GIST

Diagnóstico molecular y factores pronósticos

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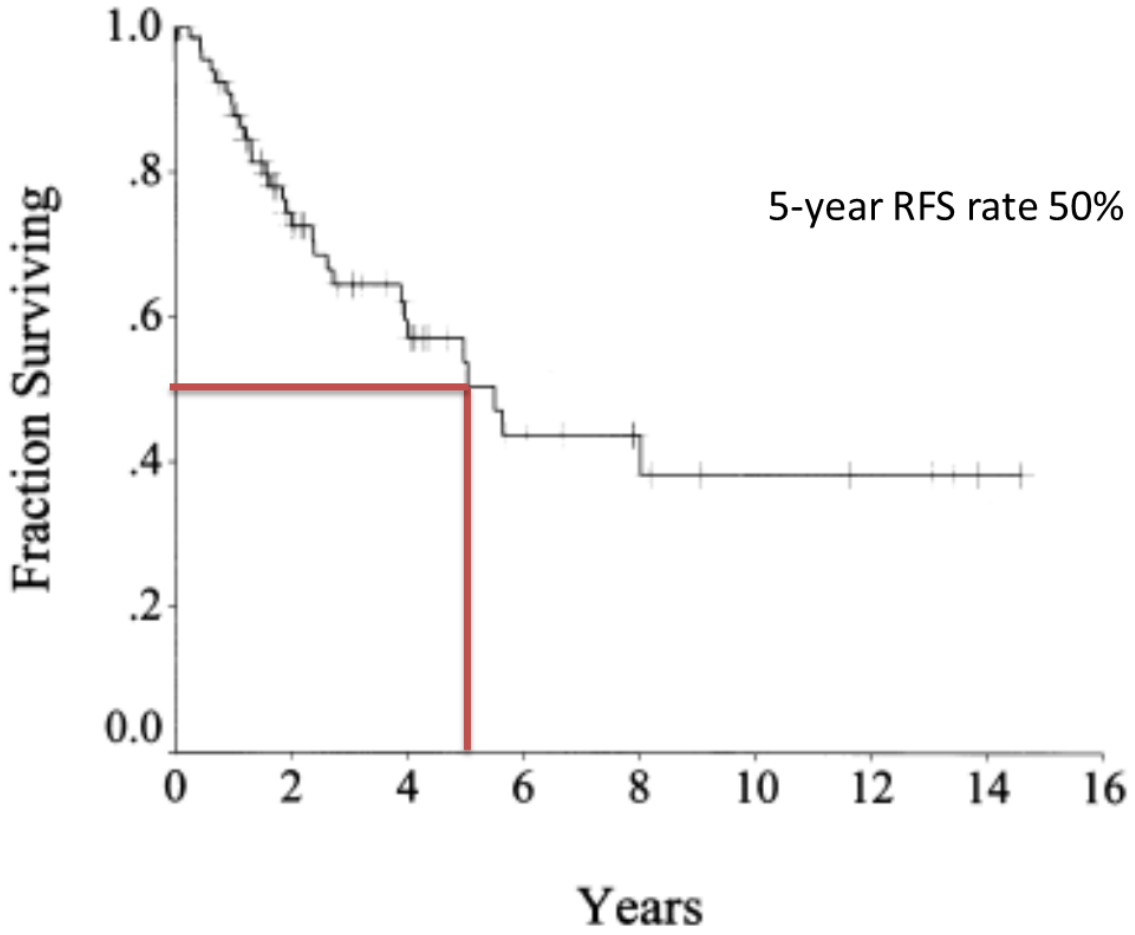
GEIS
GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS

Máster en Tumores Musculoesqueléticos

DISCLOSURE

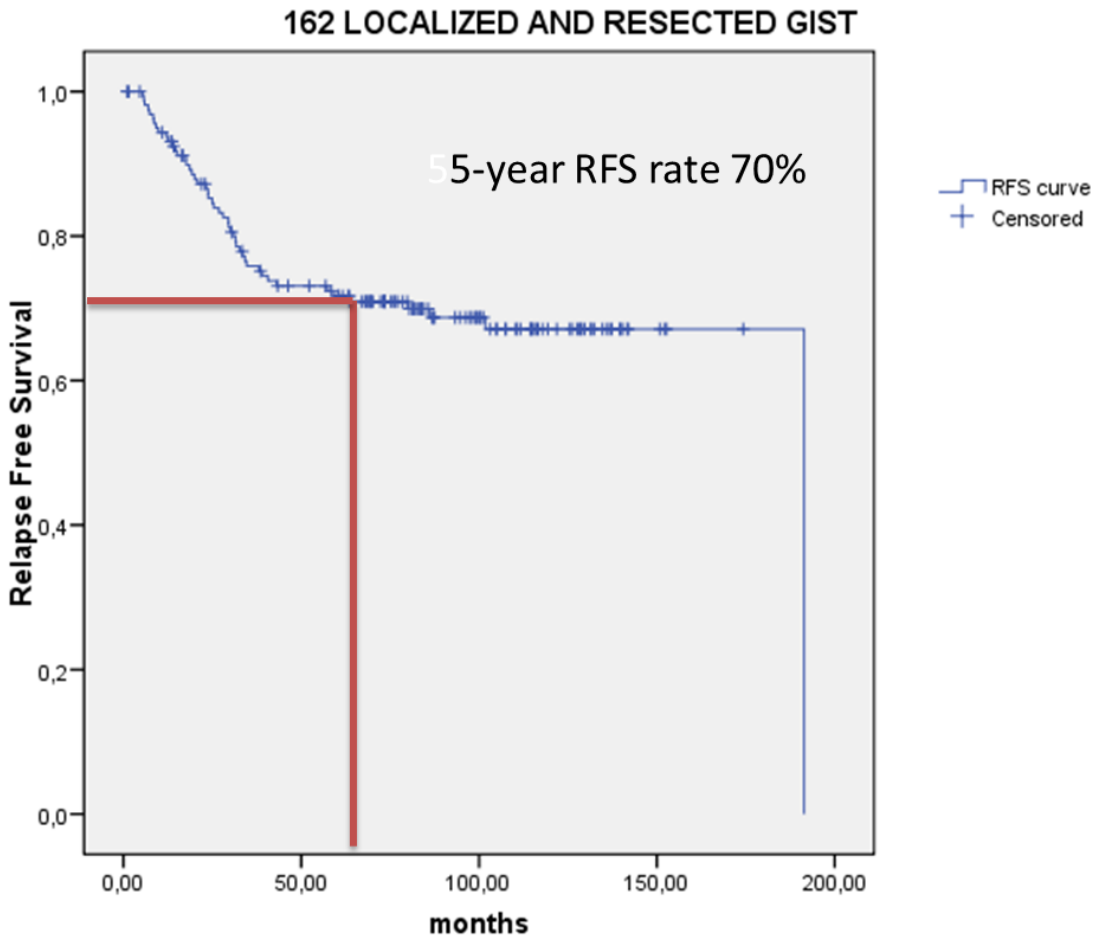
- **Consulting or Advisory Role**
  - ✓PharmaMar, GSK, Novartis, Amgen, Bayer, Lilly, Roche, Tecnofarma, Asofarma
- **Speakers' Bureau**
  - ✓PharmaMar
- **Research Funding**
  - ✓ Eli-Lilly, Novartis, Eisai, PharmaMar, Bayer, Pfizer, GSK, Lixte, Karyopharm, Celgene, BMS, Blue-Print, Deciphera, Nektar, Forma, Amgen, Daichii-Sanchyo.

RFS in Reference Centers: Selection byass



De Matteo et al, Annals of Surgery 2000 231, 51-58

RFS in Network Centers



J Clin Oncol 26, 2008. 231, 51-58

Prognostic Factors for RFS in Localized GIST

MITOSES

SIZE

ANYTHING MORE?

Mitoses and Size

Author	Year	Number of Resected cases	KIT+ (%)	Univariate Analysis	Multivariate Analysis
Ernst	1998	35 (?)	ND	Mitoses, Size, Kit mutation +	Mitoses, Size
De Matteo	1999	80	ND	Size	Size >10cm
Emory	1999	1004 (?)	ND	?	Mitoses, Size, Age, Location.
Howe	2001	1251	ND	Male, Age >60, Size, Mitoses, Surgery	Mitoses, Size Histology

Mitoses and Size

Author	Year	Number of Resected cases	KIT+ (%)	Univariate Analysis	Multivariate Analysis
Taniguchi	1999	113	89	ND	Mitoses, KIT mutation +
Singer	2002	42	100	Mitoses, Size >10cm Margins+ Epithelioid	Mitoses, Male, Deletion, Mixed cell type
Lin	2003	81	86	Mitoses, Size, Incomplete Resection	ND
Aparicio	2004	59	100	Mitoses, Size	Mitoses
Emile	2004	179 (?)	87	Mitoses, Size, Age, Necrosis; No gastric	Mitoses Deletión ?

Mitoses and Size: significant correlation

Correlation between tumor size and mitotic count in CD117-positive GIST
Pearson correlation = 0.541, *P*<0.001, [a]HPF=High power fields.

