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Risk-Stratification Models in Localised GIST: Making sense of them all

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care
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Disclosures

- I have no disclosures

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Content

- Introduction
- Current risk-stratification models

 - established systems

 - rarely-used systems
- Comparison between risk-stratifications models
- Discussion
- Conclusion

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Introduction

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- Gastrointestinal stromal tumors (GISTs) have varying malignant potentials

- Complete surgical resection is the treatment of choice

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Introduction

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Why is accurate prognostication of GIST after surgical resection important?

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Introduction

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1. Appropriate patient counselling

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Introduction

Singapore General Hospital SingHealth

1. Appropriate patient counselling
2. Determination of intensity of postoperative surveillance

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Introduction

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1. Appropriate patient counselling
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3. Selection of patients for adjuvant treatment:

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1. Appropriate patient counselling
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High risk patients:

- Adjuvant imatinib improves recurrence-free survival
- Patients with a high recurrence risk have a longer survival with 3 years vs 1 year of adjuvant imatinib

Introduction

1. Appropriate patient counselling
2. Determination of intensity of postoperative surveillance
3. Selection of patients for adjuvant treatment:

High risk patients:

- Adjuvant imatinib improves recurrence-free survival
- Patients with a high recurrence risk have a longer survival with 3 years vs 1 year of adjuvant imatinib

Low risk patients:

- Many GIST patients are cured after surgery without the need for adjuvant treatment
- Imatinib is generally well-tolerated but still has a high rate of adverse effects
- Imatinib is costly

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Introduction

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- Today - **established prognostic factors** for GIST include:

1. Tumor size
2. Mitotic count
3. Site: gastric vs non-gastric

Introduction

- Today - **established prognostic factors** for GIST include:

1. Tumor size
2. Mitotic count
3. Site: gastric vs non-gastric

- Other prognostic factors include:

1. Tumor rupture
2. Sex
3. Epitheloid subtype, necrosis
4. Mutations eg. *KIT* exon 11
5. Other biomarkers

- Several risk-stratification models are available for localized GIST today

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Risk-stratification models

NIH criteria, 2002 (Fletcher)

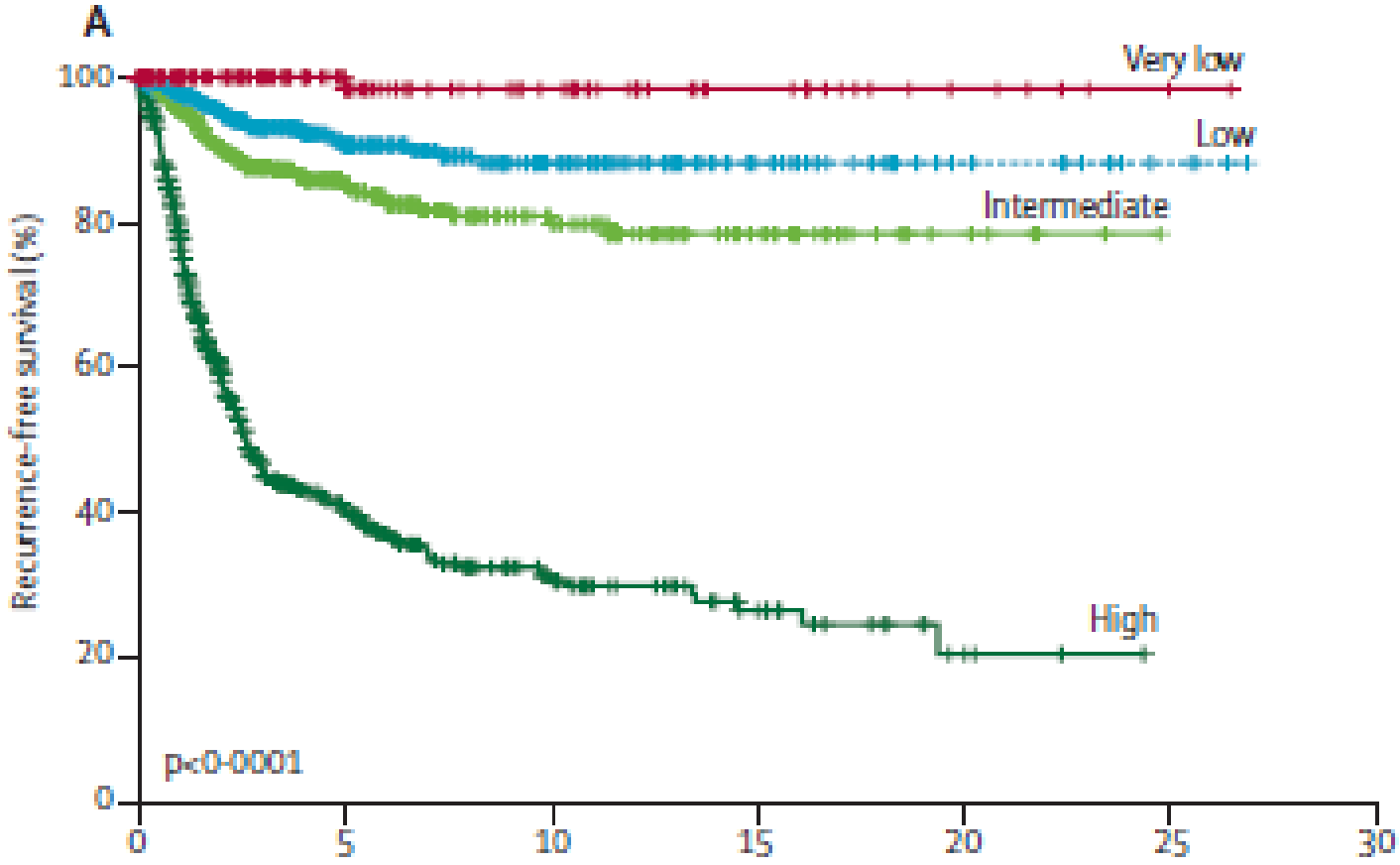
Hum Pathol 2002;33:459

- developed empirically
- workgroup consensus opinion
- Based on tumor size, mitotic count
- Not based on statistical validation
- Subsequently validated in numerous studies

Risk criteria	Tumor size (cm)	Mitotic count (per 50 HPFs)	Primary tumor site
NIH consensus criteria 2002 *(2001)*			
Very low risk	<2	<5	Any
Low risk	≥2<5	<5	Any
Intermediate risk	<5	5-10	Any
	5-10	<5	Any
High risk	≥5	≥5	Any
	>10	Any	Any
	Any	>10	Any

Validation of NIH (Fletcher) criteria

Joensuu. Lancet Oncol 2012;13:265, n = 2560



Number at risk							
Very low risk	130	59	33	16	6	1	0
Low risk	429	164	74	32	12	4	0
Intermediate risk	395	161	71	29	6	0	0
High risk	554	122	47	20	4	0	0

NIH-Miettinen criteria, 2002

Hum Pathol 2002;33:478

- developed empirically
- Workgroup consensus opinion
- Based on tumor size, mitotic count, **site**
- Not based on statistical validation

Risk criteria	Tumor size (cm)	Mitotic count (per 50 HPFs)	Primary tumor site
NIH-Miettinen criteria			
Probably benign	≤5 ≤2	≤5 ≤5	Gastric Intestinal
Uncertain	>5 ≤10 >2 ≤5	≤5 ≤5	Gastric Intestinal
Probably malignant	>10 >5	>5 >5	Gastric Intestinal

AFIP criteria, 2006 (Miettinen)
NCCN 2007

Semin Diagn Pathol 2006;23:70, Am J Surg Pathol 2006;30:477, Am J Surg Pathol 2005;29:52, Am J Surg Pathol 2003;27:625, Am J Surg Pathol 2001;25:1121

- Modification of NIH-Miettinen
- Based on size, mitotic count and **site**
- Formulated based on findings from several previously published studies
- 1055 gastric, 906 jejunum/ileum, 156 duodenum, 144 colorectal,
- No statistical validation
- 4-tier, 15 subcategories

Tumor Parameters			Percent of patients with progressive disease during long-term follow-up and characterization of risk for metastasis			
Group	TumorSize	MitoticRate	Gastric GISTs	Jejunal and Ileal GISTs	Duodenal GISTs	Rectal GISTs
1	≤2 cm	≤5-/-50-HPFs	0% none	0% none	0% none	0% none
2	>2 cm ≤5 cm	≤5-/-50-HPFs	1.9% very low	4.3% low	8.3% low	8.5% low
3a	>5 cm ≤10cm	≤5-/-50-HPFs	3.6% low	24% moderate	34% high ‡	57% high ‡
3b	>10 cm	≤5-/-50-HPFs	12% moderate	52% high		
4	≤2 cm	>5 / 50 HPFs	0% †	50% †	§	54% high
5	>2 cm ≤5 cm	>5 / 50 HPFs	16% moderate	73% high	50% high	52% high
6a	>5 cm ≤10cm	>5 / 50 HPFs	55% high	85% high	86% high	71% high ‡
6b	>10 cm	>5 / 50 HPFs	86% high	90% high		

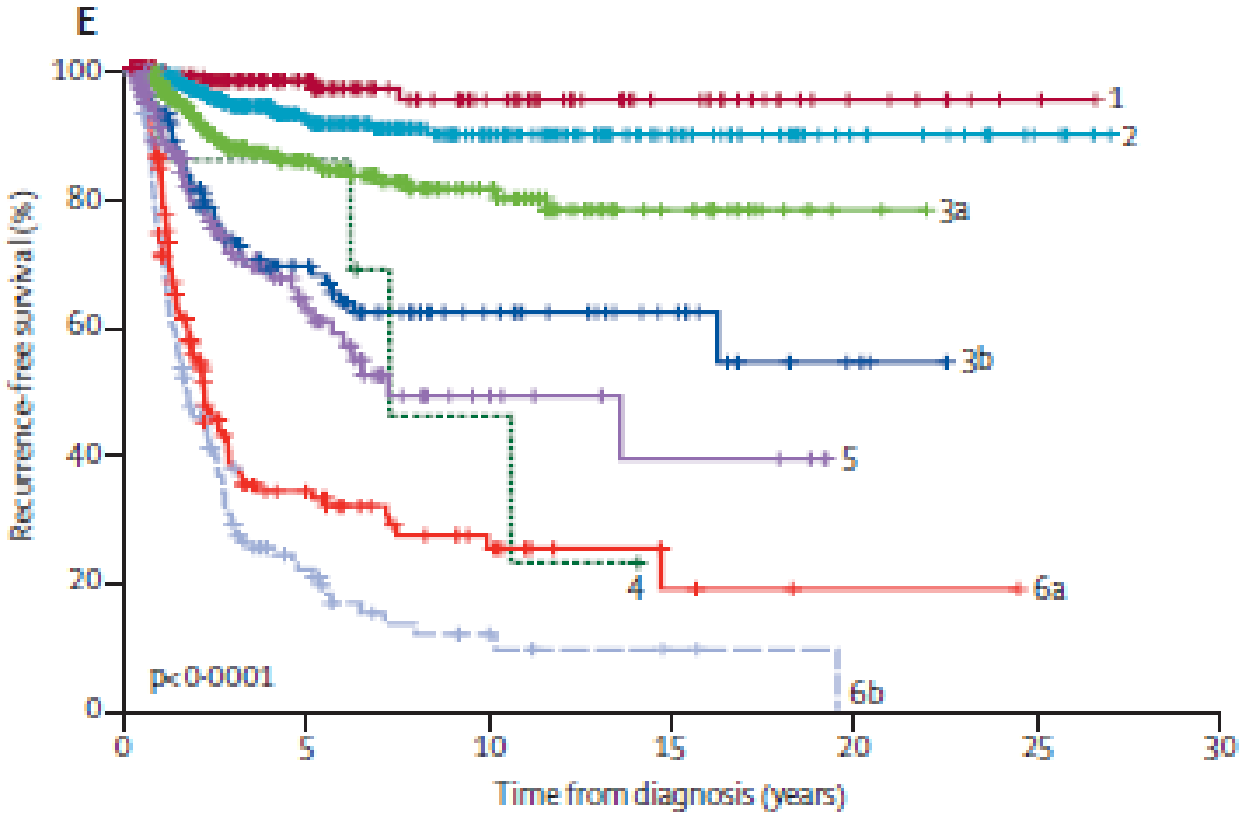
† denotes tumor categories with very few cases

‡ Groups 3a and 3b, 6a and 6b are combined in duodenal and rectal GISTs because of small number of cases.

