in collaborazione con:

Istituto Tumori "Giovanni Paolo II" IRCCS Bari

Agenzia Regionale per la Salute ed il Sociale Puglia

RTP Registro Tumori Puglia

AIRTUM

XIX Corso di aggiornamento
per operatori dei registri tumori

GIST, sindromi mielodisplastiche, mielomi e linfomi e metodologie statistiche

BARI

6-8 novembre 2019
IRCCS Istituto Tumori
"Giovanni Paolo II"
viale Orazio Flacco, 65 Bari

I SESSIONE

GIST: orientarsi nel cambiamento

Moderatori: Anna Melcarne
Paolo Contiero

GIST: punto di vista del patologo

Adele Caldarella
Istituto per lo Studio, la Prevenzione e la Rete Oncologica
Firenze

ISPRO
Istituto per lo studio, la prevenzione e la rete oncologica

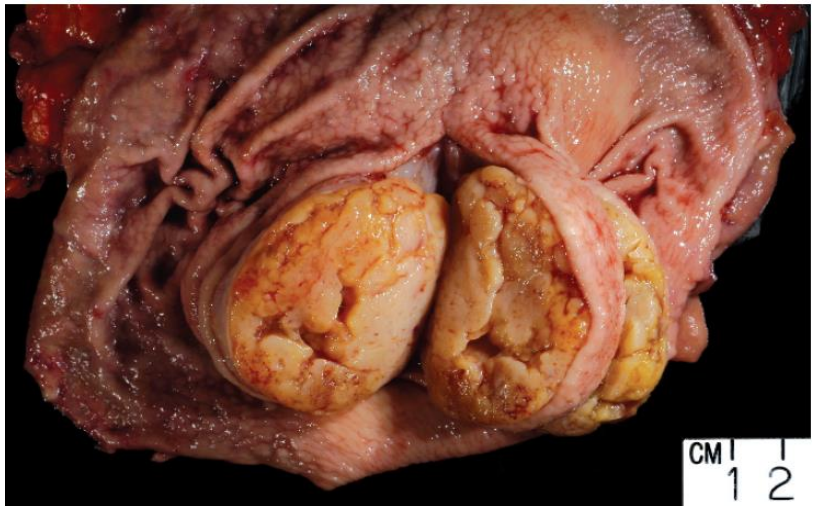
VOLUME 36 · NUMBER 2 · JANUARY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Gastrointestinal Stromal Tumors