Tumor size	Mitotic counts/50 HPF[a]		
	<5	5-10	>10
≤2 cm	10 (100 %)	0	0
2 to 5 cm	14 (56 %)	8 (32 %)	3 (12 %)
5 to 10 cm	12 (44 %)	8 (30 %)	7 (26 %)
>10 cm	2 (11 %)	5 (26 %)	12 (63 %)

Lin et al. Worl J Gastroenterol. 2003

RISK STRATIFICATION

FLETCHER

50 HPF=
10-12 mm^2

Fletcher CD et al. Hum Pathol. 2002; 33:459-65

	Size	Mitotic Count (50 hpf)
Very Low Risk	< 2 cm	≤ 5 mitoses
Low Risk	2-5 cm	≤ 5 mitoses
Intermediate Risk	≤ 5 cm	6-10 mitoses
	5-10 cm	≤ 5 mitoses
High Risk	> 5 cm	> 5 mitoses
	>10 cm	Any mitotic count
	Any size	> 10 mitosis

MIETTINEN-LASOTA

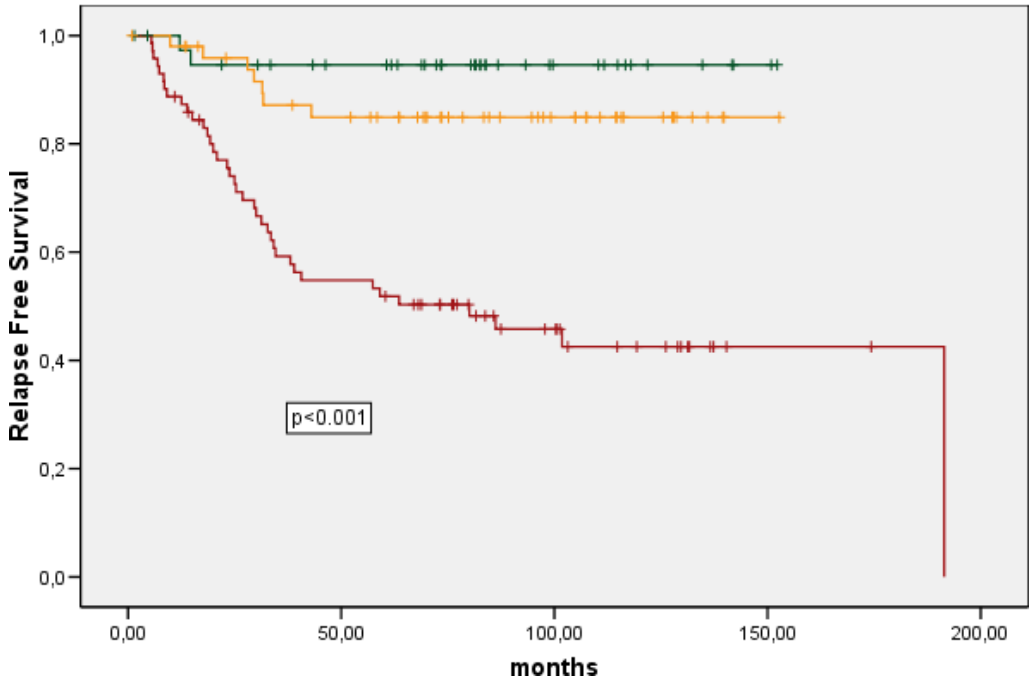
50 HPF=
5 mm^2

Miettinen M, Lasota J. Semin Diagn Pathol. 2006 May;23(2):70-83

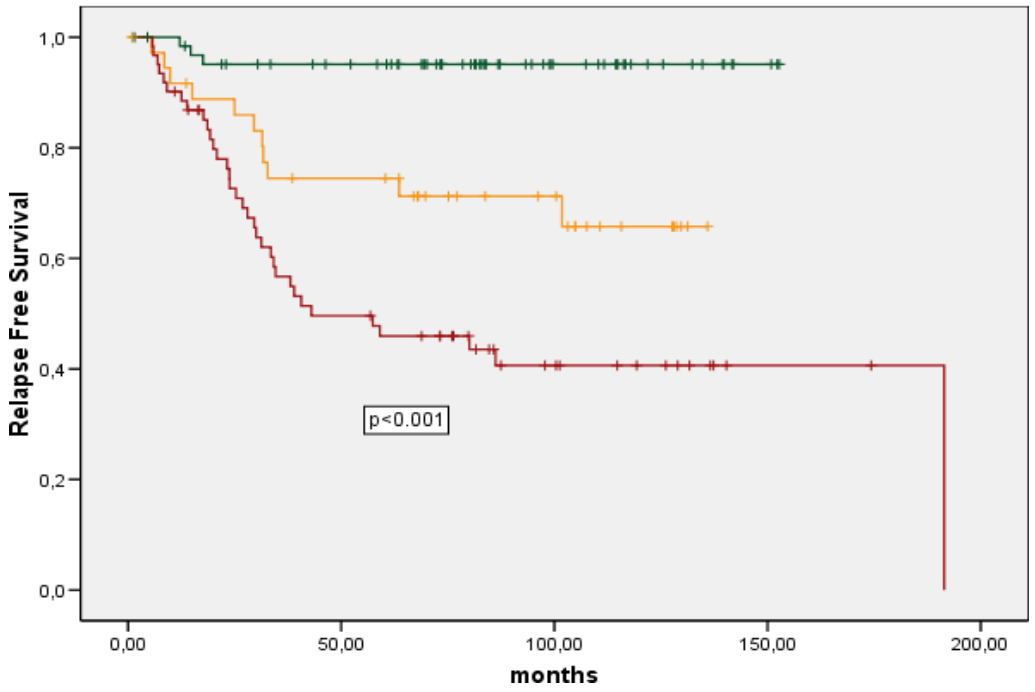
	Size	Mitotic count (50 hpf)	Location
Very Low Risk	2- 5 cm	≤ 5 mitoses	gastric
Low Risk	>5 ≤ 10 cm	≤ 5 mitoses	gastric
	2- 5 cm	≤ 5 mitoses	intestinal
Intermediate Risk	>10 cm	≤ 5 mitoses	gastric
	>5 y ≤ 10 cm	≤ 5 mitoses	intestinal
	2- 5 cm	> 5 mitoses	gastric
High Risk	2- 5 cm	> 5 mitoses	intestinal
	> 10 cm	≤ 5 mitoses	intestinal
	>5 y ≤ 10 cm	> 5 mitoses	gastric
	> 10 cm	> 5 mitoses	gastric
	>5 y ≤ 10 cm	> 5 mitoses	intestinal
	> 10 cm	> 5 mitoses	intestinal

Risk Assessment

Fletcher et al. Risk Categories



Miettinen-Lasota Risk Categories



Ann Oncol 21: 2010; 1552-1557

Fletcher vs Miettinen risk scales

RISK STRATIFICATION

Greater discrepancies

	Fletcher-NIH	Miettinen-AFIP
GASTRIC > 10 CM ≤ 5 mit	HIGH RISK (RFS 55%)	INTERMEDIATE RISK (RFS 75-85%)
NO GASTRIC ≤ 5 CM > 5 mit	INTERMEDIATE RISK (RFS 85%)	HIGH RISK (RFS 50%)

Nomogram

Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis

Jason S Gold, Mithat Gönen, Antonio Gutiérrez, Javier Martín Broto, Xavier García-del-Muro, Thomas C Smyrk, Robert G Maki, Samuel Singer, Murray F Brennan, Cristina R Antonescu, John H Donohue, Ronald P DeMatteo