Risk criteria	Tumor size (cm)	Mitotic count (per 50 HPFs)	Primary tumor site
AFIP criteria 2006			
Very low risk	≤2	≤5	Any
	>2≤5	≤5	Gastric
Low risk	>2≤5	≤5	Non-gastric
	>5≤10	≤5	Gastric
	≤2	>5	Gastric
Intermediate risk	>10	≤5	Gastric
	>2≤5	>5	Gastric
	>5≤10	≤5	Non-gastric
High risk	>10	≤5	Non-gastric
	≤2	>5	Non-gastric
	>2≤5	>5	Non-gastric
	>5≤10	>5	Any
	>10	>5	Any

Validation of AFIP (NCCN) criteria

Joensuu. Lancet Oncol 2012;13:265, n = 2560



Number at risk							
Group 1	186	78	44	22	8	1	0
Group 2	430	173	78	34	14	5	0
Group 3a	278	114	54	20	2	0	0
Group 3b	130	49	23	12	3	0	0
Group 4	8	5	2	0	0	0	0
Group 5	113	35	8	4	0	0	0
Group 6a	177	30	11	3	1	0	0
Group 6b	145	17	4	2	1	0	0

Modified NIH criteria, 2008 (Joensuu)

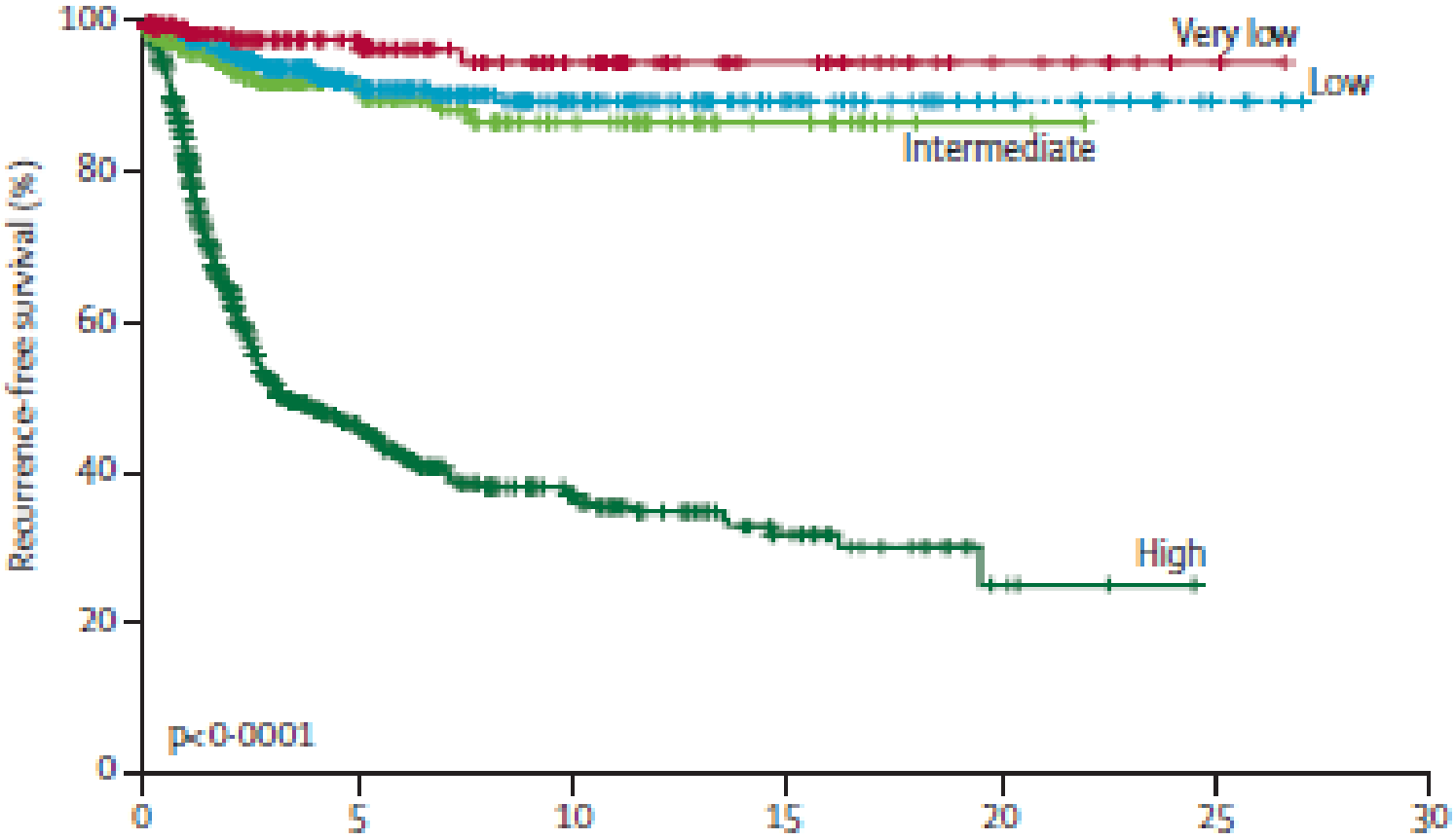
Hum Pathol 2008;39:1411

- formulated based on personal opinion
- Based on mitotic count, size, site and **rupture**
- No statistical validation
- 4 risk categories
- Very low, low and intermediate risk had excellent outcomes
- Essentially 2 risk categories

Risk criteria	Tumor size (cm)	Mitotic count (per 50 HPFs)	Primary tumor site
Joensuu criteria (modified NIH criteria) 2008			
Very low risk	≤2	≤5	Any
Low risk	>2≤5	≤5	Any
Intermediate risk	>2≤5	>5≤10	Gastric
	≤2	>5≤10	Any
	>5≤10	≤5	Gastric
High risk	Any	Any	Tumor rupture
	>10	Any	Any
	Any	>10	Any
	>5	>5	Any
	>2≤5	>5	Non-gastric
	>5≤10	≤5	Non-gastric

Validation of mNIH (Joensuu) criteria

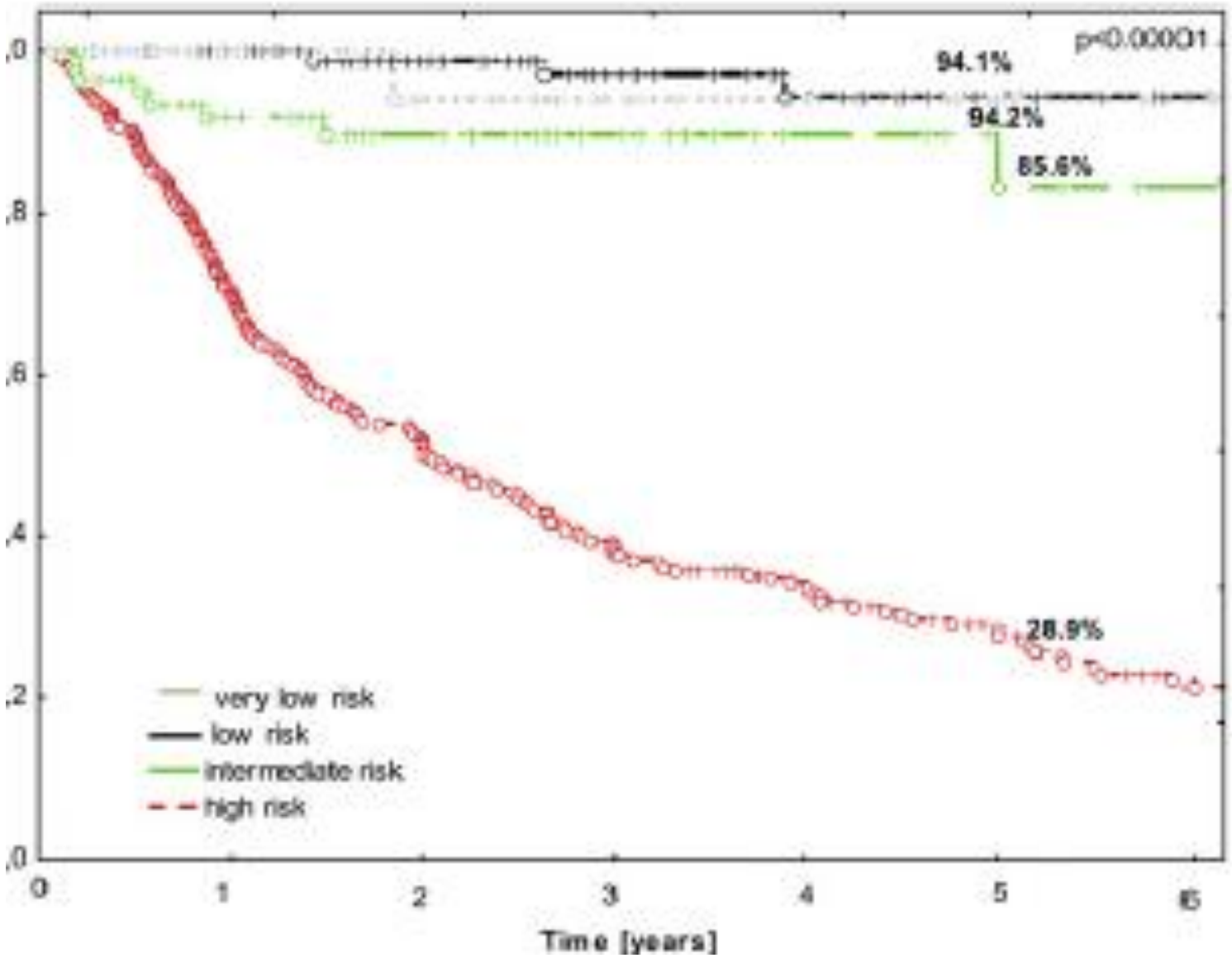
Joensuu. Lancet Oncol 2012;13:265, n = 2560



Number at risk							
Very low risk	180	77	43	22	8	1	0
Low risk	435	174	79	34	14	4	0
Intermediate risk	205	86	34	14	2	0	0
High risk	694	171	69	27	4	0	0

Validation of mNIH (Joensuu) criteria

Rutkowski. EJSO 2011;37:890, n = 640



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MSKCC nomogram

Lancet Oncol 2009;10:1045

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- Formulated based on 127 patients from MSKCC
- Median FU 4.7 years
- Validated – 2 cohorts: Spanish Group for Research on Sarcomas (GEIS) (n=212) and the Mayo Clinic (Mayo) (n=148)
- Predictive factors: **mitotic count (categorical)**, size, site
- Rupture not significant (small numbers)
- Nomogram constructed (continuous, nonlinear)

