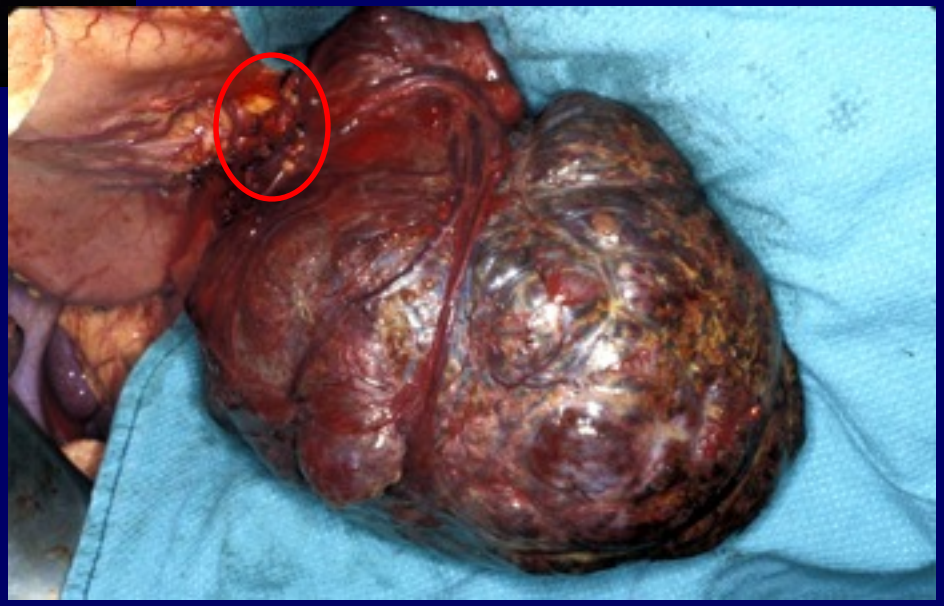
Hepatic metastatasectomy in GIST



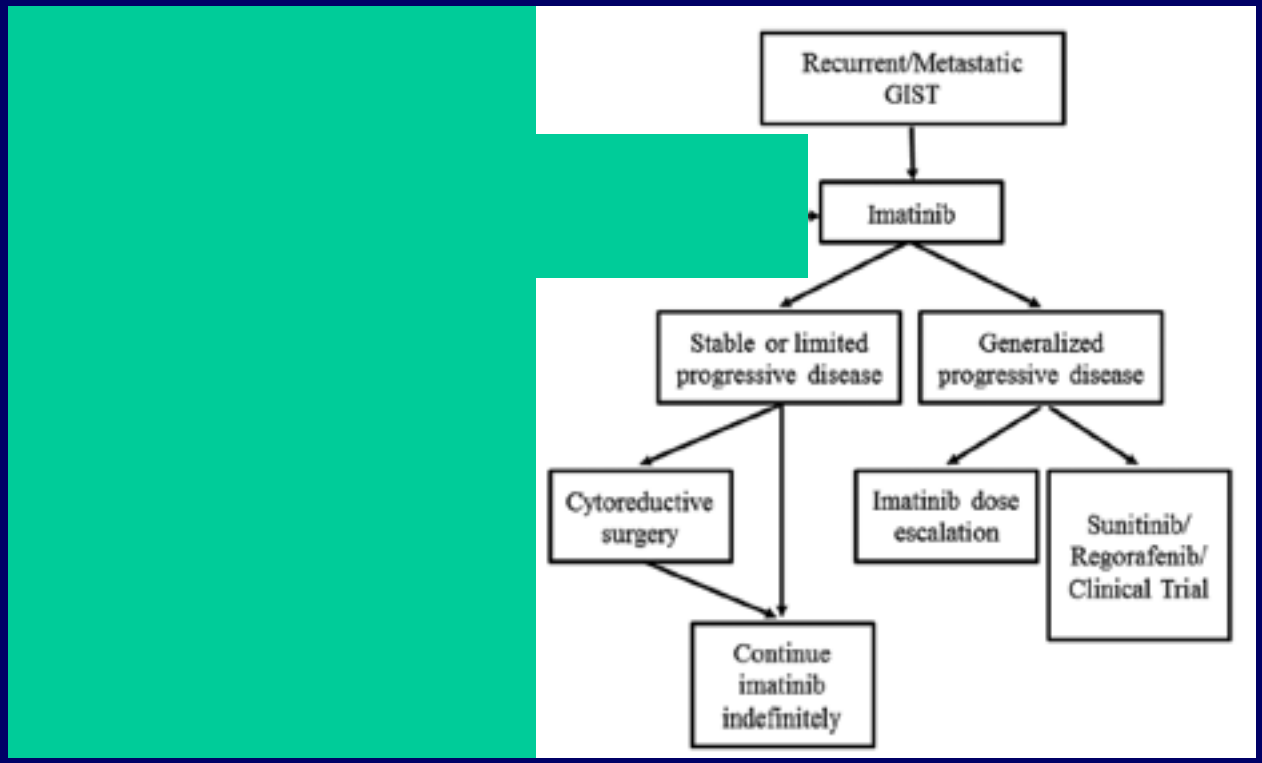
Pawlik; 2006

Recurrent/metastatic/locally advanced GIST: less favorable prognosis than smaller local disease





Approach to recurrent/metastatic GIST



Fairweather; 2015

Rationale for TKI in recurrent/metastatic disease

- Continue imatinib until disease progression (increase to 800 mg/day?) or treatment-related toxicities become unbearable (resection?)
- < 6% will achieve CR for recurrent/metastatic GIST while receiving imatinib (combine with resection?)
- ~20% of recurrent/metastatic disease patients are resectable; if resectable, R0/R1 margins achieved in 48-91%
- Remain on imatinib indefinitely if R0/R1 resection of recurrent/metastatic disease achieved

Recurrent / metastatic GIST: role of/indications for surgery

- R0/R1 resection of stable or shrinking residual disease on imatinib before disease progression: better prognosis
- Resection 6-12 months after start of imatinib: better prognosis; ~ 2 years to develop secondary resistance (EORTC)
- R0/R1: OS = 8.7 years; R2: OS = 5.3 years (EORTC)
- Emergency: bleeding, perforation, obstruction, abscess
- Disease in more than 1 organ system: worse prognosis
- Liver only mets: better prognosis than peritoneal mets
- wt *kit* or *PDGFR* mut GIST have indolent metastatic disease course; role of surgery vs imatinib/no further surgery vs observation alone ?