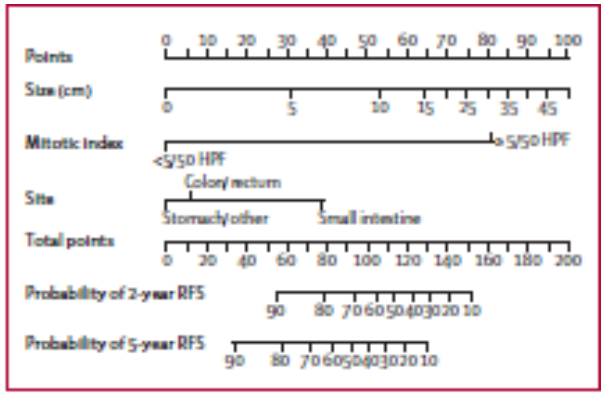
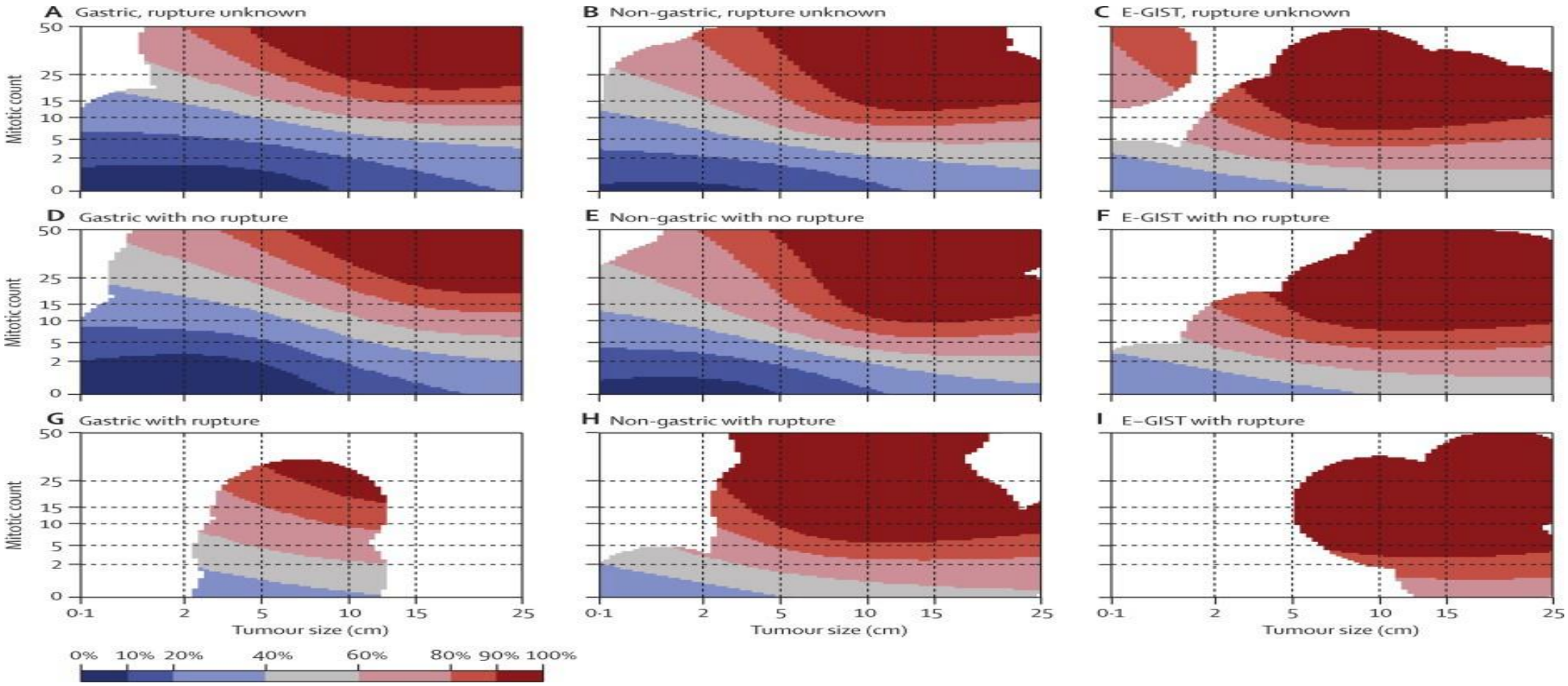


Figure 2: Nomogram to predict the probabilities of 2-year and 5-year recurrence-free survival
Points are assigned for size, mitotic index, and site of origin by drawing a line upward from the corresponding values to the "Points" line. The sum of these three points, plotted on the "Total points" line, corresponds to predictions of 2-year and 5-year recurrence-free survival (RFS).

Lancet Oncol 2009; 10: 1045–52

Heat Maps



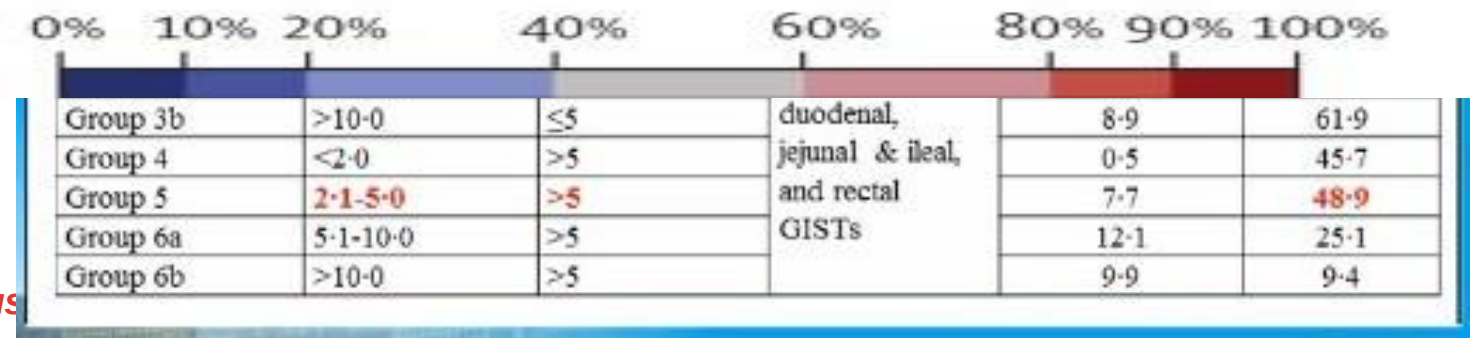
The Lancet Oncology Volume 13, Issue 3 2012 265 - 274

PATHOLOGIST A	PATHOLOGIST B
Intestinal GIST; 4.5 cm; 5 mit	Intestinal GIST; 4.5 cm; 6 mit

E Non-gastric with no rupture

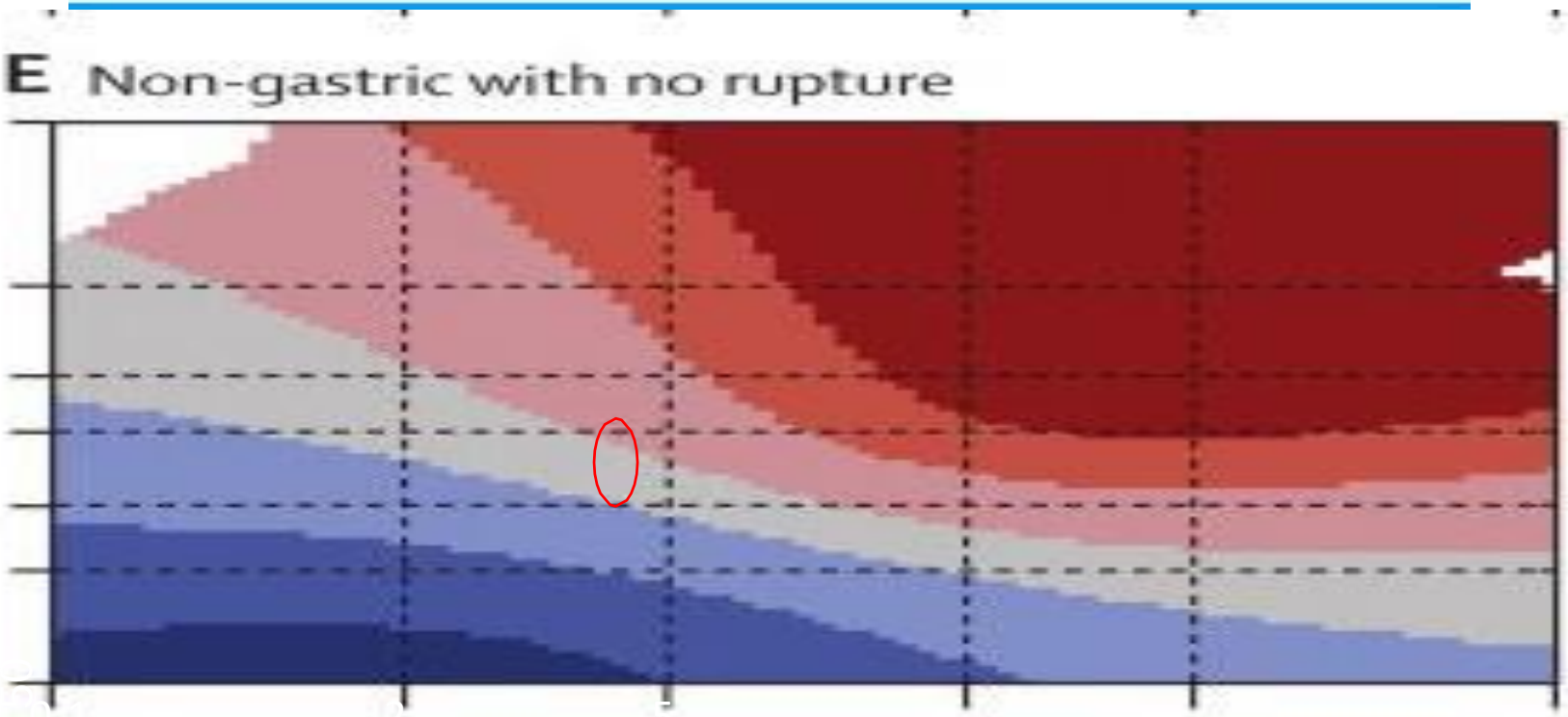
Modified NIH consensus criteria

Very low	<2	≤5	Any site	94.9
Low	2.1–5.0	≤5	Any site	89.7
Intermediate	≤5.0	6-10	Gastric	86.9
	5.1–10.0	≤5	Gastric	36.2
High	>10.0	Any count	Any site	
	Any size	>10	Any site	
	>5.0	>5	Any site	
	≤5.0	>5	Non-gastric	
	5.1–10.0	≤5	Non-gastric	
	Any size	Any site	Tumor rupture	