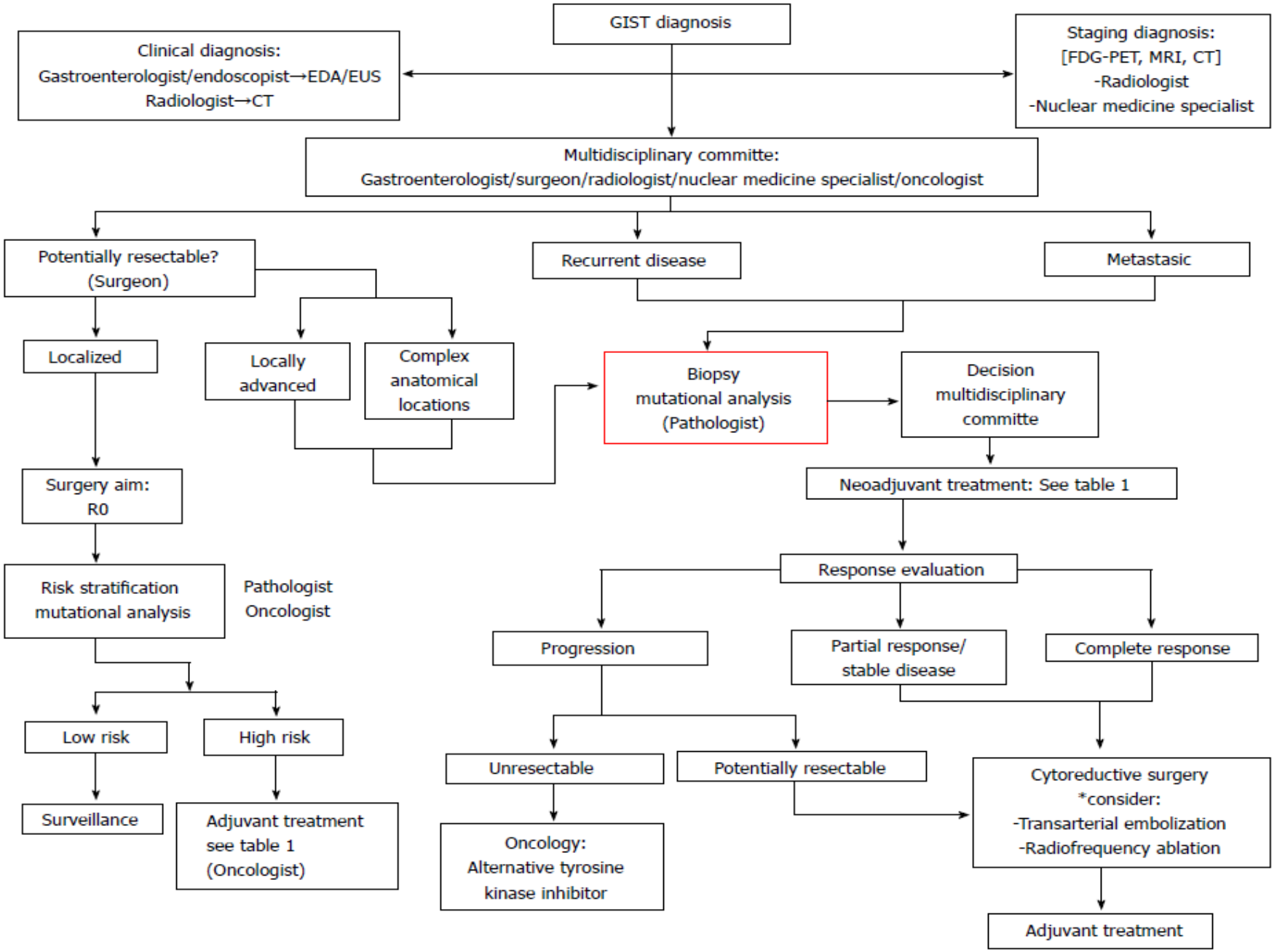
Margaret von Mehren and Heikki Joensuu



Arch Pathol Lab Med—Vol 135, October 2011

I tumori stromali gastrointestinali (GIST) costituiscono circa il 20% dei sarcomi dei tessuti molli

Figure 8 Management algorithm of gastrointestinal stromal tumors. GIST: Gastrointestinal stromal tumor.



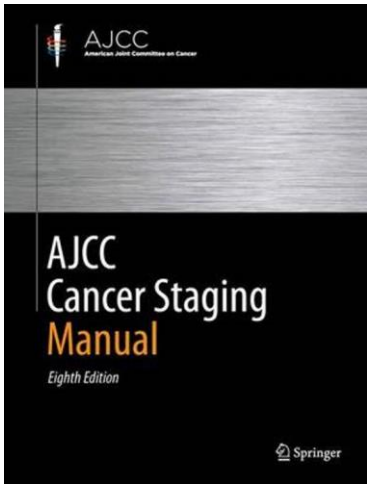
GIST – il ruolo del patologo

- Diagnosi
  - esame morfologico
  - immunofenotipo (CD117 e/o DOG-1)
  - (analisi delle mutazioni)
- Stadiazione e valutazione della categoria di rischio
- Analisi delle mutazioni
  - marcatore prognostico
  - marcatore predittivo

Diagnosi – aspetti istologici

- La sottotipizzazione tumorale (GIST a cellule fusate, a cellule epitelioidi e misti) non ha alcuna rilevanza prognostica
- Correlazione fra morfotipo e sede anatomica
  - >95% dei GIST a localizzazione nel piccolo intestino sono a cellule fusate
- Correlazione fra morfotipo e aspetti clinici
  - GIST associati a NF1: morfologia a cellule fusate
  - GIST pediatrici: > morfologia a cellule epitelioidi
  - GIST associati alla triade di Carney e alla diade di Carney-Stratakis): > morfologia a cellule epitelioidi

Courtesy prof Comin



Il grado dipende dall'indice mitotico

Indice mitotico basso → </=5 per 5 mm^2

Indice mitotico alto → >5 per 5 mm^2

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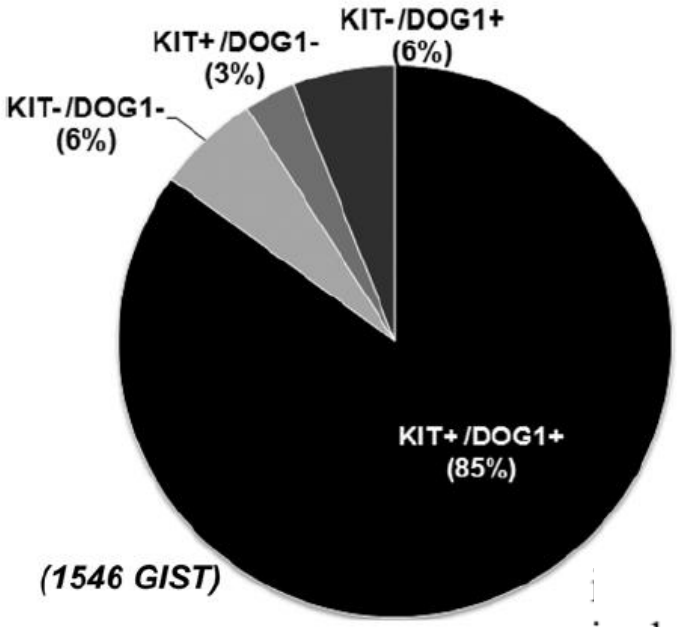
The Utility of Discovered on Gastrointestinal Stromal Tumor 1 (DOG1) Antibody in Surgical Pathology—the GIST of It

Cheng-Han Lee, MD, PhD, Cher-wei Liang, MD,† and Inigo Espinosa, MD‡*



- **DOG1** is especially useful in KIT-negative **gastric epithelioid GISTs**

- **KIT** is more sensitive than DOG1 in the **intestinal GISTs**

DOG1 should be included as part of the diagnostic work-up for any cases in which the differential diagnosis of GIST is considered.