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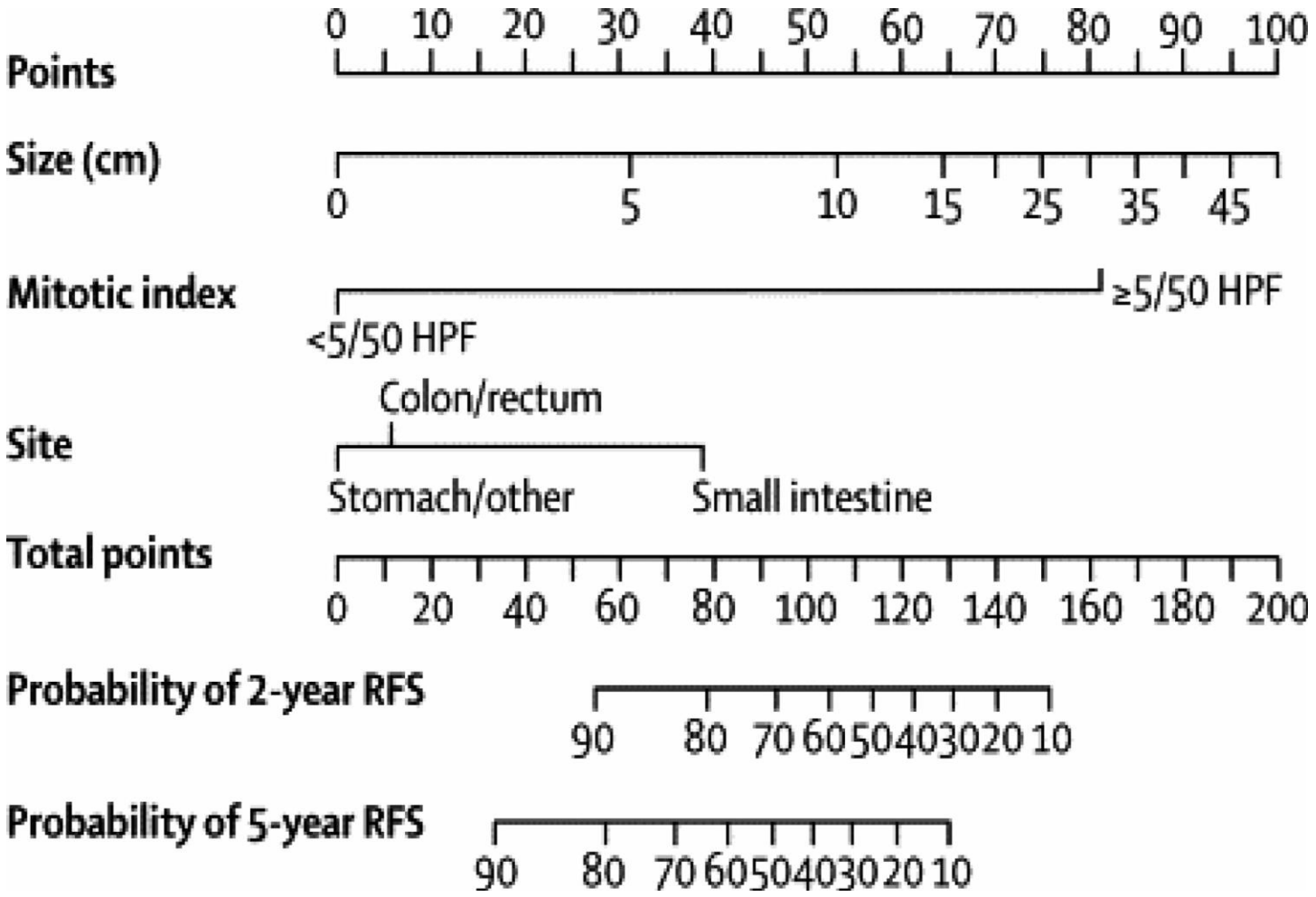
MSKCC Nomogram

Singapore General Hospital SingHealth



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MSKCC nomogram

Lancet Oncol 2009;10:1045

Singapore General Hospital SingHealth

- MSKCC nomogram compared to NIH, AFIP and NIH-Miettinen

- Nomogram significantly superior to NIH and NIH-Miettinen not AFIP

	Nomogram	NIH-Fletcher		NIH-Miettinen		AFIP-Miettinen	
	Concordance	Concordance	p-value*	Concordance	p-value*	Concordance	p-value*
MSKCC	0.78 (±0.02)	0.72 (±0.03)	0.03	0.56 (±0.04)	<0.01	0.76 (±0.004)	0.33
GEIS	0.76 (±0.03)	0.70 (±0.04)	0.04	0.66 (±0.04)	0.01	0.73 (±0.004)	0.28
Mayo	0.80 (±0.02)	0.74 (±0.02)	0.04	0.78 (±0.02)	0.05	0.76 (±0.003)	0.09

Joensuu Contour map

Lancet Oncol 2012;13:265

- Observation cohort study- derived from published population-based studies
- Assess prognostic factors of RFS in resectable GISTs
- Pooled analysis of **2560** patients from 10 studies
- Median overall survival 12.4 years
- Validation in 920 patients from Italy

	Time period	Number of patients	Sex: male	Median age at diagnosis in years (range)	Patients or tumours with data available					
					Tumour size	Mitotic count	Tumour site	Tumour rupture	RFS	Overall survival
Population-based series										
Modena, Italy[9]	1988–2010	157	90 (57·3%)	67 (25–90)	148 (94·3%)	148 (94·3%)	157 (100%)	0	156 (99·4%)	157 (100%)
Iceland[18]	1990–2003	50	29 (58·0%)	68 (24–89)	49 (98·0%)	50 (100%)	50 (100%)	49 (98·0%)	50 (100%)	50 (100%)
South Switzerland[20]	1999–2009	63	36 (57·1%)	67 (31–96)	61 (96·8%)	57 (90·5%)	63 (100%)	0	62 (98·4%)	63 (100%)
Ancona, Italy[21]	1987–2006	72	35 (48·6%)	62 (30–92)	72 (100%)	72 (100%)	72 (100%)	0	72 (100%)	72 (100%)
Western Sweden[16]	1971–2001	231	116 (50·2%)	68 (19–92)	231 (100%)	231 (100%)	231 (100%)	0	231 (100%)	231 (100%)
Northern Norway[15]	1971–2003	457	238 (52·1%)	67 (23–94)	336 (73·5%)	457 (100%)	430 (94·1%)	0	0	457 (100%)
Poland[12]	1981–2010	580	271 (46·7%)	60 (9–89)	566 (97·6%)	528 (91·0%)	580 (100%)	543 (93·6%)	580 (100%)	580 (100%)
Osaka, Japan[13]	1972–2009	474	251 (53·0%)	63 (10–93)	465 (98·1%)	408 (86·1%)	474 (100%)	470 (99·2%)	474 (100%)	474 (100%)
Slovak Republic[22]	1996–2010	224	104 (46·4%)	62 (20–94)	211 (94·2%)	81 (36·2%)	224 (100%)	136 (60·7%)	0	149 (66·5%)
Czech Republic[22]	1993–2010	252	133 (52·8%)	60 (14–90)	239 (94·8%)	227* (90·1%)	251 (99·6%)	0	0	226 (89·7%)
Total	1971–2010	2560	1303 (50·9%)	63 (9–96)	2378 (92·9%)	2259† (88·2%)	2532 (98·9%)	1198 (46·8%)	1625 (63·5%)	2459 (96·1%)
Validation series										
Italy	1980–2000	920	520 (56·5%)	66 (12–95)	903 (98·2%)	920 (100%)	920 (100%)	0	920 (100%)	909 (98·8%)

Data are number (%) unless otherwise indicated. RFS=recurrence-free survival. *Only categorised data available. †Mitosis count available both as a continuous and categorical variable for 1773 tumours, and as a categorical variable only for 486 tumours in the pooled series.

Table 1: **Characteristics of the series**

Joensuu Contour map

Lancet Oncol 2012;13:265

- Tumor size, mitotic count, location (gastric vs non-gastric vs EGIST), sex and rupture independent predictor of RFS
- Non-linear (GP-Cox models) were applied – prognostic heat maps and contour maps were produced using the above variables except sex

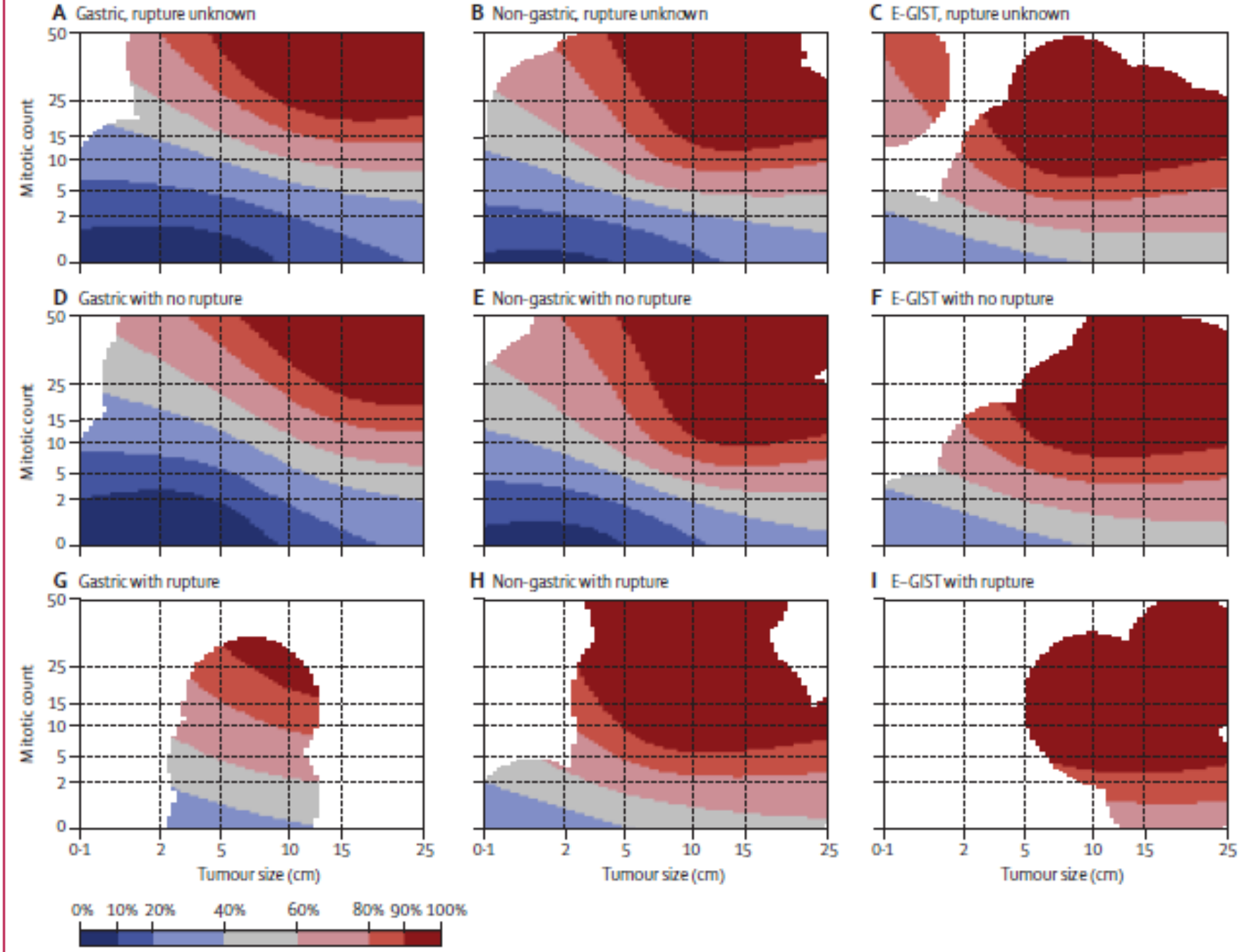


Figure 4: **Contour maps for estimating the risk of GIST recurrence after surgery**