Group 3b	>10·0	≤5	duodenal, jejunal & ileal, and rectal GISTs	8·9	61·9
Group 4	<2·0	>5		0·5	45·7
Group 5	2·1-5·0	>5		7·7	48·9
Group 6a	5·1-10·0	>5		12·1	25·1
Group 6b	>10·0	>5		9·9	9·4

PATHOLOGIST A	PATHOLOGIST B
Intestinal GIST; 4.5 cm; 5 mit	Intestinal GIST; 4.5 cm; 6 mit



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Group 5	2·1-5·0	>5		7·7	48·9
Group 6a	5·1-10·0	>5		12·1	25·1
Group 6b	>10·0	>5		9·9	9·4

Genotype as prognostic for RFS

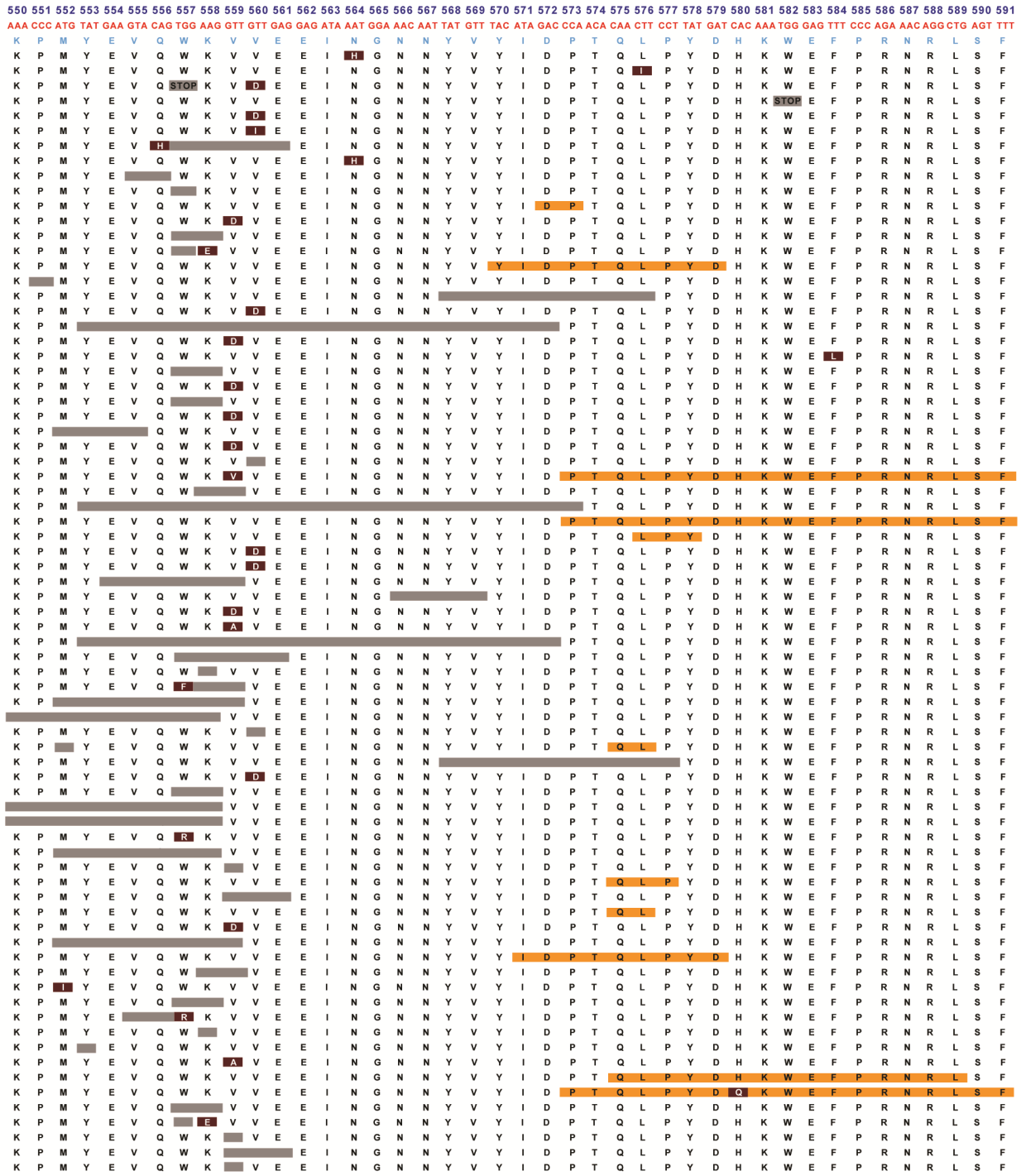
Table 2. Distribution of *c-KIT* and *PDGF-α* Mutations in Gastrointestinal Stromal Tumors (n = 162)

Type of Mutations	No. of Patients
No mutations	66
c-KIT	82
Exon 11	
Deletions	36
Missense	23
Deletion and missense	5
Duplications	10
Duplications and missense	1
Nonsense	1
Nonsense and missense	1
Exon 9	
Duplications	3
Missense	1
Exon 13	
Missense	1
Exon 17	0
PDGF	14
Exon 12	
Deletions	5
Missense	2
Exon 18	
Deletions	1
Missense	5
Deletions and missense	1

Mutations

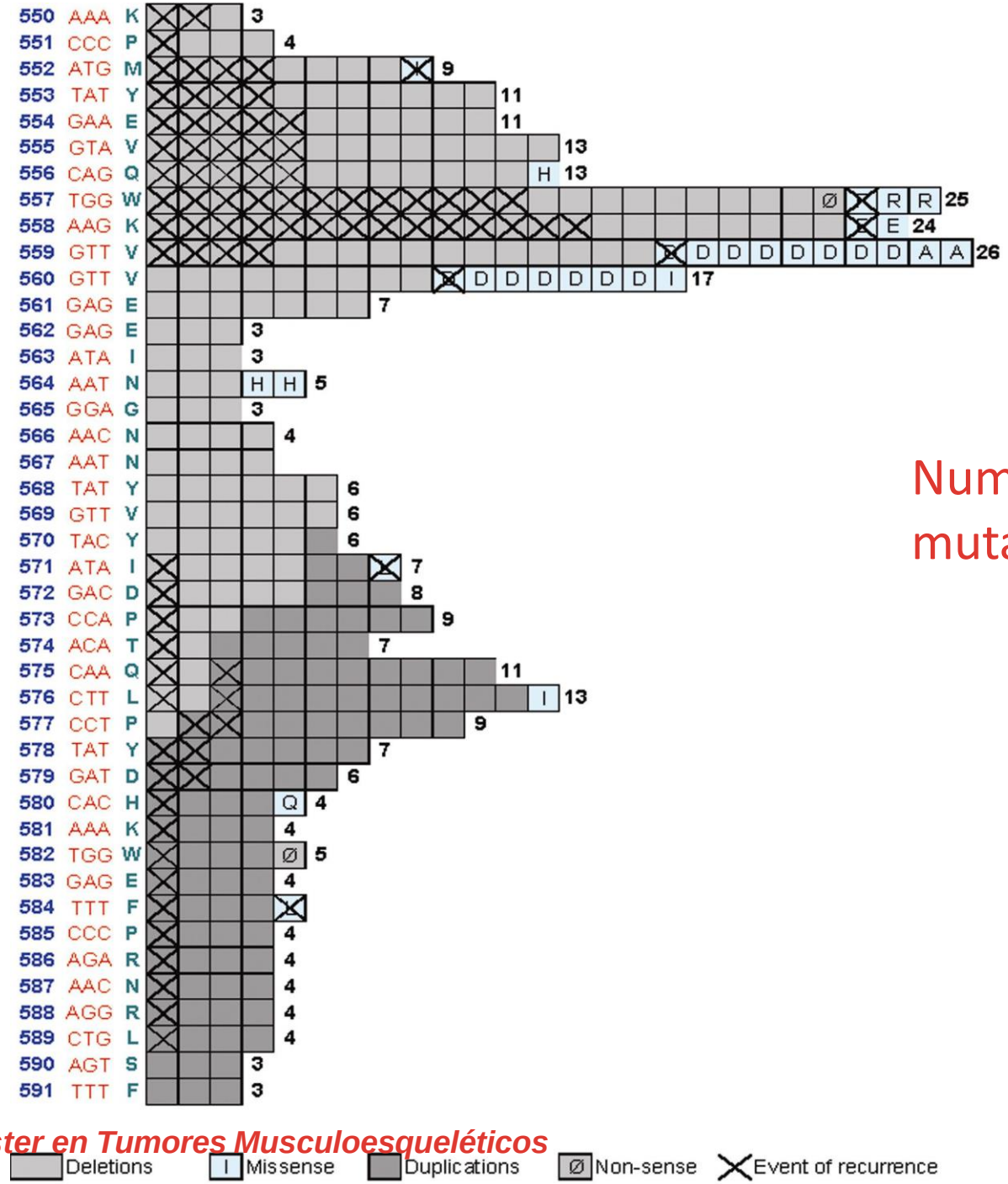
(level and type)