Adv Anat Pathol • Volume 17, Number 3, May 2010

Diagnosi differenziale

- **GIST a cellule fusate**
  - Tumori del muscolo liscio
  - Fibromatosi desmoide
  - Schwannoma
  - Tumore infiammatorio miofibroblastico
  - Polipo fibroide infiammatorio
  - Tumore fibroso solitario
- **GIST a cellule epitelioidi**
  - Carcinoma neuroendocrino
  - Tumore glomico
  - Melanoma
  - Leiomiosarcoma epitelioide
  - MPNST epitelioide
  - Sarcoma a cellule chiare

Table 1. Immunohistochemistry in Differential Diagnosis of Gastrointestinal Stromal Tumor (GIST)[a]

Diagnosis	KIT	Smooth Muscle Actin	Desmin	S100	CD34	Keratin
GIST	+++	+ (40)	−	−	+++ (70)	−
Leiomyoma	−	+++	+++	−	±	±
Leiomyosarcoma	−	+++	+ to +++ (80)	−	+ (10)	+ (25)
Schwannoma	−	−	−	+++	−	−
Fibromatosis	−	++	−	+ (occasionally)	−	−
Carcinoma	−	+ to +++ (metaplastic/ sarcomatoid)	−	−	−	+ to +++
Melanoma	+ (50)	−	−	+++	−	−

Abbreviations: −, no cells positive by immunohistochemistry; ±, sometimes weak positive, sometimes negative by immunohistochemistry; +, <25% of cells positive by immunohistochemistry; ++, 25%–50% of cells positive by immunohistochemistry; +++, >50% of cells positive by immunohistochemistry.

[a] Parenthetical numbers indicate approximate percentage of cases that are positive.

Arch Pathol Lab Med—Vol 135, October 2011

- **GIST a cellule fusate**
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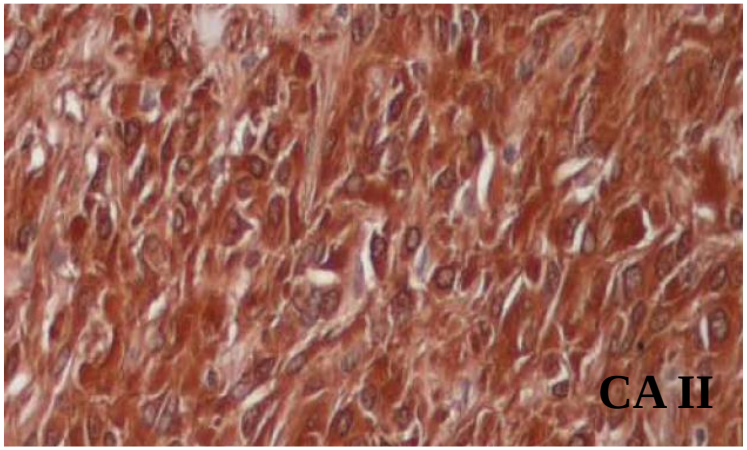
  - Leiomiosarcoma epitelioide
  - MPNST epitelioide
  - Sarcoma a cellule chiare

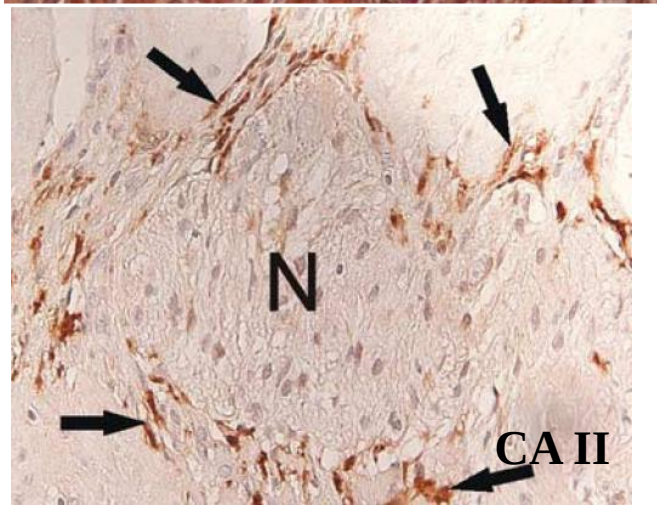
Carbonic anhydrase II. A novel biomarker for gastrointestinal stromal tumors

Seppo Parkkila[1,2], Jerzy Lasota[3], Jonathan A Fletcher[4], Wen-bin Ou[4], Antti J Kivelä[5], Kyösti Nuorva[6], Anna-Kaisa Parkkila[7], Jyrki Ollikainen[8], William S Sly[9], Abdul Waheed[9], Silvia Pastorekova[10], Jaromir Pastorek[10], Jorma Isola[2] and Markku Miettinen[3]