Joensuu Contour map

Lancet Oncol 2012;13:265

- Comparison between the contour map vs NIH vs mNIH and AFIP in predicting 10-year RFS
- Contour map was the most accurate
- Same results for 5-year RFS

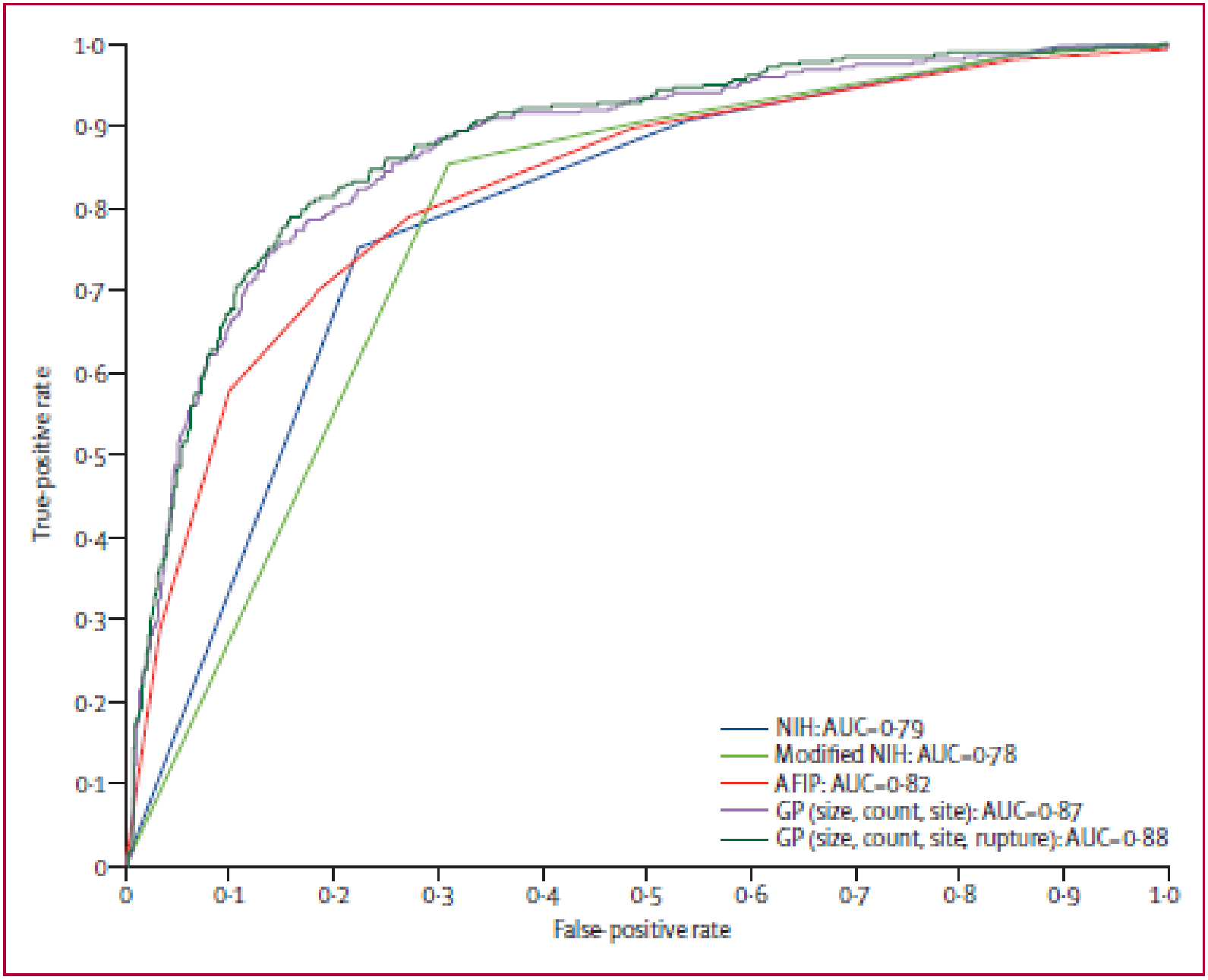


Figure 5: Receiver operating characteristic (ROC) analysis of the risk of GIST recurrence during the first 10 years of follow-up after surgery

Summary of 5 current prognostication systems (? most popular)

System	N	Variables	Type	Remarks
NIH ’02 Fletcher	Nil	size, mitot ct	Categorical	Consensus opinion
AFIP ’06 Miettinen	Nil	size, mitot ct, site (gastric vs nongastric)	Categorical	Consensus opinion
mNIH ’08 Joensuu	Nil	size, mitot ct, site, rupture	Categorical	Personal opinion
MSKCC ‘09	127	size, mitot ct, site	Continuous, nonlinear	Validated in 212 and 148 patients
Joensuu contour map ‘12	2560	size, mitot ct, rupture, site (gastric vs nongastric vs EGIST)	Continuous, nonlinear	Validated in 920 patients

OTHER RISK STRATIFICATION MODELS

Modified NIH system, 2007 (Huang)

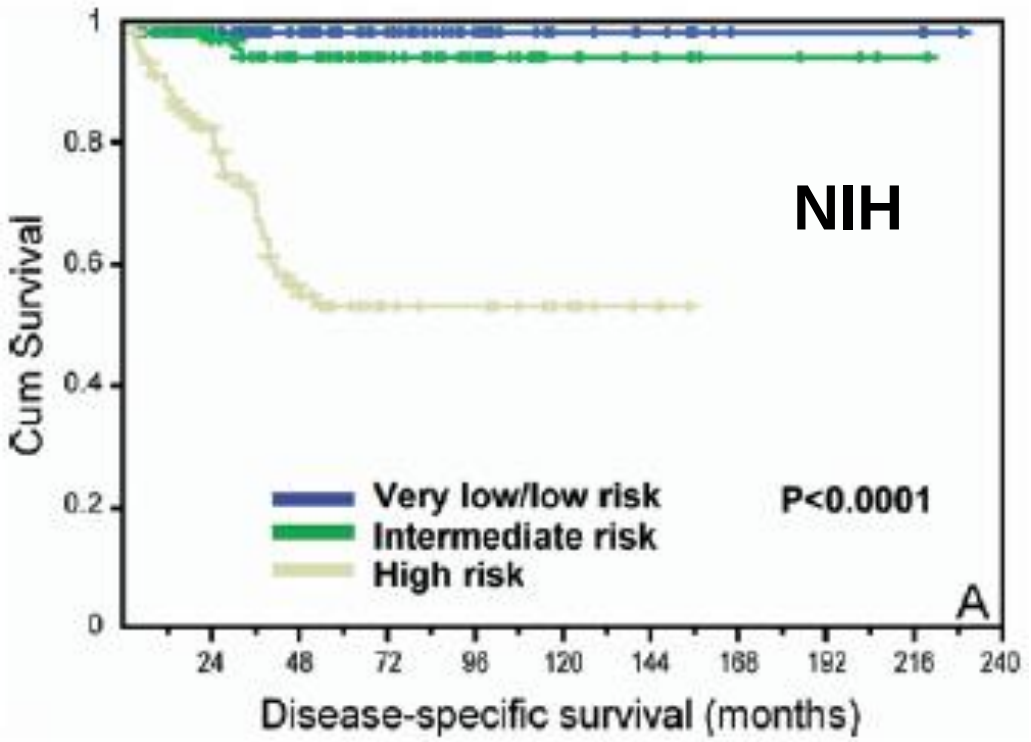
Surgery 2007;141:748

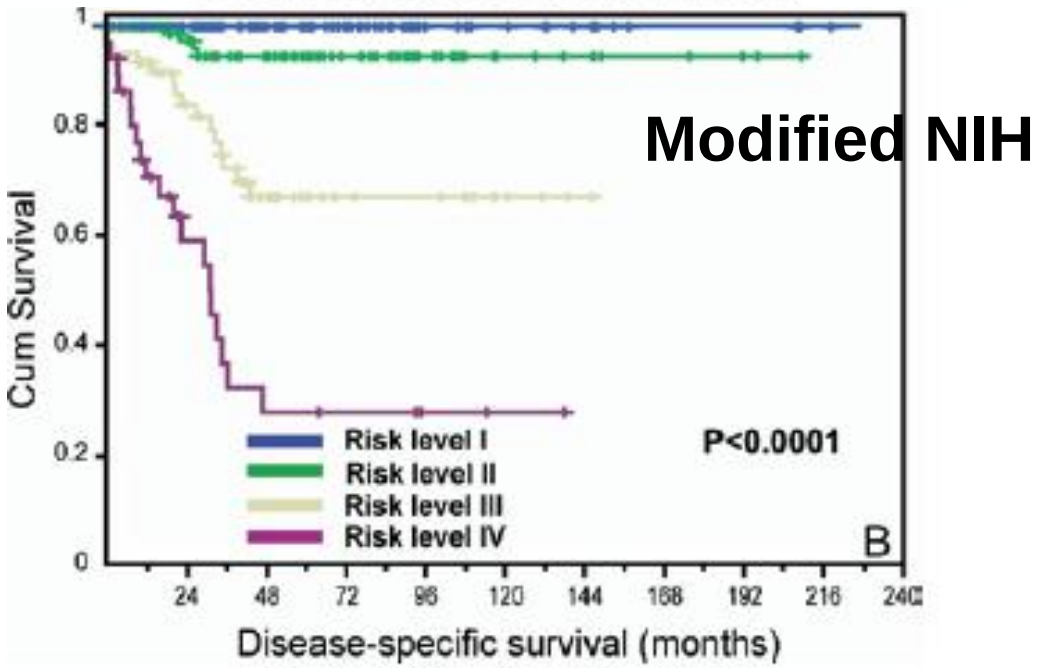
- 289 resected GISTs in Taiwan
- Modified NIH system
- Mitotic count and size
- Very low and low risk categories combined
- High risk: stratified into 2 groups

Table I. Criteria of the original vs modified NIH schemes to define aggressiveness of GISTs

Original NIH scheme	*Modified scheme*
Very low-risk	Risk level I
<2 cm, <5/50 HPF	≦5 cm, <5/50 HPF
Low-risk	
2-5 cm, <5/50 HPF	
Intermediate-risk	Risk level II
<5 cm, 6-10/50 HP	<5 cm, 6-10/50 HPF
5-10 cm, <5/50 HPF	5-10 cm, <5/50 HPF
High-risk	Risk level III
>5 cm, >5/50 HPF	≦5 cm, >10/50 HPF
>10 cm, any mitosis	5-10 cm, 6-10/50 HPF
any size, >10/50 HPF	>10 cm, <5/50 HPF
	Risk level IV
	>5 cm, >10/50 HPF

NIH, National Institutes of Health; *GIST*, gastrointestinal stromal tumor; *HPF*, high power field.