J Clin Oncol. 2005;23(25):6190-8



Exon 11 of *KIT* gene shows clustering of different mutation types

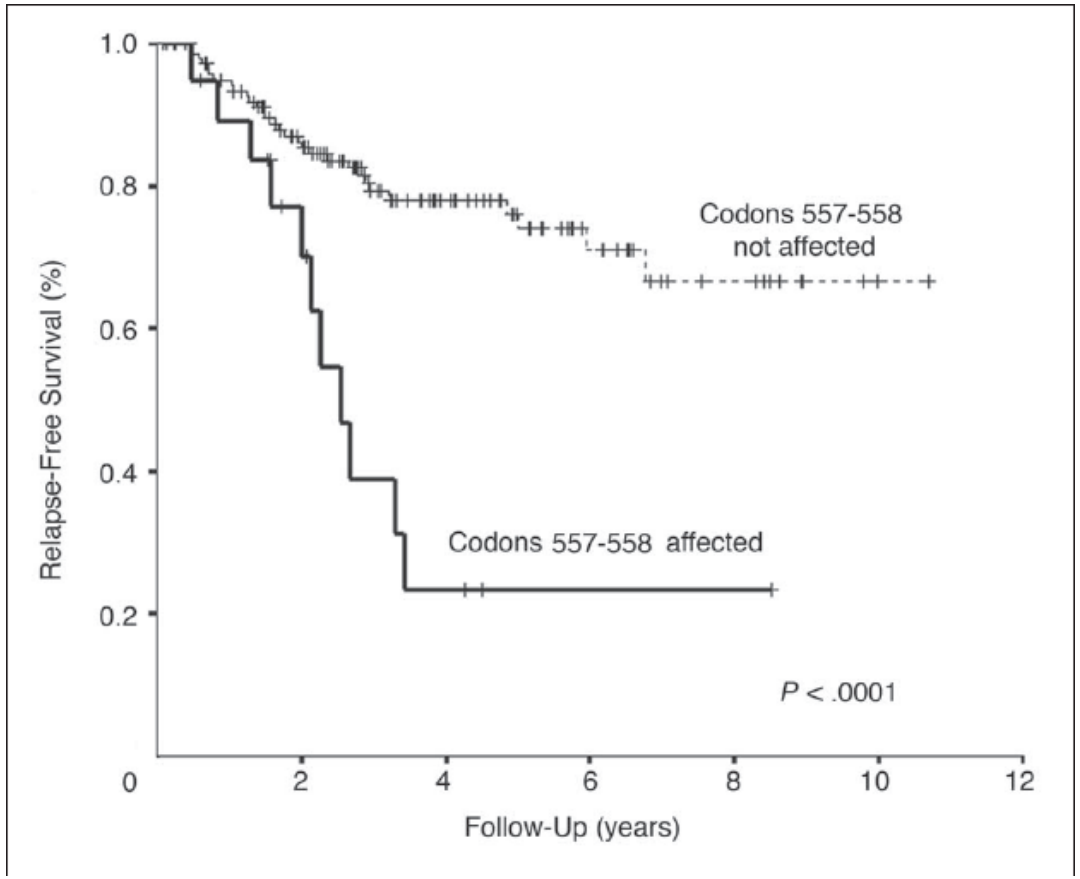
J Clin Oncol. 2005;23(25):6190-8

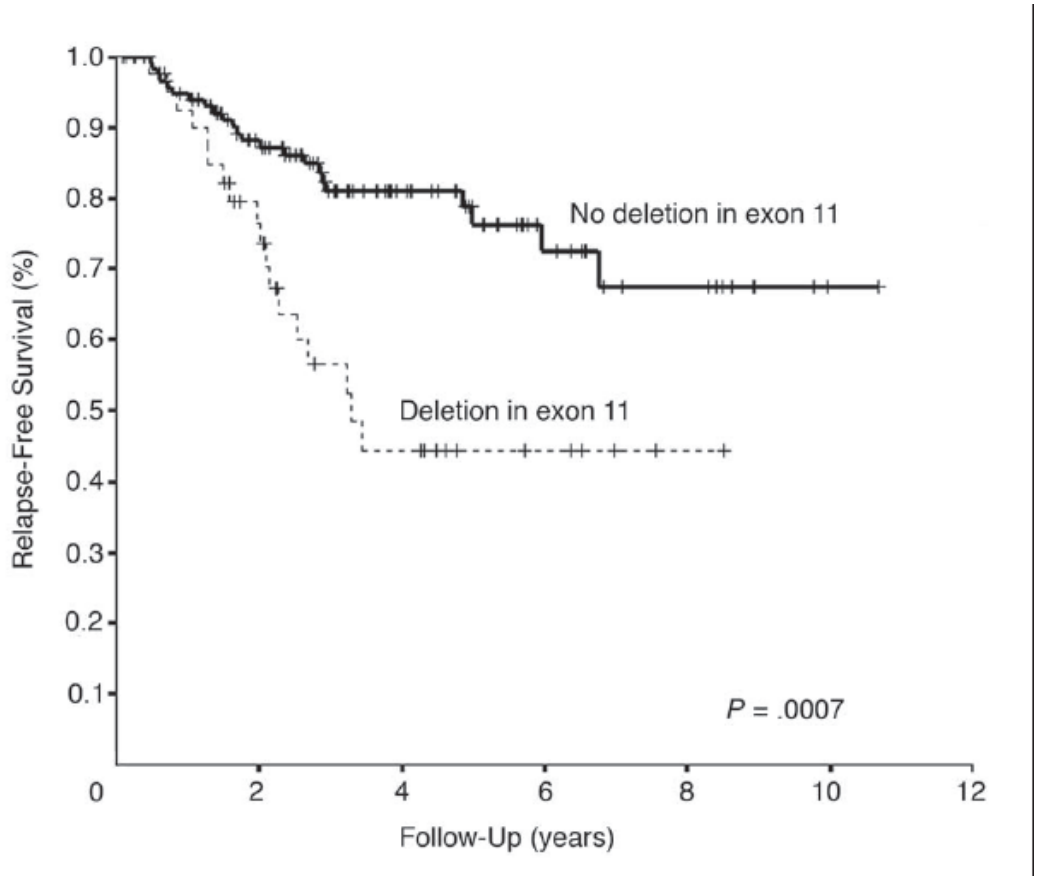


Number of relapse events in accordance to mutation type

J Clin Oncol. 2005;23(25):6190-8

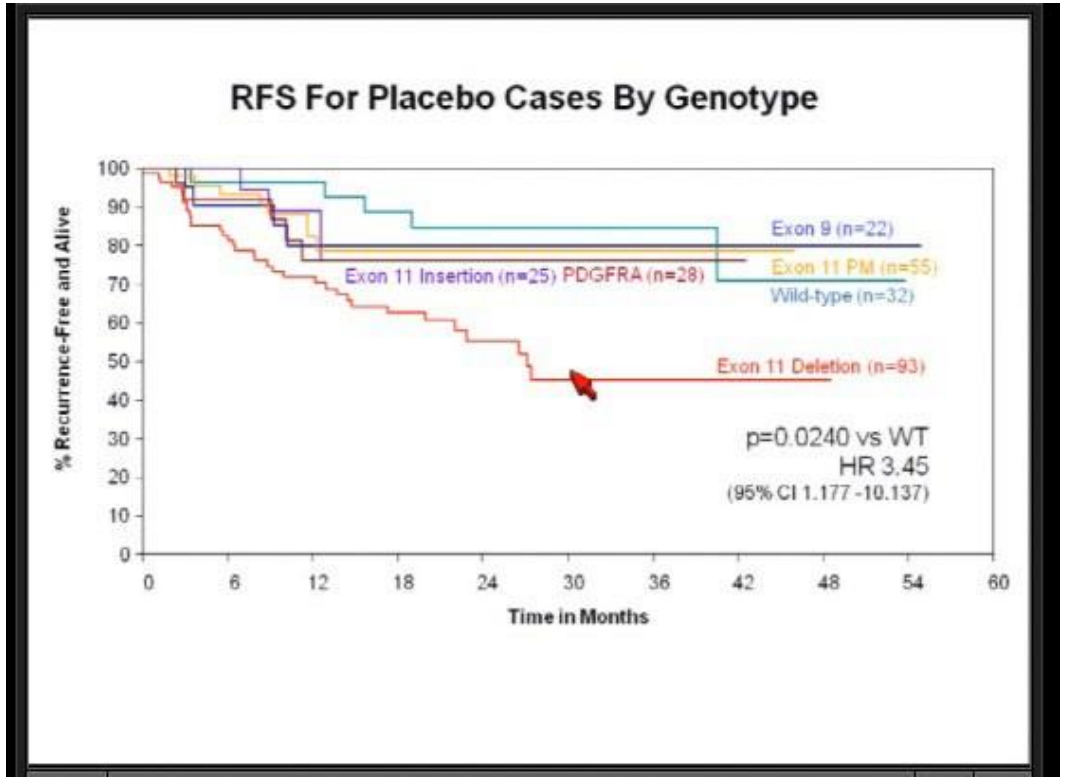
Genotype as prognostic for RFS





J Clin Oncol. 2005;23(25):6190-8

Genotype as prognostic for RFS

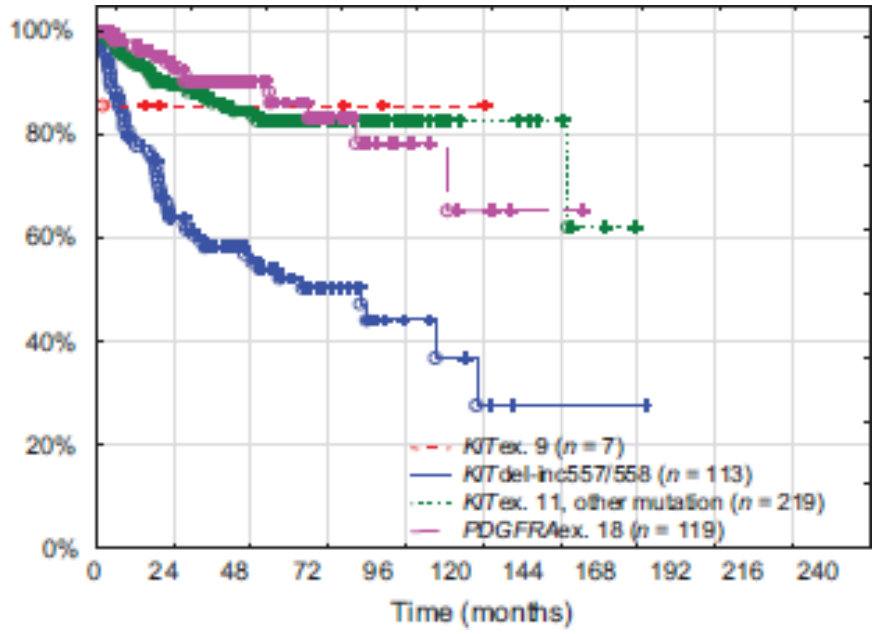


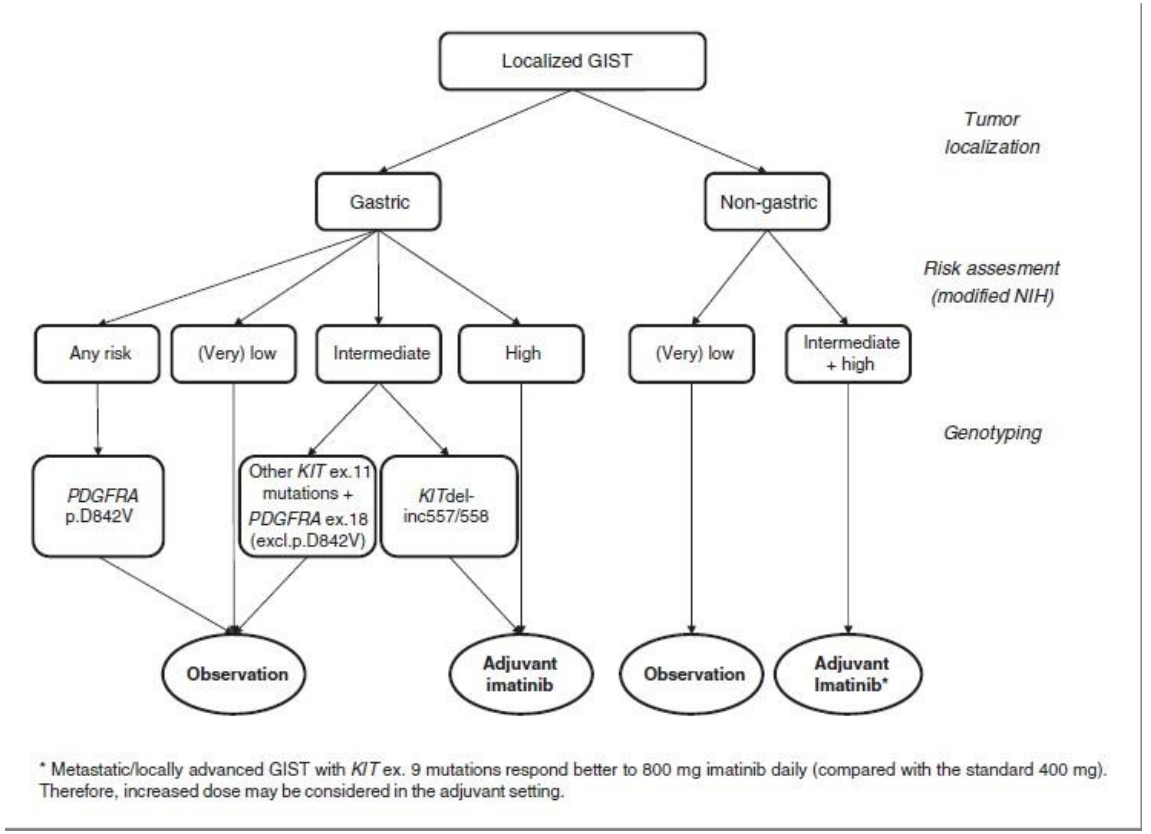
Multivariate Analyses For Recurrence Risk
Placebo Group

	p value	Hazard Ratio	(95% CI)
Mitotic rate			
<5/50 hpf			
≥5/50 hpf	<0.0001	17.07	(6.620, 44.043)