MODERN PATHOLOGY (2010) 23, 743–750

- 175 GIST (stomaco e piccolo intestino) + una serie di altre categorie tumorali
- CA II era espressa nel 95% dei casi di GIST, indipendentemente dallo stato mutazionale





Courtesy prof Comin

- Significativa correlazione negativa con l'indice mitotico (p=0,007)
- Nessuna differenza significativa fra i diversi morfotipi tumorali
- Nessuna differenza significativa con le dimensioni tumorali
- I pazienti con GIST intensamente e diffusamente positivo per CA II avevano prognosi migliore (p<0,0001)

Table 1 CA II-positive immunostaining in different tumor categories

Diagnosis	*Positive/total number of cases*
Glomus tumor (stomach)	0/12
Leiomyoma (esophagus)	3/8
Leiomyoma (retroperitoneum, estrogen receptor-positive)	0/27
Leiomyosarcoma (retroperitoneum)	1/14
Schwannoma (stomach)	1/7
Cellular schwannoma (retroperitoneum)	2/16
Metastatic melanoma (small intestine)	2/25
Malignant peripheral nerve sheath tumor (MPNST)	4/14
Plexiform neurofibroma	0/5
Solitary fibrous tumor	2/15
Dermatofibrosarcoma protuberans (7 with fibrosarcomatous transformation)	0/16
Kaposi sarcoma (skin)	2/15
Mesothelioma (peritoneum)	2/6

MODERN PATHOLOGY (2010) 23, 743–750

Courtesy prof Comin

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Analisi delle mutazioni

L’analisi delle mutazioni dei geni KIT (esoni 11, 9, 13, 17) e PDGFRA (esoni 14, 18):

- Può essere utile nella **diagnosi** dei GIST CD117/DOG-1-negativi
- **Parametro predittivo**
- **Parametro prognostico**

- Correlazione fra morfotipo e analisi mutazionale (GIST sporadici):
  - GIST a cellule fusate
    - Mutazione KIT
    - Wild-type
  - GIST a cellule epitelioidi
    - Mutazione PDGFRα
  - GIST a cellularità mista
    - Mutazione PDGFRα
    - Wild-type

Table 1 Mutations and clinicopathological features

Genes	Exon	Frequent mutations	Frequency	Characteristics and site	Imatinib sensitivity
KIT	All exons		80 %	All sites	
	8		Rare	Small bowel	Yes, intermediate
	9	Insertion of AY 502–503	5–10 %	Small bowel, colon, spindle, aggressive	
	11	Deletions, missense mutations, insertions	60–70 %	All sites	Yes
		Deletion of codon 557 or 558		Aggressive, poor prognosis	
		Internal tandem duplication		Benign features, clinically indolent, female, stomach	
	13	K642E	1 %	All sites	Yes
	17	D820Y, N822K, Y823D	1 %	All sites	No for D816V
PDGFRA	All exons		10 %	Epithelioid, clinically indolent	
	12	Missense mutations	1–2 %	All sites	Yes
	14	N659K	<1 %	Stomach, epithelioid	Yes
	18	D842V	10–5 %	Stomach, mesentery, omentum, epithelioid	No for D842V
Wild-type			10–15 %	All sites	Probably no
BRAF		V600E	Rare		
SDHA/*SDHB*/*SDHC*/*SDHD* mutations			~2 %	Carney–Stratakis syndrome[a]; stomach, multiple, immunohistochemically SDHB negative	
				Juvenile GIST; stomach, clinically indolent, multiple, immunohistochemically SDHB negative	
Loss of SDH expression				Carney triad[b]; stomach, clinically indolent, juvenile onset, immunohistochemically SDHB negative	
HRAS, *NRAS* mutation			<1 %		
NF1 mutation			1–2 %	Small bowel, clinically indolent, multiple, spindle	

SDH succinate dehydrogenase, *SDHB* succinate dehydrogenase iron–sulfur subunit (subunit B)