NIH
Cum Survival
1
0.8
0.6
0.4
0.2
0
Very low/low risk
Intermediate risk
High risk
P<0.0001
A
24
48
72
96
120
144
168
192
216
240
Disease-specific survival (months)

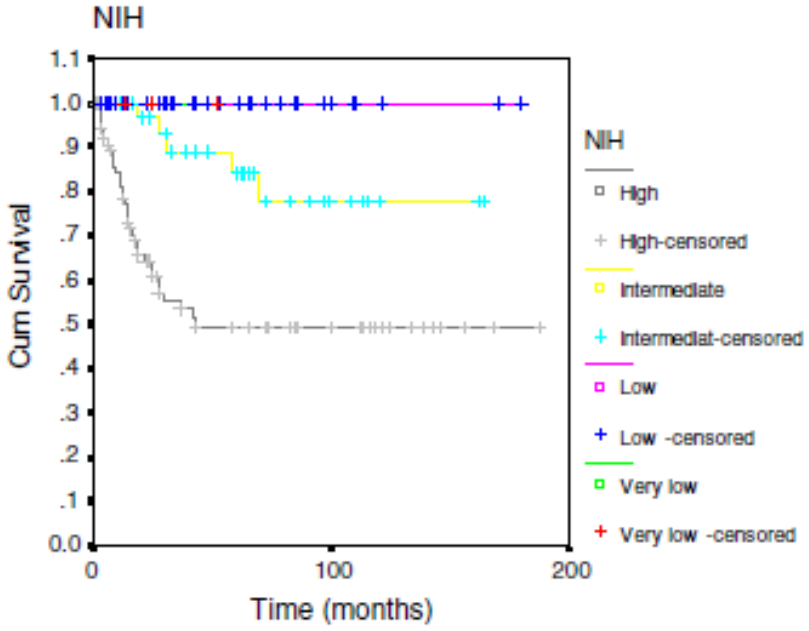

Modified NIH
Cum Survival
1
0.8
0.6
0.4
0.2
0
Risk level I
Risk level II
Risk level III
Risk level IV
P<0.0001
B
24
48
72
96
120
144
168
192
216
Disease-specific survival (months)

Modified AFIP criteria, 2008 (Goh)

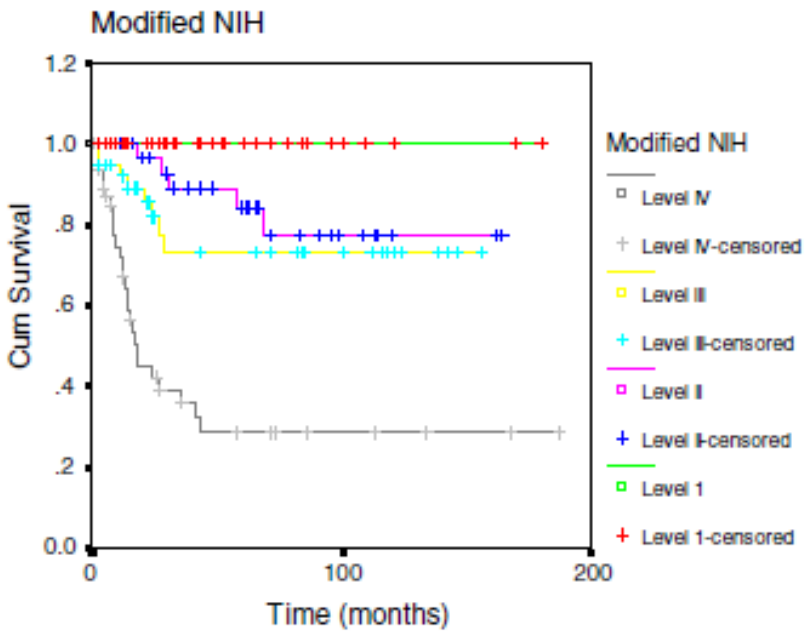
Ann Surg Oncol 2008;15(8):2153

- 171 resected GISTs in Singapore
- Modified AFIP system
- Mitotic count, size and **site**
- Very low and low risk categories combined
- High risk: stratified into 2 groups

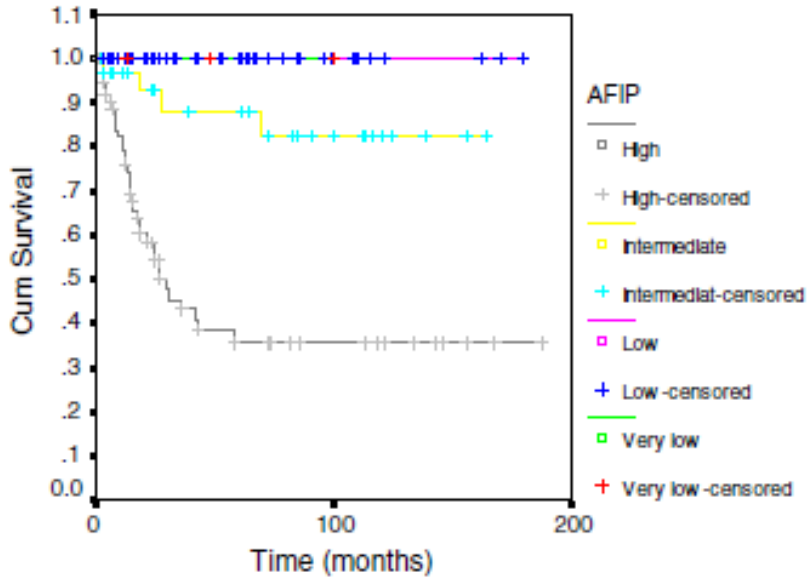
a) NIH



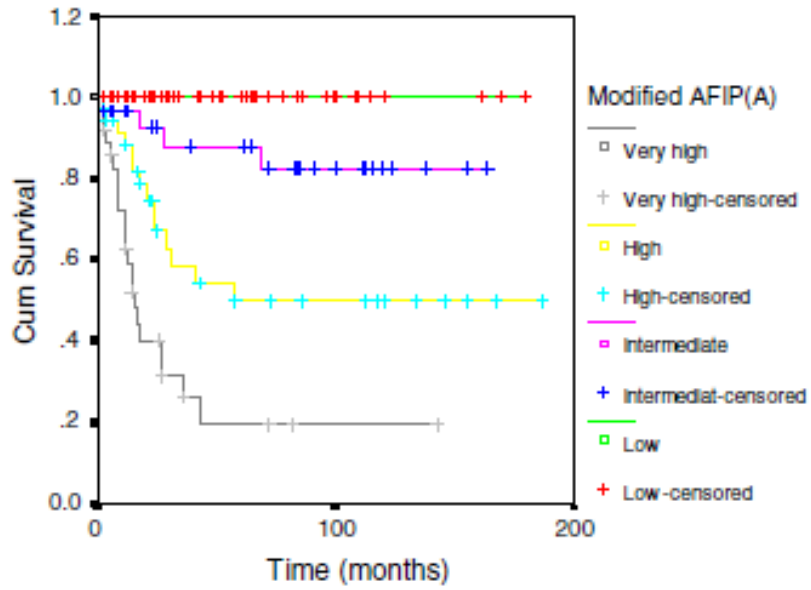
b) Modified NIH by Huang et al (10)



c) AFIP



d) Modified AFIP(A)



TGM system, 2009 (Woodall)

Arch Surg 2009;144:670-78.

- **Not restricted to localized GIST**
- Review of SEER database, USA – 2537 patients
- Median FU 21 months
- Size, grade and metastases
- No documentation of mitotic count in database
- TG – for localized GIST

Table 4. Proposed TGM Staging System for Gastrointestinal Stromal Tumors

Stage	T	G	M	No. (%) of Patients (n=1175)	*P* Value	HR (95% CI)
I	T1	G1	M0	187 (15.9)	. . .	1 [Reference]
II	T2	G1	M0	153 (13.0)	.08	1.61 (0.94-2.75)
III	Any T	G2	M0	196 (16.7)	<.001	4.09 (2.57-6.51)
IV	Any T	Any G	M1	639 (54.4)	<.001	6.73 (4.39-10.31)

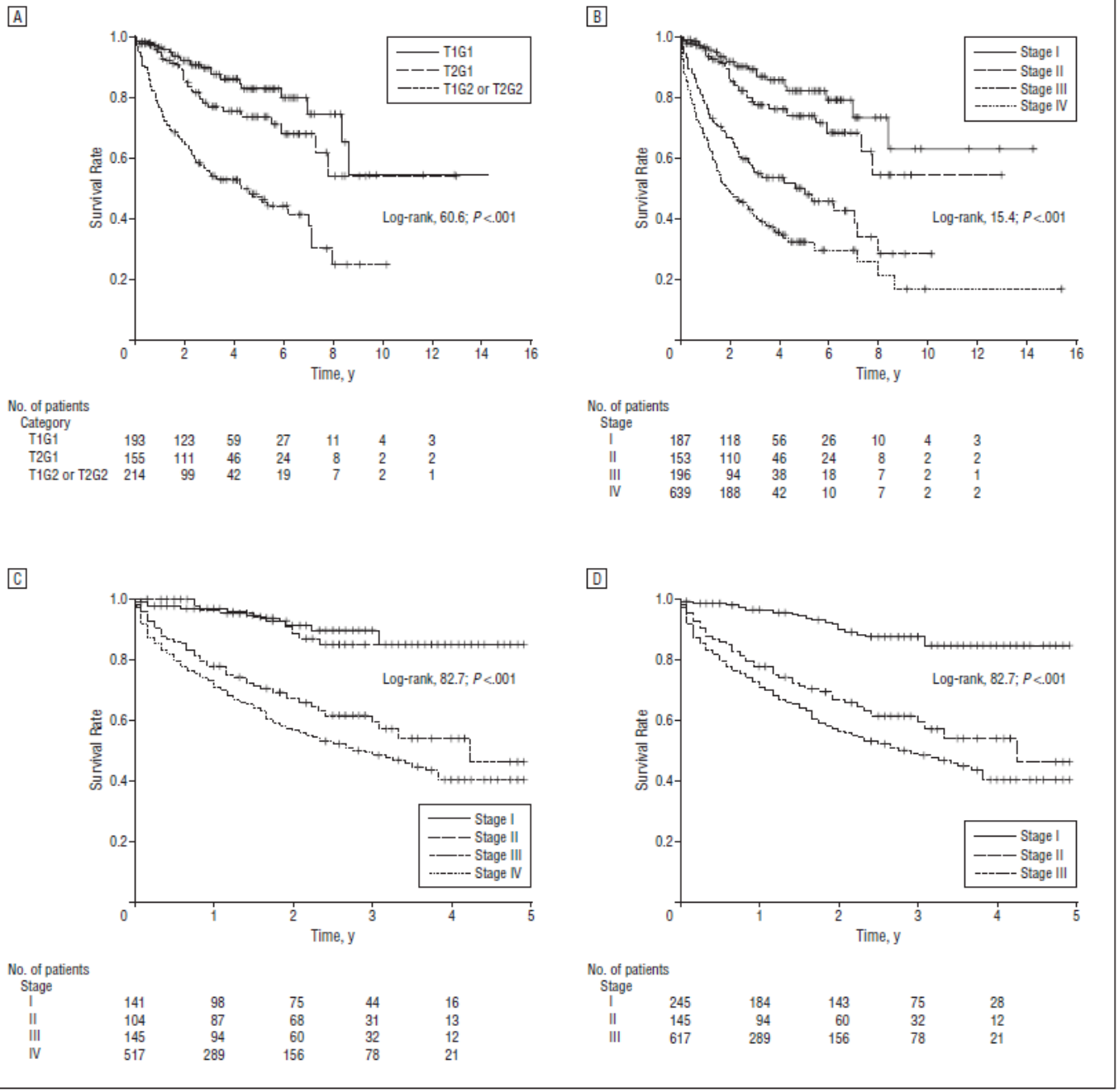


Figure 2. Kaplan-Meier survival curves for patients with gastrointestinal stromal tumors (GISTs). A, TG classification for patients without metastatic disease. B, TGM classification for all patients. C, TGM classification for patients diagnosed as having GISTs in 2000 or later. D, GM classification for patients diagnosed as having GISTS in 2000 or later.