Genotype			
WT	----	----	
Exon 9	0.45	1.74	(0.413, 7.359)
Exon 11	0.042	2.97	(1.307, 8.537)
PDGFRA	0.255	2.30	(0.547, 9.722)
Tumor location			
Stomach	----	----	
Small intestine	0.0267	2.08	(1.089, 4.001)
Rectum	0.7895	1.31	(0.178, 9.681)
Tumor size			
<5 cm			
>5-10 cm	0.0026	1.70	(1.203, 2.402)
>10 cm			

J Clin Oncol 28:15s, 2010 (suppl; abstr 10006)

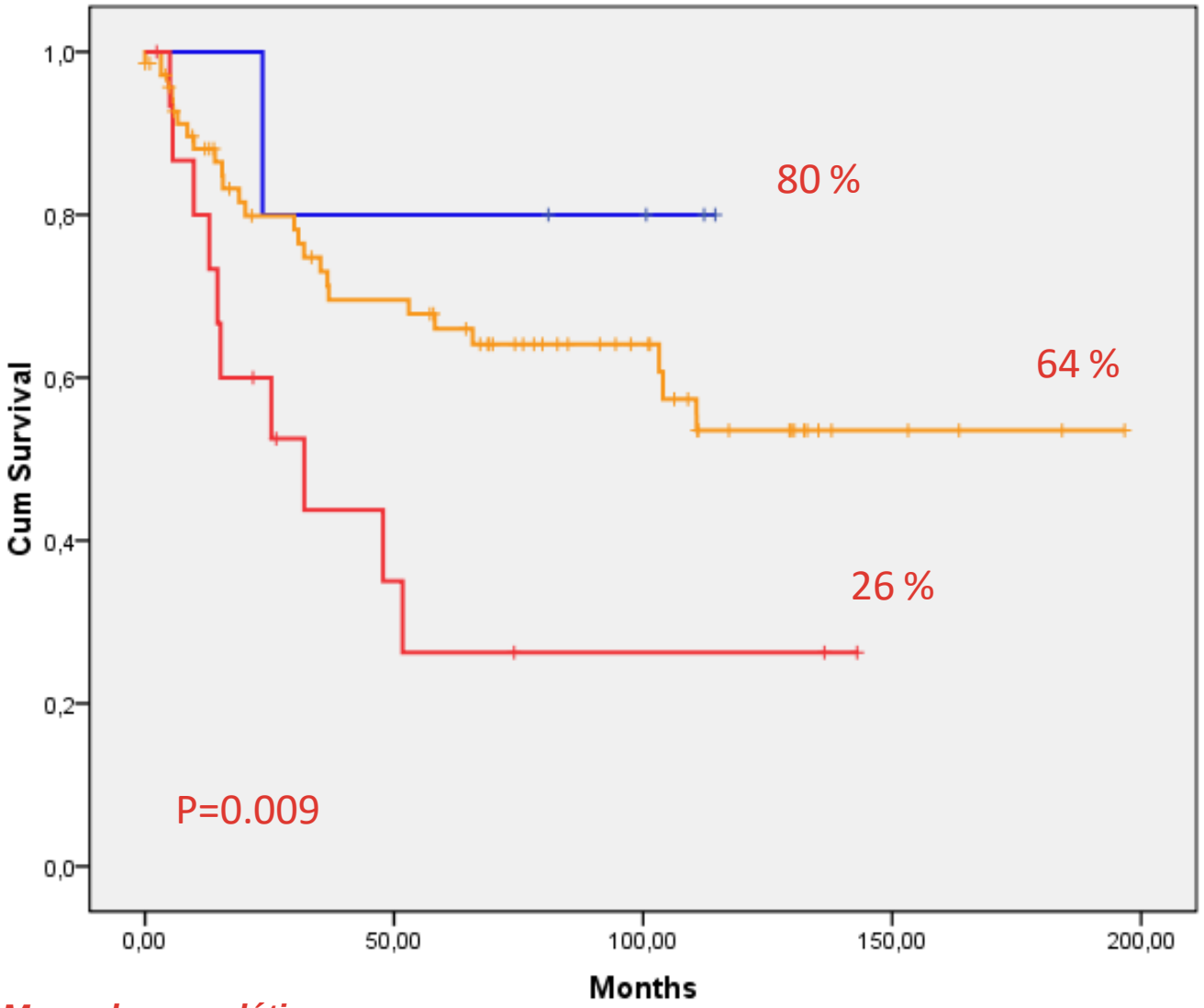
Genotype as prognostic for RFS





Agnieszka Wozniak et al, Clin Cancer Res 20(23), 2014

Integrating genotype in the risk assessment



PDGFRa mut

Other

Del 557/558 mut

KIT and PDGFRa MUT in GIST
Small GIST

Genotype	Small GISTs	Overt GISTs	p
Mutant	74%	84%	0.078
KIT exon 11	46%	61%	0.025