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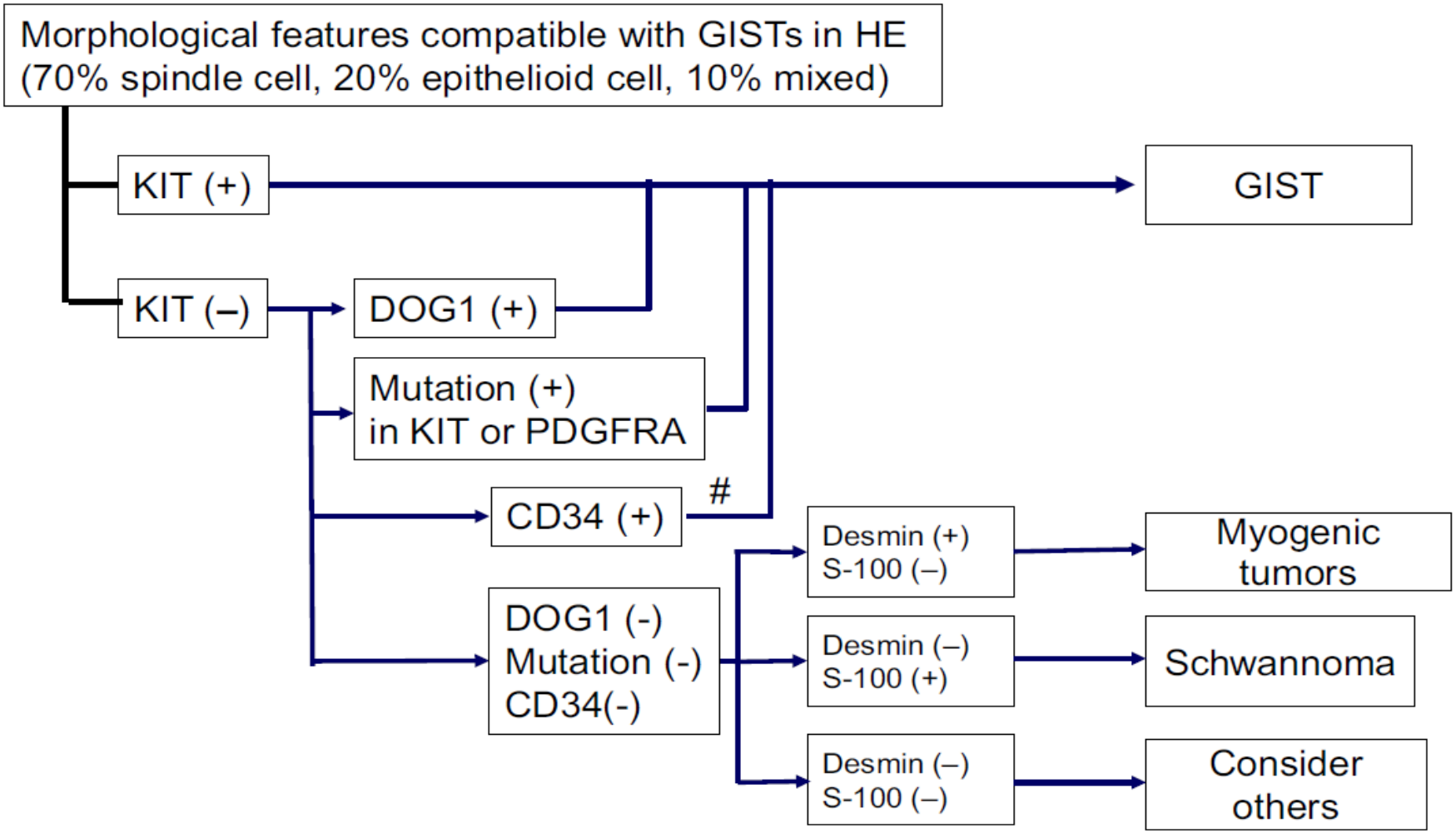
Table 1. Clinical Interpretation of Molecular Analysis Findings

Analysis Result	Prognostic Implication	Predictive Implication
PDGFRA mutation (various types, most commonly in exon 12 or 18)	Usually gastric; low mitotic count; favorable prognosis	Many imatinib sensitive; *PDGFRA* D842V is unresponsive to imatinib and other standard TKIs
KIT exon 11 deletion mutation (various types)	Variable	Response to imatinib likely
KIT exon 11 deletion of codons 557/558	Often a high mitotic count; a high risk of recurrence	Response to imatinib likely
KIT exon 11 duplication	Often favorable prognosis	Response to imatinib likely
KIT exon 9 (98% are Ala502_Tyr503dup)	Usually intestinal location; often unfavorable prognosis	Imatinib sensitive, but a high dose required (400 mg twice daily)
SDH deficient	Female predominance; multiple gastric GISTs; lymph node involvement common; often indolent clinical course; may be associated with paraganglioma and germline mutations; genetic counseling recommended	No documented benefit from imatinib; limited benefit reported for sunitinib or regorafenib
NF1 mutation	Intestinal; often multiple; may sometimes harbor also *KIT* mutation	Little or no benefit from TKIs