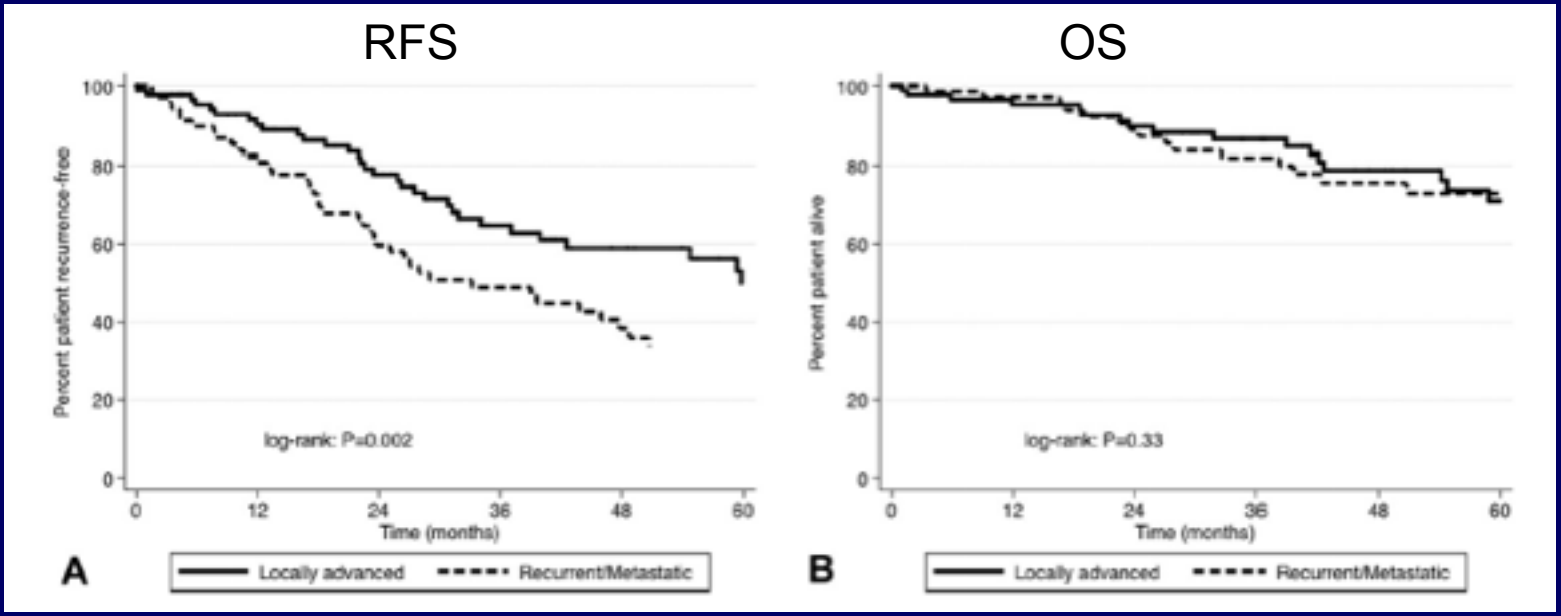
GIST radiographic response to neoadj. imatinib

Response	Patients with locally advanced primary GIST[a]	Patients with recurrent or metastatic GIST	
		Complete resection	Incomplete resection
Complete response (no., %)	1 (9%)	0 (0%)	0 (0%)
Partial response (no., %)	8 (73%)	10 (91%)	1 (4%)
Continuous regression (no.)	4	2	0
Initial regression then stable disease (no.)	4	8	1
Stable disease (no., %)	1 (9%)	0 (0%)	0 (0%)
Progressive disease (no., %)	1 (9%)	1 (9%)	23 (96%)
Initial regression then progression (no.)	0	0	18
Continuous progression (no.)	1	1	5