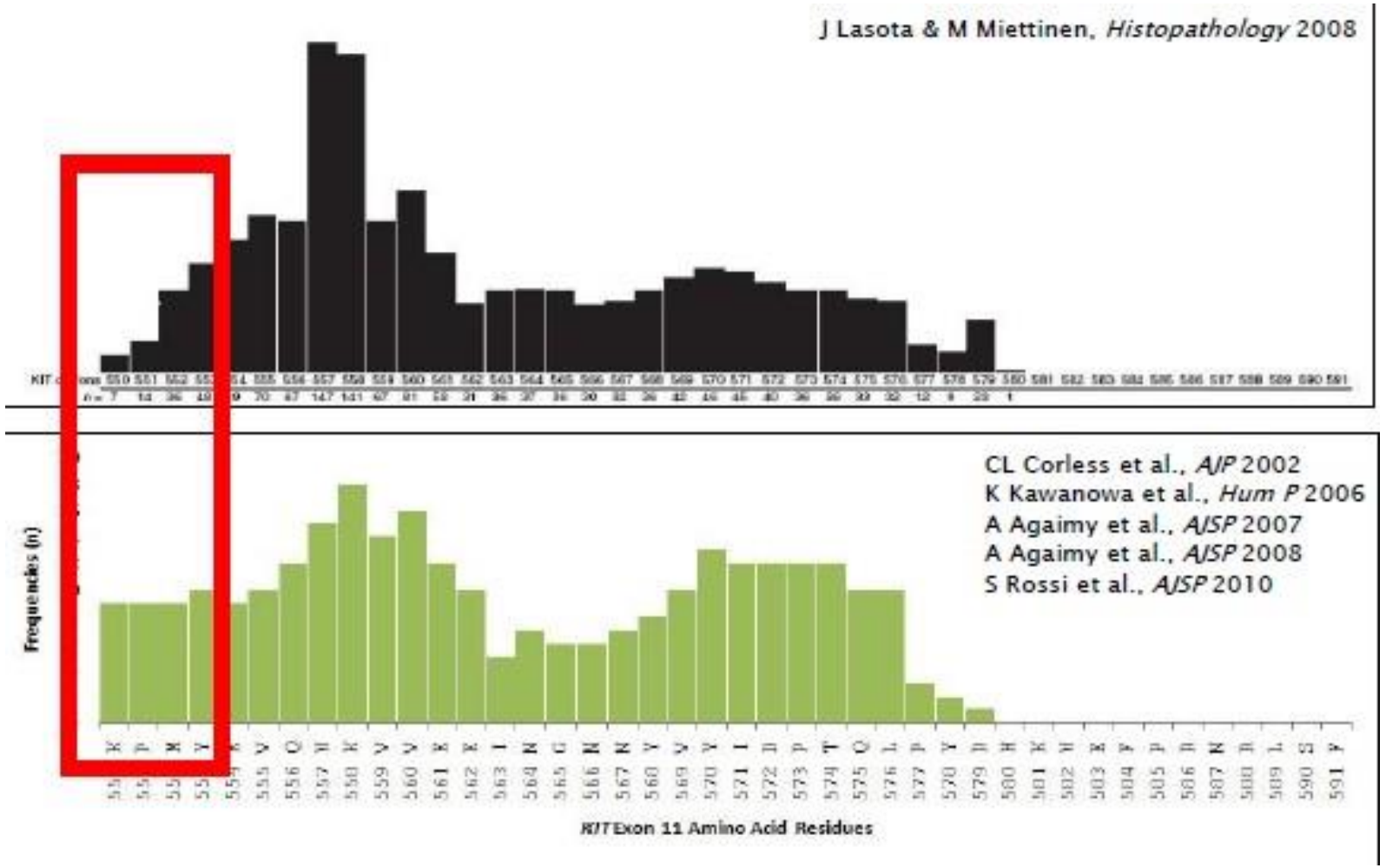
S Rossi, Am J Surg Pathol. 2011;35

ETIO-
PATHO
GENIC

KIT and PDGFRa MUT in GIST
Micro GIST (< 1 cm)

CLINICAL GIST

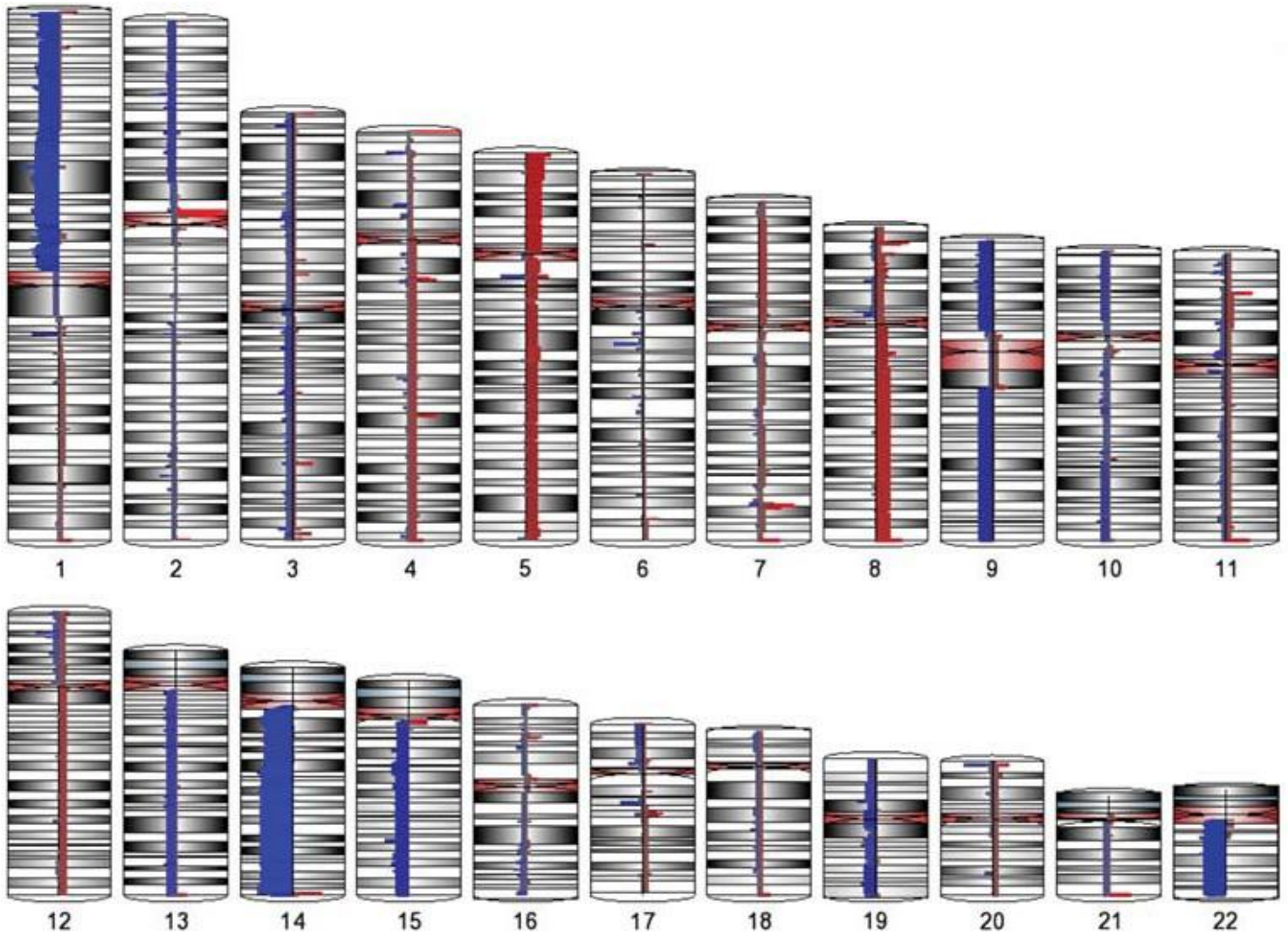
MICRO GIST



ETIO-
PATHO
GENIC

GIST GENETIC PROGRESSION

KIT or *PDGFRa* mutations 14q→ 22q→1p



A Astolfi, Lab Invest 90, 2010

ETIO-
PATHO
GENIC

GENE COPY NUMBER ABERRATIONS

	n	14q	22q	1p	Other	Potential gene Targets
SF Schoppmann Clin Cancer Res, 2013	29	59%	38%	45%	5q gain 15q loss	SYNE2 (14q)
A Astolfi Lab Invest 90, 2010	25	68%	40%	56%	5q gain 15 q loss	RTN1 (14q)
B Gunawan J Pathol 211, 2007	151	70%	46%	53%	15q loss 13q loss	
A Ylipaa Cancer 117, 2011	42	65%	84%	53%	15q loss 8q gain	OXA1L (14q)