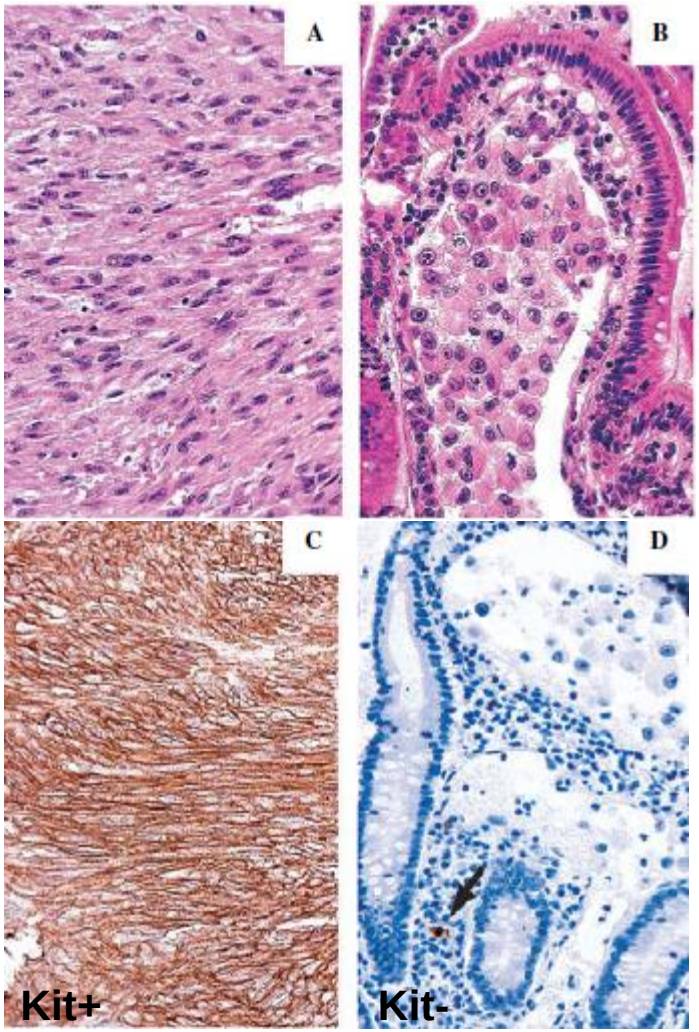
Abbreviations: GIST, GI stromal tumor; TKI, tyrosine kinase inhibitor.

- Stomaco
- Perdita funzione SDH
- Gran parte dei GIST pediatrici e dei GIST nella sindrome Carney-stratakis e nella triade di Carney


Morphological features compatible with GISTs in HE
(70% spindle cell, 20% epithelioid cell, 10% mixed)
KIT (+)
GIST
KIT (–)
DOG1 (+)
Mutation (+)
in KIT or PDGFRA
CD34 (+)
#
DOG1 (-)
Mutation (-)
CD34(-)
Desmin (+)
S-100 (–)
Myogenic tumors
Desmin (–)
S-100 (+)
Schwannoma
Desmin (–)
S-100 (–)
Consider others

Changing phenotype of gastrointestinal stromal tumours under imatinib mesylate treatment: a potential diagnostic pitfall

P Pauwels, M Debiec-Rychter,[1] M Stul,[1] I De Wever,[2] A T Van Oosterom[3] & R Sciot[4]



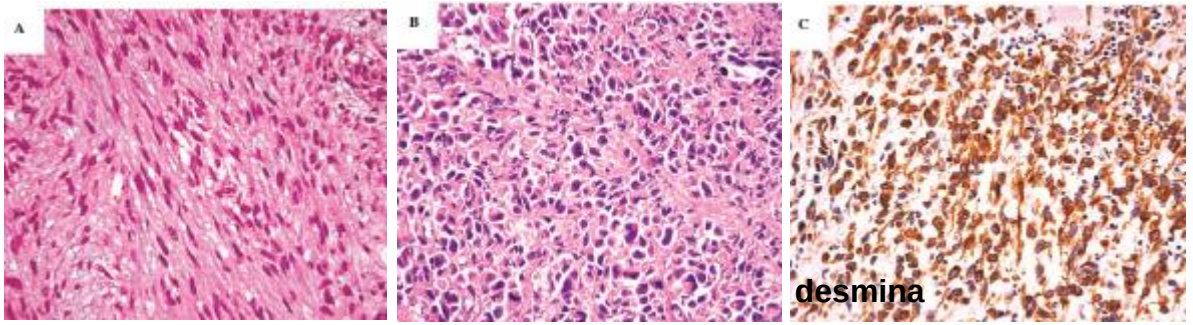


Table 2. Immunohistochemical features and genotype of primary and recurrent tumours in three presented patients

			Tumour immunophenotype					
Case	Tumour biopsy	Tumour genotype	CD117	CD34	α-SMA	S100	Desmin	Keratin
1	Base-line	KIT del WK 557–558	+++ cytoplasmic	+	+ focal	–	–	–
	Imatinib-resistant	KIT del WK 557–558	–	–	–	–	–	–
2	Base-line	KIT del VYIDPTQL 569–576	+++ cytoplasmic	+	+ focal	–	–	–
	On-therapy	KIT del VYIDPTQL 569–576	–	–	+ focal	–	–	–
3	Base-line	KIT K558N	+++ cytoplasmic	+++	+ focal	+	–	–
	Imatinib-resistant	KIT K558N	–	+	+ focal	–	+++ diffuse	–

Courtesy prof Luca Messerini

Histopathology 2005, **47**, 41–47.