AJCC, TNM 2010

AJCC 7th edition

- Adopted from the AFIP/NCCN system
- Translated into TNM
- Mitotic count, size, site, metastases/LN involvement

Primary Tumor (T)

TX: Primary tumor cannot be assessed

T0: no evidence for primary tumor

T1: tumor 2 cm or less

T2: tumor more than 2 cm but not more than 5 cm

T3: tumor more than 5 cm but not more than 10 cm

T4: tumor more than 10 cm in greatest dimension

Regional Lymph Nodes (N)

NX: regional lymph nodes cannot be assessed

N0: no regional lymph node metastasis

N1: regional lymph node metastasis

Distant Metastasis (M)

M0: no distant metastasis

M1: distant metastasis

Mitotic Rate

low mitotic rate: 5 or fewer per 50 HPF

high mitotic rate: over 5 per 50 HPF

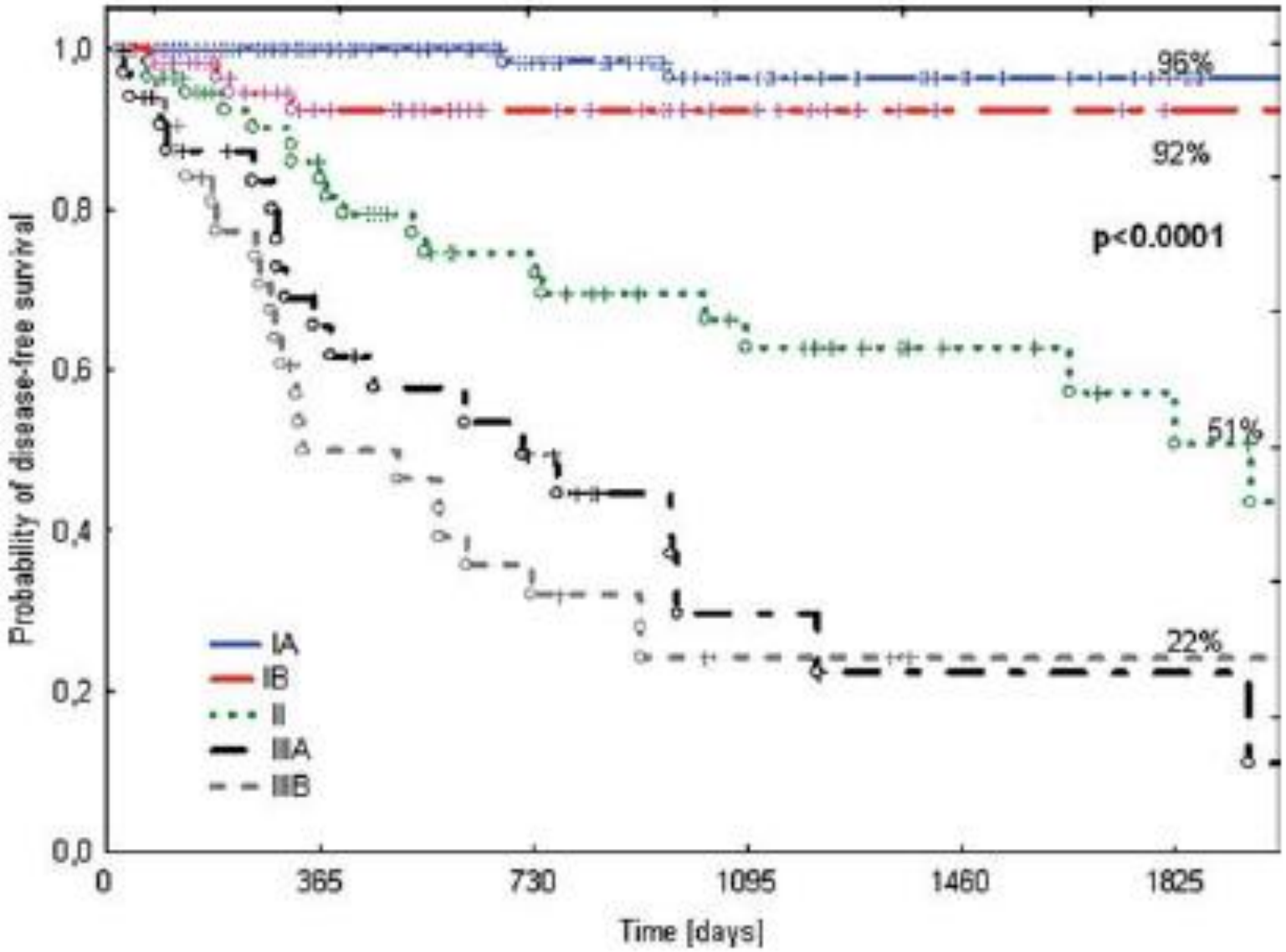
Gastric GIST * Group	T	N	M	Mitotic Rate
Stage IA	T1 or T2	N0	M0	low
Stage IB	T3	N0	M0	low
Stage II	T1 T2 T4	N0 N0 N0	M0	high high low
Stage IIIA	T3	N0	M0	high
Stage IIIB	T4	N0	M0	high
Stage IV	any T any T	N1 any N	M0 M1	any rate any rate

Small Intestinal GIST** Group	T	N	M	Mitotic Rate
Stage I	T1 or T2	N0	M0	Low
Stage II	T3	N0	M0	Low
Stage IIIA	T1 T4	N0 N0	M0 M0	High Low
Stage IIIB	T2 T3 T4	N0 N0 N0	M0 M0 M0	High High High
Stage IV	any T any T	N1 any N	M0 M1	any rate any rate

Validation of AJCC system

Rutkowski. Cancer 2011;1174916, n = 640

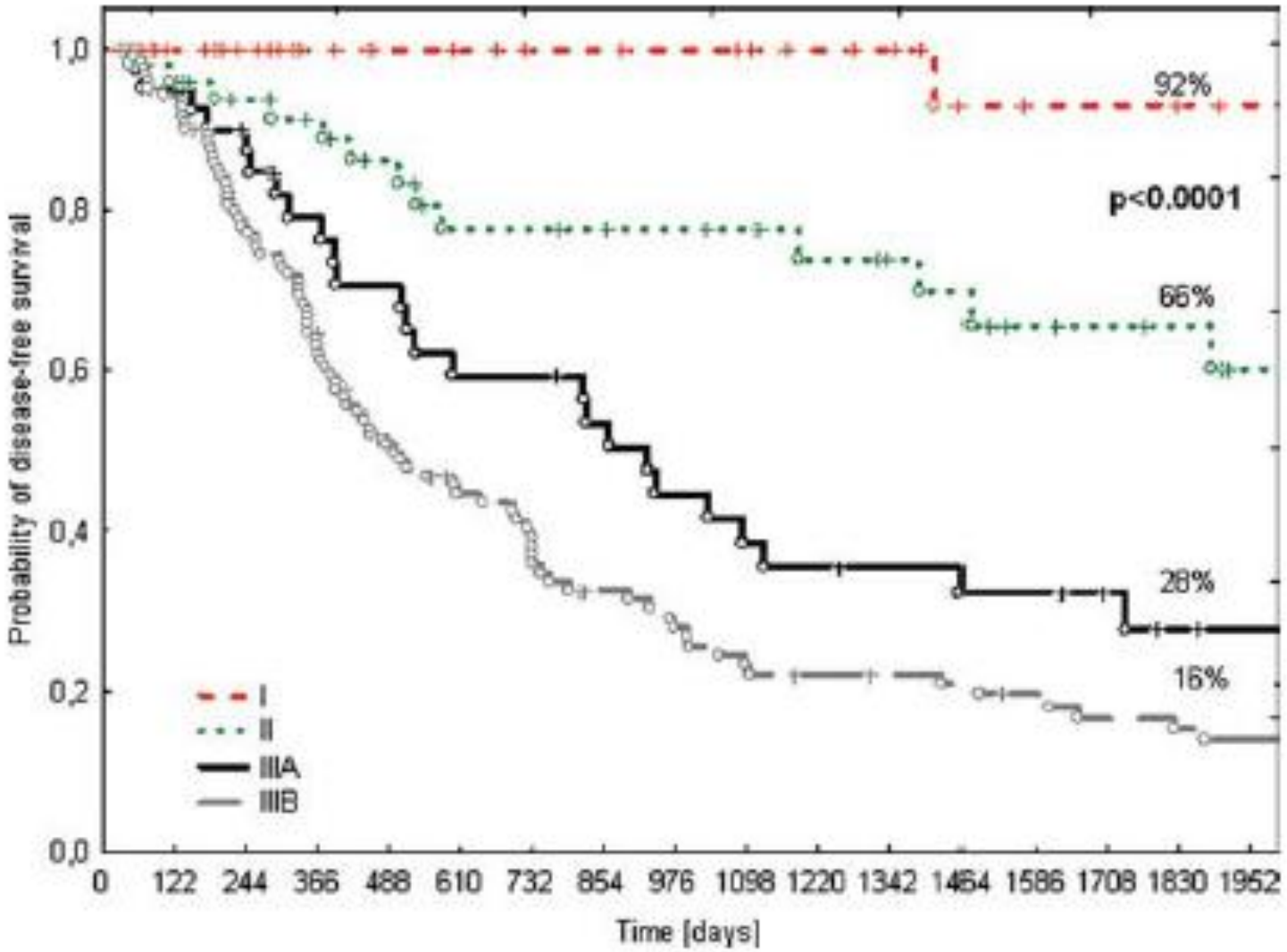
Gastric GIST



Validation of AJCC system

Rutkowski. Cancer 2011;1174916, n = 640

Non-gastric GIST



Italian nomogram, 2011 (Rossi)

Am J Surg Pathol 2011;35:1646

- 929 resected GISTs reviewed in Italy
- Nomogram developed from 526 patients to predict overall survival
- No external validation
- Median FU 126 months
- Based on mitotic count, size, site, age
- Mitosis and size as continuous variables