Neoadjuvant imatinib partial response is associated with complete resection

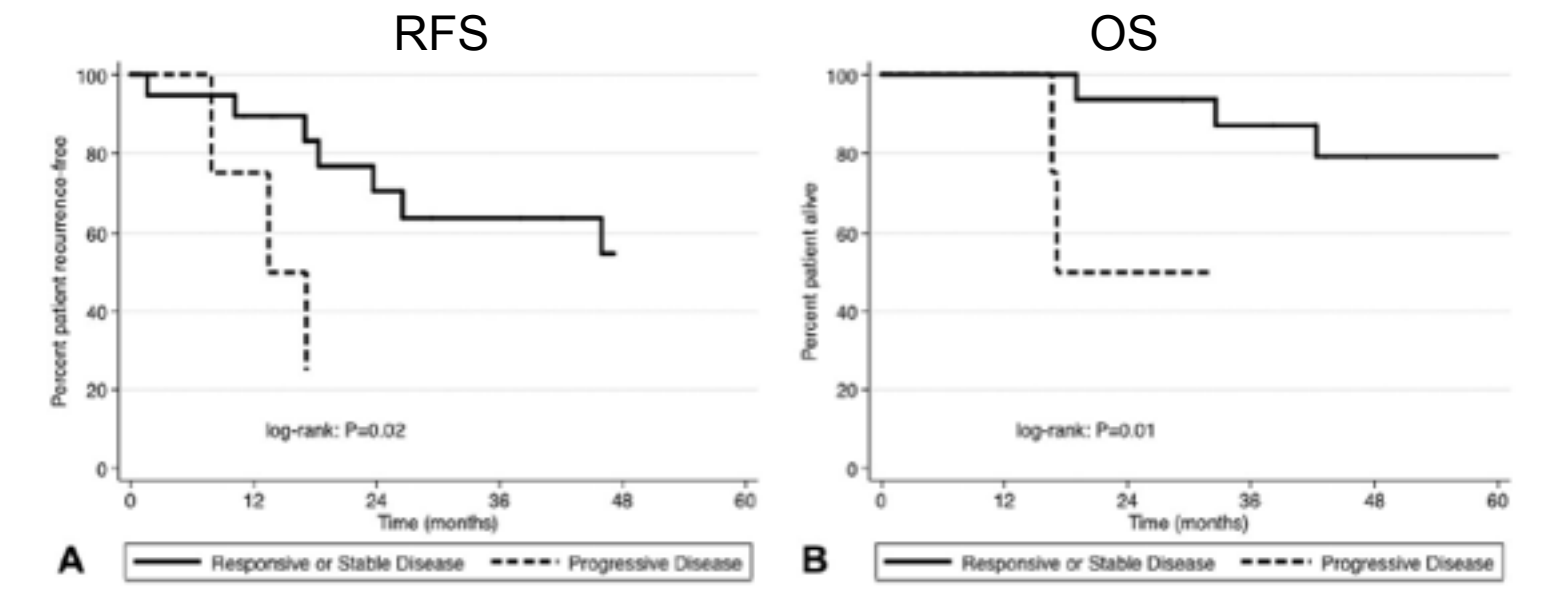
Antbacka; 2006

RFS and OS after surgical therapy for recurrent/metastatic/locally advanced GIST



Bischof; 2015

RFS and OS after surgical therapy for recurrent/metastatic/locally advanced GIST txed w/ neoadjuvant TKI (radiographic response)



Bischof; 2015

Multivariate analysis: recurrent/locally advanced/metastatic GIST RFS

	HR	95 % CI	*p* value
Age <60 years	Ref	–	–
Age 60+ years	2.10	0.99–4.44	0.05
Female	Ref	–	–
Male	1.58	0.79–3.17	0.20
Tumor size <5.0 cm	Ref	–	–
Tumor size ≥5.0 cm	1.84	0.86–3.92	0.12
Mitotic rate group			
≤5/50 HPF	Ref		
>5/50 HPF	3.42	1.61–7.28	0.001
Open	Ref	–	–
MIS	0.70	0.30–1.64	0.42
Margin R0	Ref		
Margin R1 or R2	1.28	0.44–3.76	0.65
No neoadjuvant TKI	Ref		
Neoadjuvant TKI	2.88	0.81–10.22	0.10
No adjuvant TKI	Ref		
Adjuvant TKI	0.52	0.22–1.23	0.14

Bischof; 2015

Unresolved surgical controversies

- Management of GIST < 2 cm?
- Benefit of metastatectomy in TKI responders?
- Does antecedent RFS duration impact prognosis after metastatasectomy?
- Is there site specificity as an indicator or prognostic factor for metastatesectomy?
- Observe vs operate for metastasis in *wt* or *PDGFR* mut patients?
- How to surgically handle multifocal GIST?
- Benefit of resecting > than one contiguous organ?

So, although the pathway to progress in GIST is not clearly marked out…

By working together we will make things better!!

Many thanks to my Ohio State sarcoma colleagues!

Pathology
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Radiation Oncology
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James Chan, MD, PhD

Orthopedic Oncology
Thomas Scharschmidt, MD
Joel Mayerson, MD

Surgical Oncology
Harrison Howard, MD

Neurosurgery
Ehud Mendel, MD

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Bethany Prudner, PhD (Post-doc)
Hemant Bid, PhD (Post-doc)
Abby Zewdu, BS (Pre-doc)
Danielle Braggio, PhD (Post-doc)
Kara Batte, PhD (Lab manager)
Anne Strohecker, PhD (Asst. Professor)
Dennis Guttridge, PhD (Professor)
Dina Lev, MD (Professor)

Thank you for your attention!