Rhabdomyosarcomatous Differentiation in Gastrointestinal Stromal Tumors After Tyrosine Kinase Inhibitor Therapy

A Novel Form of Tumor Progression

Bernadette Liegl, MD,† Jason L. Hornick, MD, PhD,* Cristina R. Antonescu, MD,‡ Christopher L. Corless, MD,§ and Christopher D. M. Fletcher, MD, FRCPath**

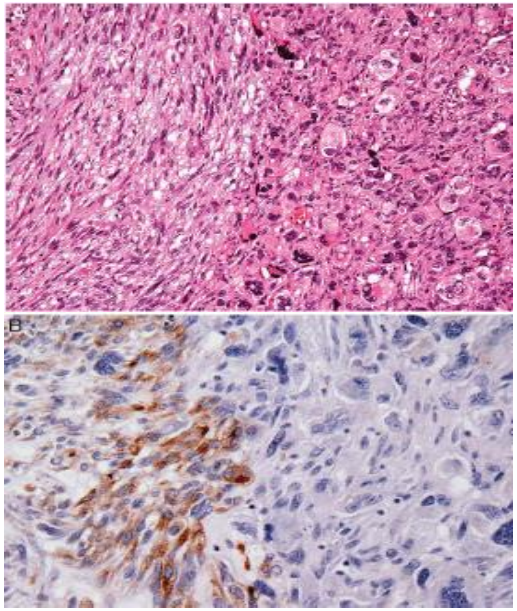


FIGURE 4. Case 3: Abrupt transition in a GIST metastasis showing spindle cell morphology to an area resembling pleomorphic rhabdomyosarcoma (A). The transition is further highlighted by loss of KIT immunopositivity in the rhabdomyoblastic component (B).

TABLE 3. Summary of Mutational Analysis

Case	Anatomic Location	Morphology	Mutational Analysis	
			Primary Mutation	Secondary Mutation
1	Omentum (A)	Spindle cell	*KIT* exon 11 point mutation V559D (heterozygous)	ND
	Omentum (B)	Rhabdomyoblastic differentiation	*KIT* exon 11 point mutation V559D (heterozygous)	ND
	Liver	Epithelioid	*KIT* exon 11 point mutation V559D (heterozygous)	*KIT* exon 13 V654A
2	Omentum	Rhabdomyoblastic differentiation	*KIT* exon 11 deletion 556-574 (homozygous)	ND
	Liver	Spindle cell	*KIT* exon 11 deletion 556-574 (homozygous)	ND
3	Abdomen/colonic mesentery	Pleomorphic with rhabdomyoblastic differentiation	*KIT* exon 11 point mutation V559D (heterozygous)	ND
	Mesenteric deposit	Pleomorphic with rhabdomyoblastic differentiation	*KIT* exon 11 point mutation V559D (heterozygous)	ND
4	Left upper quadrant mass (gastrosplenic ligament)	Rhabdomyoblastic differentiation	*KIT* exon 11 deletion 556-574 (heterozygous)	ND
	Left upper quadrant mass (gastrosplenic ligament)	Spindle cell	*KIT* exon 11 deletion 556-574 (heterozygous)	ND
5	Stomach	Epithelioid	*PDGFRA* exon 18 deletion, *KIT* wild-type	ND
	Peritoneum	Rhabdomyoblastic differentiation	*PDGFRA* exon 18 deletion, *KIT* wild-type	ND

ND indicates not detected; PDGFA, platelet-derived growth factor receptor α.

Am J Surg Pathol 2009;33:218–226

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Gastrointestinal stromal tumors: pathology and prognosis at different sites

Markku Miettinen, MD, Jerzy Lasota, MD

From the Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington, DC.

Table 1 Rates of metastases or tumor related death in GISTs of stomach and small intestine by tumors grouped by mitotic rate and tumor size*

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

*Based on previously published long-term follow-up studies on 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.[12,15,18,30]

†Denotes tumor categories with very small numbers of cases.

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

§No tumors of such category were included in the study. Note that small intestinal and other intestinal GISTs show a markedly worse prognosis in many mitosis and size categories than gastric GISTs.

Seminars in Diagnostic Pathology (2006) 23, 70-83

Risk stratification of patients diagnosed with gastrointestinal stromal tumor☆

Heikki Joensuu MD, PhD

Human Pathology (2008) **39**, 1411–1419

Table 4 Proposed modification of consensus classification for selecting patients with GIST for adjuvant therapy

Risk category	Tumor size (cm)	Mitotic index (per 50 HPFs)	Primary tumor site
Very low risk	<2.0	≤5	Any
Low risk	2.1-5.0	≤5	Any
Intermediate risk	2.1-5.0	>5	Gastric
	<5.0	6-10	Any
	5.1-10.0	≤5	Gastric
High risk	Any	Any	Tumor rupture
	>10 cm	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1-5.0	>5	Nongastric
	5.1-10.0	≤5	Nongastric