PROG
NOSTIC

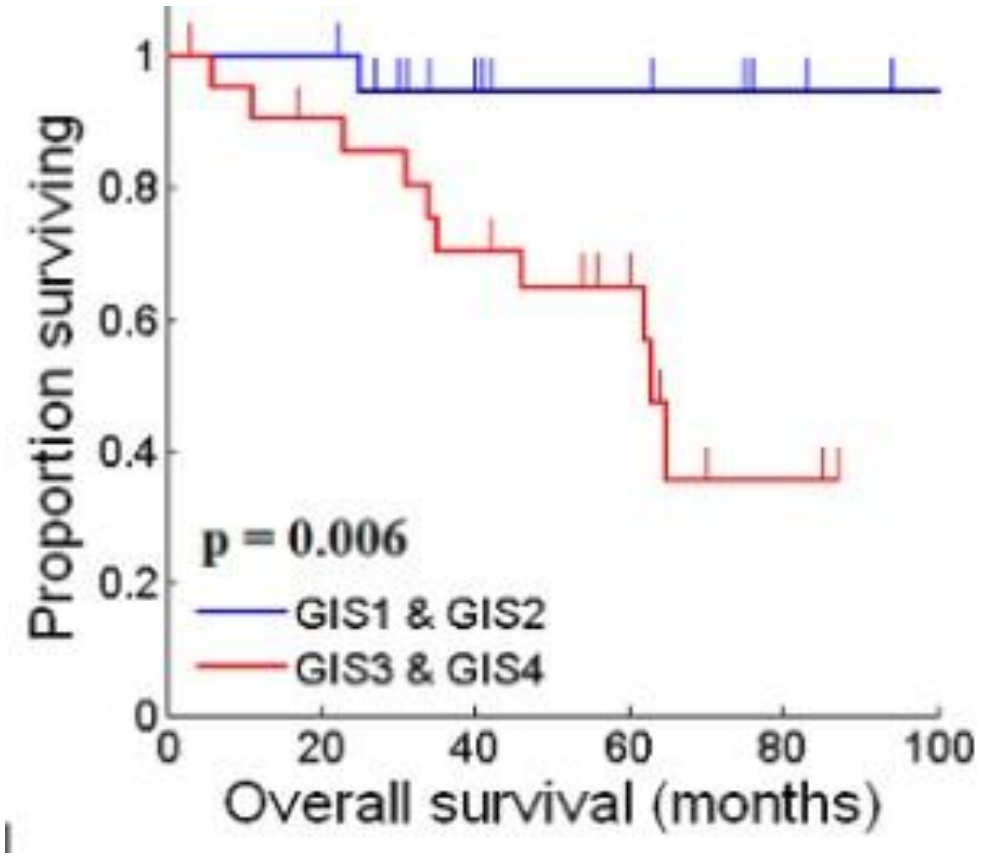
GENOMIC INSTABILITY

1
- Loss 1p distal
- Loss 19q and 22q

2
- Loss 14q

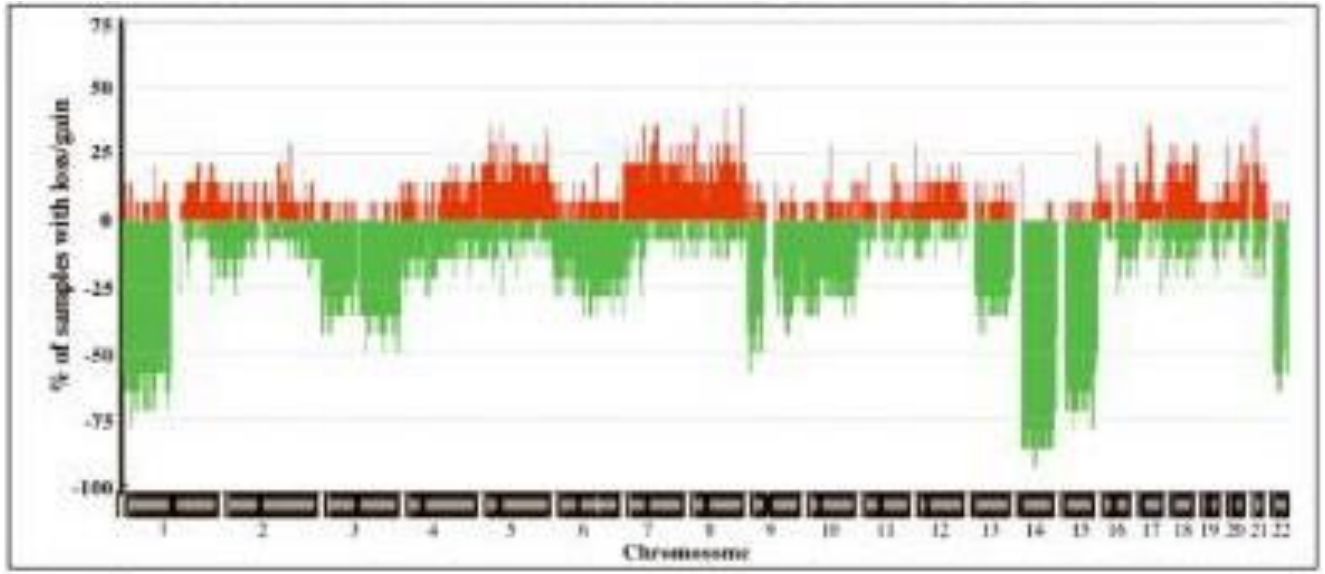
3
- Loss of 1p proximal
- Loss 15q

4
- Loss of 10p

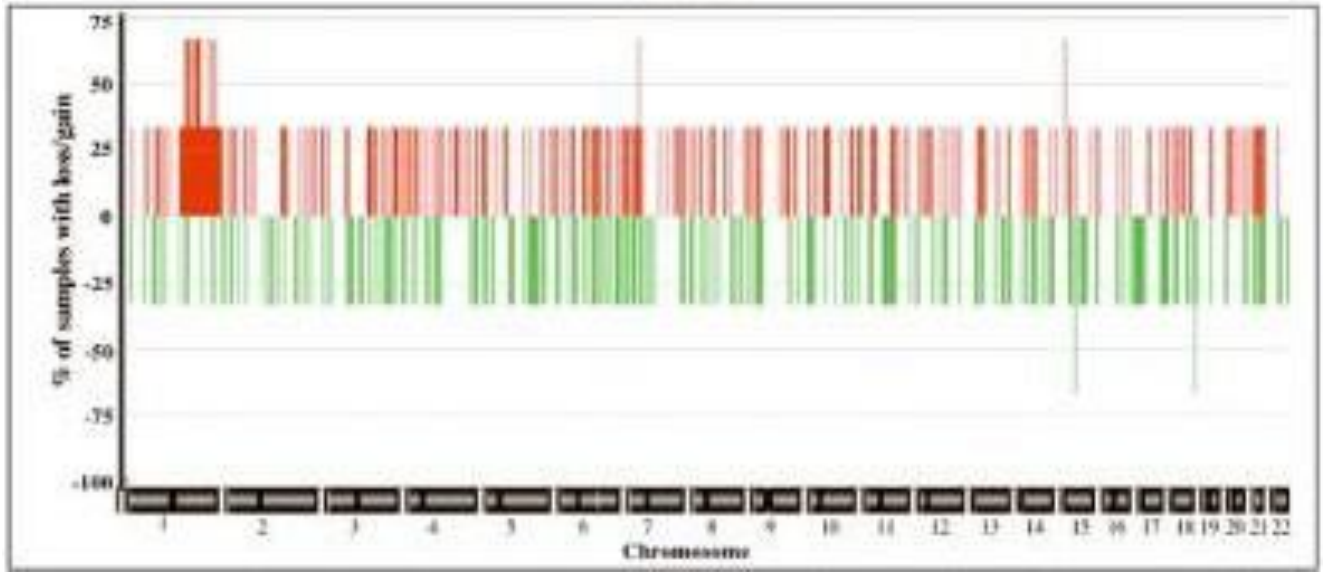


A Ylipaa, Cancer, 117, 2011

MUTATED GIST



WILD TYPE GIST



M Belinsky, Genes Chromosomes Cancer.48, 2009.

Conclusions

- Nomogram (heat maps) is the most precise prognostic risk information we have for localized GIST.
- Size, Mitotic count and Location are the relevant prognostic factors in localized GIST.
- Genotype has a prognostic role in localized disease. Critical mutations in intermediate risk positions patients into high-risk group
- Multinational efforts are being made to analyze if molecular biomarkers can be included in risk classification.

GRACIAS

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