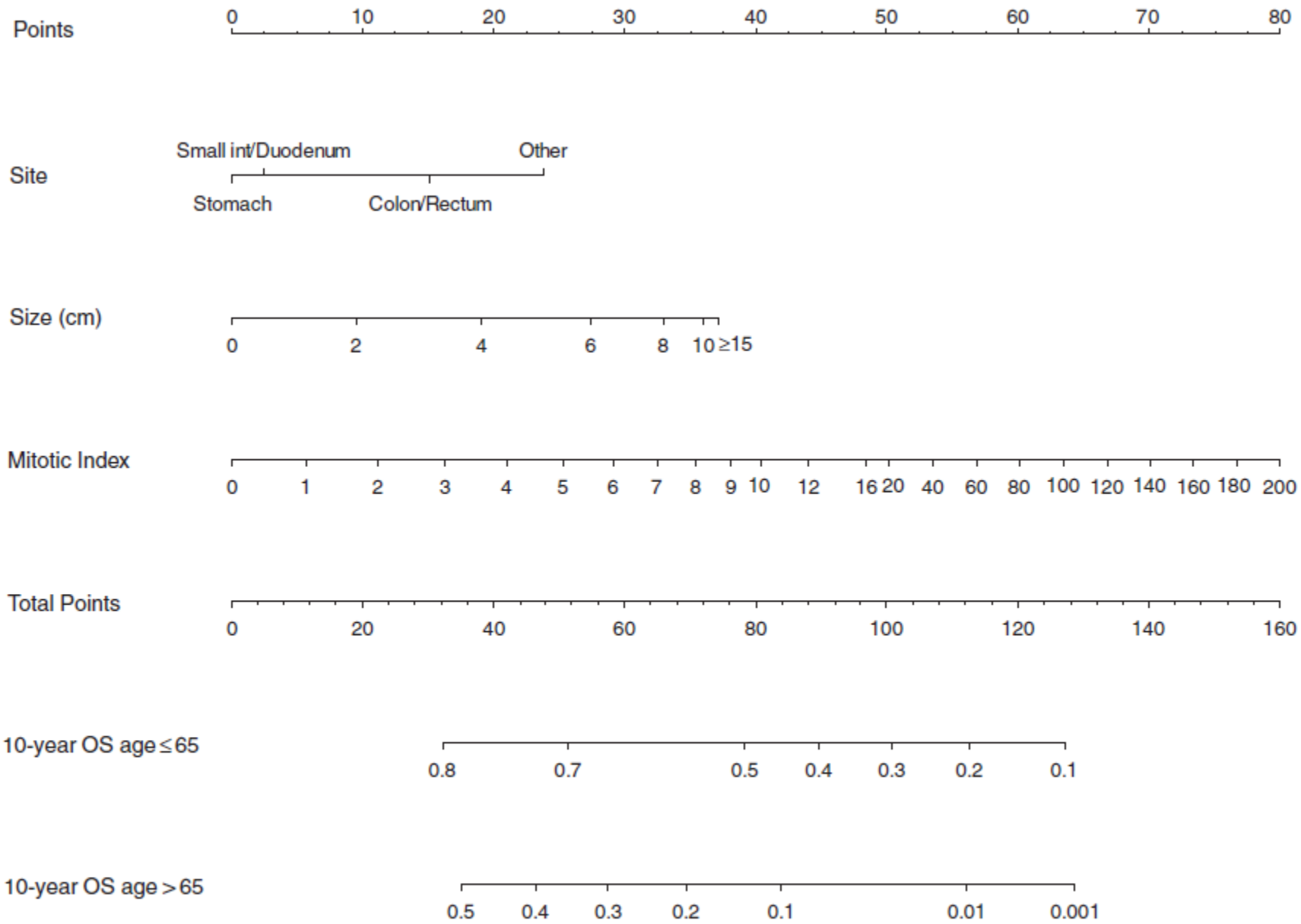


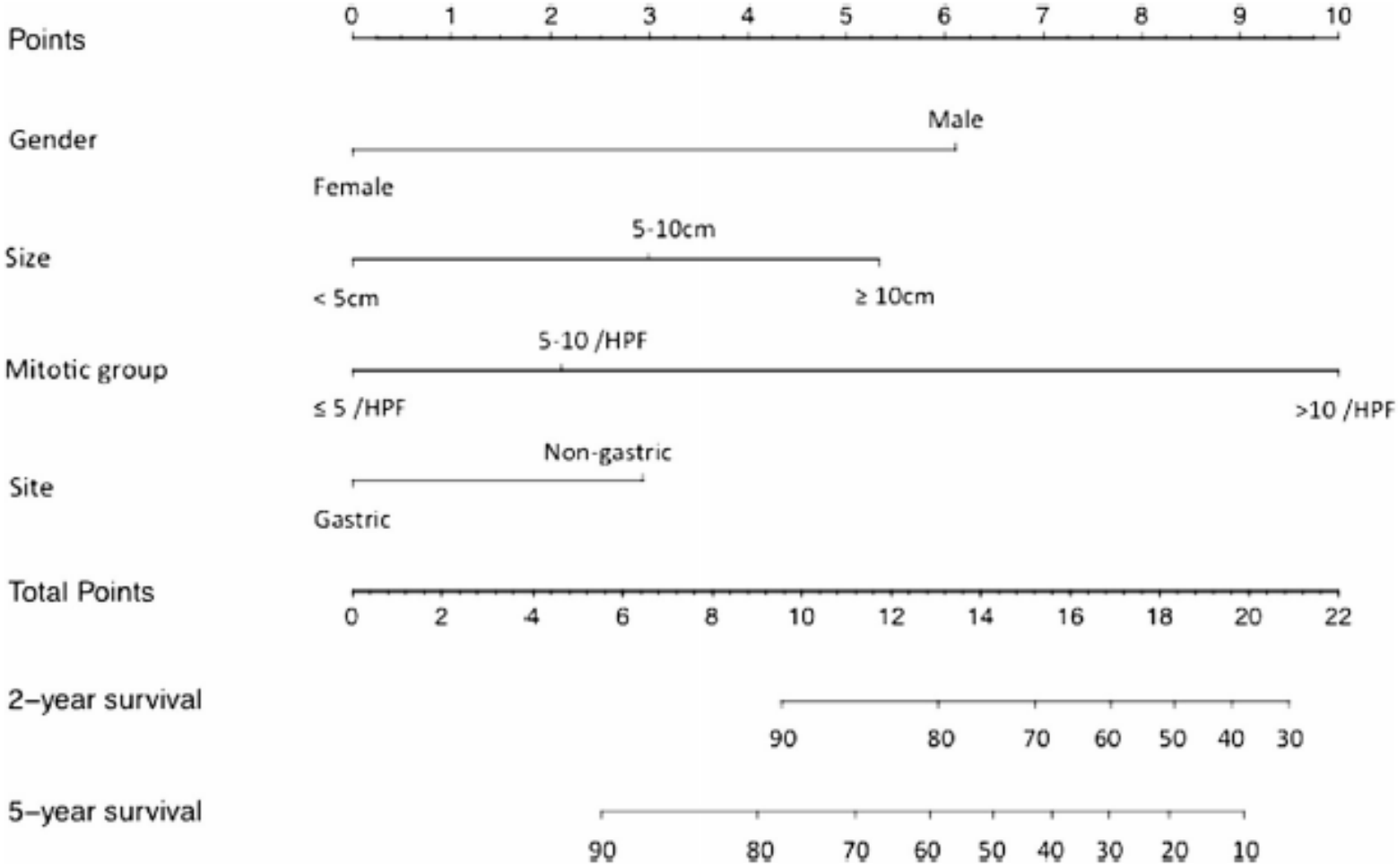
FIGURE 2. Nomogram for 10-year OS according to patient's age at diagnosis (≤65, >65 y). Instructions: The nomogram yields the 10-year OS probability corresponding to a patient's combination of covariates. Locate the patient's tumor site and draw a line straight upward to the Points axis to determine the score associated with that site. Repeat the process for tumor size and mitotic index, sum the 3 resulting scores, and locate the sum on the Total Points axis. Then, on the basis of patient's age at diagnosis (≤65 or >65 y), draw a line straight down to the corresponding 10-year OS axis to find OS probability.

Nomogram, 2014 (Bischof)

J Gastrointest Surg 2014;18:2123

- 356 resected GISTs in North America
- Nomogram developed to predict DFS
- No external validation
- Median FU 20 months
- Based on mitotic count, size, site, **sex**
- **Tumor rupture not significant predictor**
- Mitosis and size as categorical variables

Nomogram, 2014 (Bischof et al)



Nomogram, 2014 (Bischof)

J Gastrointest Surg 2014;18:2123

- Nomogram superior to NIH, mNIH and MSKCC C-index (0.77 vs 0.73, 0.71, 0,71)
- Similar to AFIP (0.78)

Summary of Risk-stratification models for GIST

Categorical	Continuous, non-linear
NIH-Fletcher ’02 MI, size	MSKCC nomogram, ’09 MI (cat), size, site
NIH-Miettinen ’02 MI, size, site	Italian nomogram ’11 MI, size, site, age
AFIP ‘06 MI, size, site	Joensuu heat map ’12 MI, size, site, rupture
mNIH ‘08 (Joensuu) MI, size, site, rupture	Bishof nomogram ’14 MI (cat), size (cat), site, sex
AJCC, TNM ‘10 MI, size, site, metastases	
*** Cat = categorical**	

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Comparison between Risk-stratification models

Goh et al. Ann Surg Oncol 2008

Annals of Surgical Oncology **15**(8):2153–2163
DOI: 10.1245/s10434-008-9969-z

Which Is the Optimal Risk Stratification System for Surgically Treated Localized Primary GIST? Comparison of Three Contemporary Prognostic Criteria in 171 Tumors and a Proposal for a Modified Armed Forces Institute of Pathology Risk Criteria

Brian K. P. Goh, MBBS, MRCS, MMed (Surgery), FRCS,[1]
Pierce K. H. Chow, MBBS, FRCS, PhD,[1,2] Wai-Ming Yap, MBBS, FRCPa,[3]
Sittampalam M. Kesavan, MBBS, FRCPa,[3] In-Chin Song, DipMT,[4]
Pradeep G. Paul, BSMS, MSc,[5] Boon-Swee Ooi, MBBS, FRCS,[6]
Yaw-Fui A. Chung, MBBS, FRCS,[1] and Wai-Keong Wong, MBBS, FRCS[1]

Goh et al. Ann Surg Oncol 2008

- 171 patients with resected GIST, without adjuvant imatinib
- To validate and compare the NIH, AFIP, Hwang modified NIH
- AFIP > Hwang modified NIH > NIH
- Proposed modified AFIP the most accurate

TABLE 7. *Comparison of the prognostic stratification of five risk criteria for gastrointestinal stromal tumor, including our two proposed modifications to the AFIP criteria*

Risk criteria	Discriminatory ability linear trend (χ^2 test)[a]	Homogeneity likelihood ratio (χ^2 test)[b]	Akaike information criteria[c]
NIH	17.9	38.8	341.9
Modified NIH	33.5	52.4	328.2
AFIP	22.4	61.9	320.9
Modified AFIP(A)	44.0	67.2	313.5
Modified AFIP(B)	38.2	61.9	318.7

AFIP, Armed Forces Institute of Pathology; NIH, National Institutes of Health.

[a] Higher discriminatory ability linear trend indicates a higher linear trend between stages.

[b] Higher homogeneity likelihood ratio indicates there is a smaller difference within the stages.

[c] Lower Akaike information criteria signify that the model is a better fit and a better predictor of survival.

Chok et al. Ann Surg Oncol 2015

Ann Surg Oncol
DOI 10.1245/s10434-015-4400-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Validation of the MSKCC Gastrointestinal Stromal Tumor Nomogram and Comparison with Other Prognostication Systems: Single-Institution Experience with 289 Patients

Aik-Yong Chok, MBBS, MRCS[1], Brian K. P. Goh, MBBS, MMed, MSc, FRCS[1,2], Ye-Xin Koh, MBBS, MRCS[1], Weng-Kit Lye, MSc[2], John C. Allen Jr., PhD[2], Richard Quek, MBBS, MRCP[3], Melissa C. C. Teo, MBBS, MRCS, FRCS[4], Pierce K. H. Chow, MBBS, FRCS, PhD[1,2], Hock-Soo Ong, MBBS, FRCS[5], Alexander Y. F. Chung, MBBS, FRCS[1], and Wai-Keong Wong, MBBS, FRCS[5]

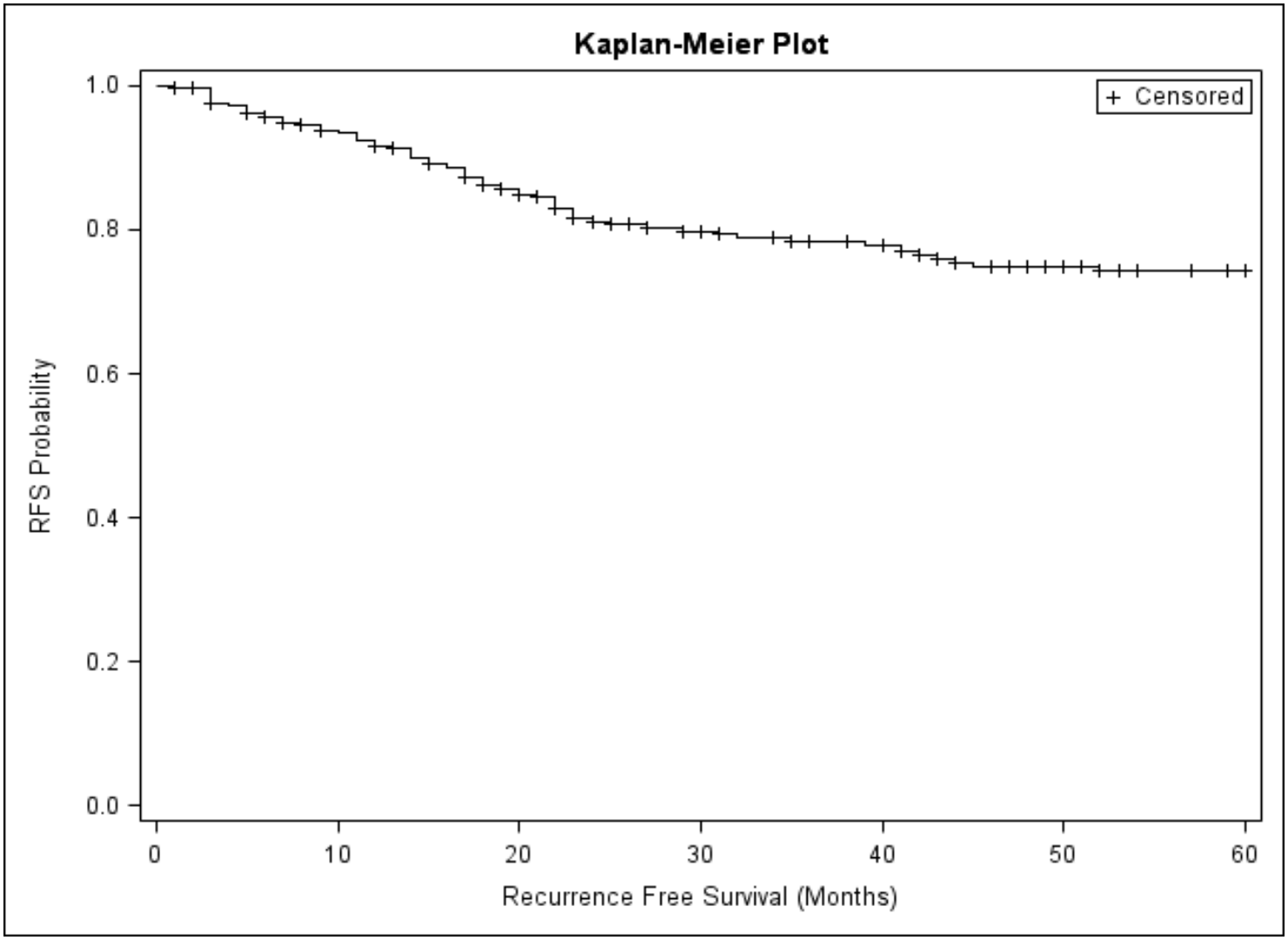
Chok et al. Ann Surg Oncol 2015

- 289 patients with resected GIST, without adjuvant imatinib
- To validate the MSKCC nomogram
- To compare the predictive accuracy of the GIST nomogram versus current established classification systems (NIH, mNIH and AFIP)
- Median FU 61 months

RFS of GIST

2-yr RFS was 77.2% (95%CI: 71.6-81.8)

5-yr RFS was 67.9% (95%CI: 61.7-73.4)



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Results

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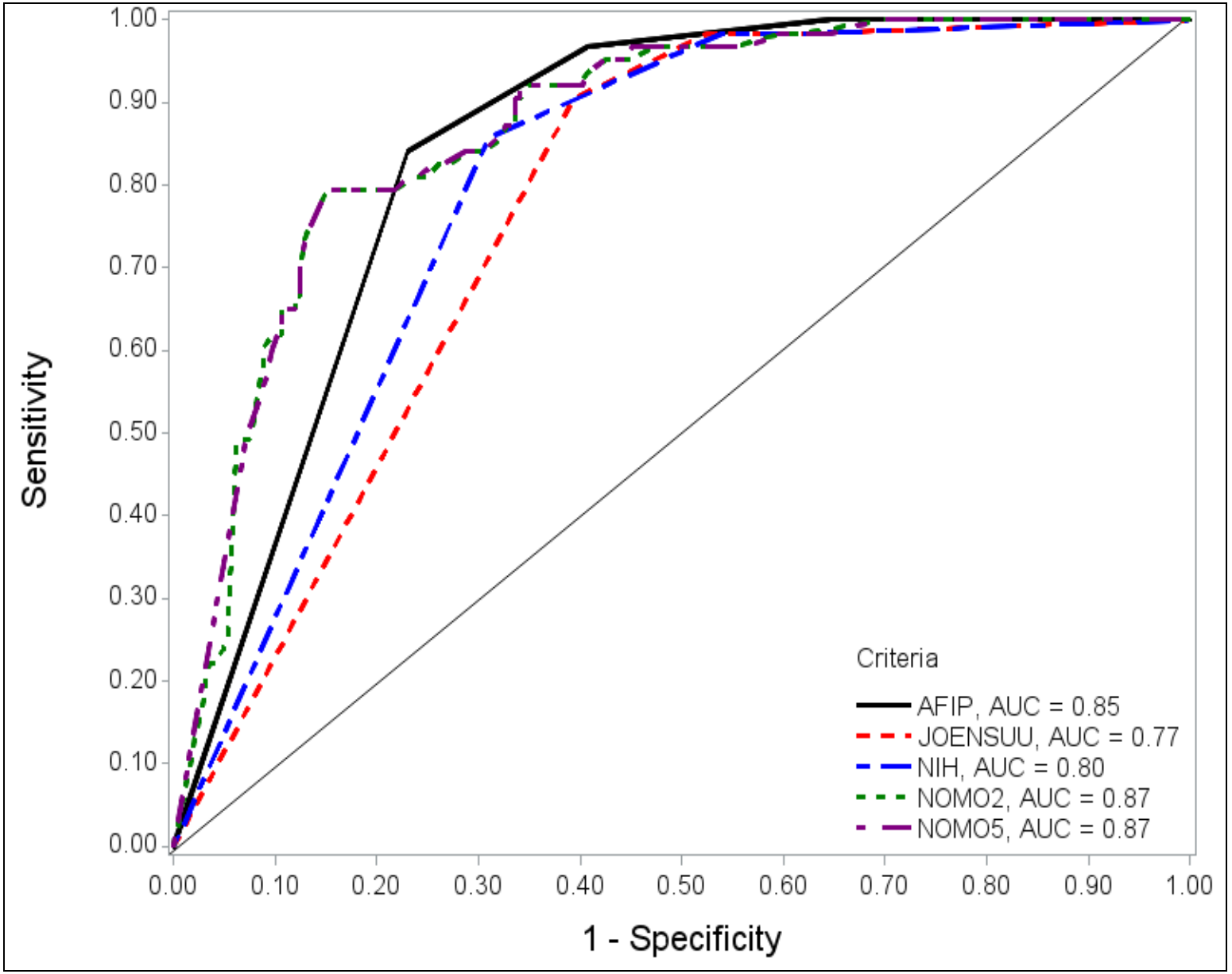
- All 4 systems: NIH, AFIP, mNIH (Joensuu) criteria and MSKCC were useful in stratifying patients according to risk of recurrence
- MSKCC nomogram was significantly more accurate than the NIH and Joensuu criteria
- Difference between the MSKCC nomogram and AFIP was not significant

Receiver operating characteristic (ROC) curve analysis of the risk of GIST recurrence during the first 5 years



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Limitations

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- The predictive ability of the nomogram - dependent on the proportion of high/low risk tumors in a particular study cohort.
- MSKCC nomogram - overestimated the probability of recurrence especially for low risk tumors
- Hence, it performance tended to be poorer in study cohorts with a high proportion of low risk tumors

Selected studies comparing the accuracy of the various staging systems

Author, yr	N	NIH	AFIP	mNIH	MSKCC	Remarks
Gold ‘09	127 212 148	0.72 0.70 0.74	**0.76** **0.73** **0.76**	Nil	**0.78** **0.76** **0.80**	3 cohorts
Rossi ‘11	526	0.64	**0.73**	Nil	Nil	**Nomo 0.72**
Joensuu ‘12	2560	0.79	0.82	0.78	-	**Contour map 0.88**
Bishof ‘14	365	0.73	**0.78**	0.71	0.71	**Nomo 0.77**
Yanagimoto ’15	712	0.74	0.80	0.74	Nil	**AJCC 0.83** JNIH 0.66
Chok ‘15	289	0.80	**0.85**	0.77	**0.87**	Asian population

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Discussion

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- Risk stratification models: categorical vs continuous
- Remains uncertain which risk-stratification model is superior
- In general, systems which are derived from a continuous, non linear model probably more accurate

  - more individualized

  - less user friendly
- Variables to include: mitotic count, size, site, *rupture, sex, age*

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Future

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- Current prognostication systems may be improved with incorporation of additional variables
- Kit mutational status
- Genomic-based methods – CINSARC, AURKA expression, Genomic index
- Inflammatory markers – CRP, NLR, PLR

Singapore General Hospital
SingHealth

British Journal of Cancer (2012) 107, 1433–1441
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www.bjcancer.com

Genomic Grade Index predicts postoperative clinical outcome of GIST

F Bertucci*[,1,2,3], P Finetti[1], J Ostrowski[4], WK Kim[5], H Kim[5], MA Pantaleo[6], A Astolfi[7], M Polkowski[8] and D Birnbaum[1]

[1]Department of Molecular Oncology, Centre de Recherche en Cancérologie de Marseille; UMR1068 Inserm; Institut Paoli-Calmettes, 232 Boulevard Sainte Marguerite, 13273 Marseille Cedex 09, France; [2]Department of Medical Oncology, Institut Paoli-Calmettes, Centre de Recherche en Cancérologie de Marseille, UMR1068 Inserm, Marseille, France; [3]Aix-Marseille University, Marseille, France; [4]Department of Oncological Genetics, M Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [5]Department of Pathology, Yonsei University College of Medicine, Seoul, Korea; [6]Department of Hematology and Oncological Sciences, L.A. Seragnoli, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [7]Interdepartmental Centre for Cancer Research G. Prodi, University of Bologna, Bologna, Italy; [8]Department of Gastroenterology, Medical Center of Postgraduate Education, Warsaw, Poland

BACKGROUND: Prognosis of localised gastrointestinal stromal tumour (GIST) is heterogeneous, notably for patients with AFIP intermediate or high risk of relapse, who are candidates to adjuvant imatinib. We hypothesised that gene expression profiles might improve the prognostication and help to refine the indications for imatinib.

METHODS: We collected gene expression and histoclinical data of 146 pre-treatment localised GIST samples treated with surgery alone. We searched for a gene expression signature (GES) predictive for relapse-free survival (RFS) and compared its performances to that of three published prognostic proliferation-based GES (Genomic Grade Index (GGI), 16-Kinase, and CINSARC) and AFIP classification. We also analysed a data set from 28 patients with advanced GIST treated with neo-adjuvant imatinib.

RESULTS: We identified a 275-gene GES (gene expression signature) predictive of RFS in a learning set and validated its robustness in an independent set. However, the GGI outperformed its prognostic performances, and those of the two other signatures and the AFIP intermediate-risk classification in two independent tests sets in uni- and multivariate analyses. Importantly, GGI could split the AFIP intermediate/high-risk samples into two groups with different RFS. Genomic Grade Index 'high-risk' tumours were more proliferative and genetically unstable than 'low-risk' tumours, and more sensitive to imatinib.

CONCLUSION: GGI refines the prediction of RFS in localised GIST and might help tailor adjuvant imatinib.

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Conclusions

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- Still uncertain which risk-stratification system is superior
- Established prognostic factors – size, mitotic index, site
- Models that address the continuous and non-linear nature of the prognostic variables for GIST – more accurate than models that categorise these variables
- These models are more likely to produce the most precise individualized risk estimation for GIST
- mNIH system (Joensuu) produces a single high-risk group – useful for selection for adjuvant therapy

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Thank You

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