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

	Features
NIH-Fletcher[14]	
Very low	<2 cm and <5 mitotic index
Low	2–5 cm and <5 mitotic index
Intermediate	5–10 cm and <5 mitotic index or <5 cm and 6–10 mitotic index
High	>5 cm and >5 mitotic index or >10 cm and any mitotic index or any size and >10 mitotic index
NIH-Miettinen[15]	
Probably benign	Gastric: ≤5 cm and ≤5 mitotic index Intestinal: ≤2 cm and ≤5 mitotic index
Uncertain or low malignant potential	Gastric: >5 cm, ≤10 cm, and ≤5 mitotic index Intestinal: >2 cm, ≤5 cm, and ≤5 mitotic index
Probably malignant	Gastric: >10 cm or >5 mitotic index Intestinal: >5 cm or >5 mitotic index
AFIP-Miettinen[18]	
Very low, if any malignant potential	≤2 cm and ≤5 mitotic index
Low malignant potential	Gastric: >2 cm and ≤10 cm, and ≤5 mitotic index; ≤2 cm and >5 mitotic index Intestinal: >2 cm and ≤5 cm, and ≤5 mitotic index
Intermediate malignant potential	Gastric: >10 cm and ≤5 mitotic index; >2 cm and ≤5 cm, and >5 mitotic index Intestinal: >5 cm and ≤10 cm, and ≤5 mitotic index
High malignant potential	Gastric: >5 cm and >5 mitotic index Intestinal: >10 cm or >5 mitotic index

Mitotic index=number of mitoses per 50 high-power fields.

Table 1: **Commonly used staging systems for assessing risk of GIST**

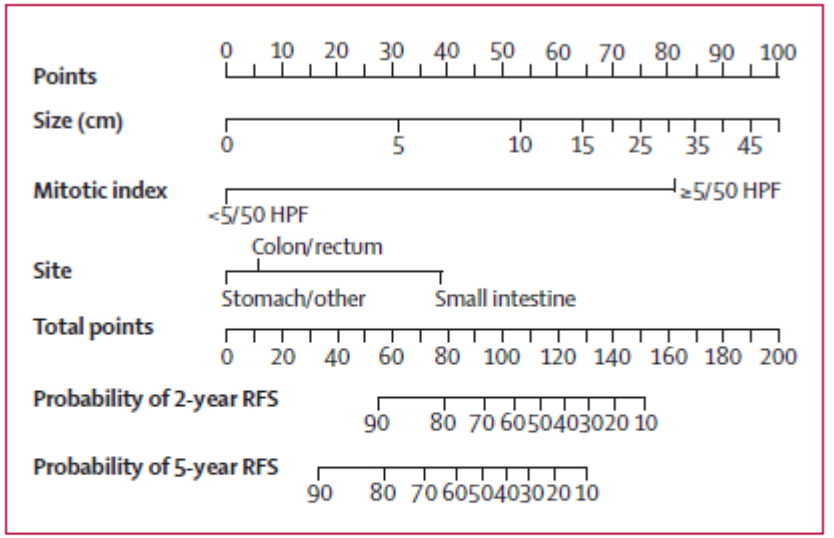

Figure 2: **Nomogram to predict the probabilities of 2-year and 5-year recurrence-free survival**

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

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Table 2. Selected Methods for Estimation of the Risk of GIST Recurrence After Macroscopically Complete Surgery

Method	GIST Feature				Prognostic Risk Groups
	Diameter (cm)	Mitotic Count	Sites	Rupture	
Modified NIH[2,28]	≤ 2.0, 2.1-5.0, 5.1-10.0, or > 10.0	≤ 5, 6-10, or > 10 per 50 HPFs	Gastric or nongastric	Rupture or no rupture	Four groups (very low, low, intermediate, or high risk)
AFIP[29]	≤ 2.0, 2.1-5.0, 5.1-10.0, or > 10.0	≤ 5 or > 5 per 50 HPFs	Criteria available for gastric, duodenal, jejunal, ileal, and rectal GISTs	Not considered	Eight groups (1, 2, 3a, 3b, 4, 5, 6a, 6b)
Nomogram[30]	Continuous	≤ 5 or > 5 per 50 HPFs	Stomach/other, colon/rectum, or small intestine	Not considered	Risk of recurrence 2 and 5 years after surgery
Prognostic contour map[5]	Continuous	Continuous	Gastric, nongastric, or extra-GI GIST	Rupture or no rupture	Risk of recurrence within 15 years of surgery

Abbreviations: AFIP, Armed Forces Institute of Pathology; GIST, GI stromal tumor; HPF, high-power field; NIH, National Institutes of Health.

GASTROINTESTINAL STROMAL TUMOR STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS FOR GIST AT ALL SITES	PATHOLOGIC *Extent of disease during and from surgery*
❑ y clinical– staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____	❑ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)	
❑ TX	Primary tumor cannot be assessed	❑ TX
❑ T0	No evidence of primary tumor	❑ T0
❑ T1	Tumor 2 cm or less	❑ T1
❑ T2	Tumor more than 2 cm but not more than 5 cm	❑ T2
❑ T3	Tumor more than 5 cm but not more than 10 cm	❑ T3
❑ T4	Tumor more than 10 cm in greatest dimension	❑ T4
	REGIONAL LYMPH NODES (N)	
❑ NX	Regional lymph nodes cannot be assessed	❑ NX
❑ N0	No regional lymph node metastasis	❑ N0
❑ N1	Regional lymph node metastasis	❑ N1
	DISTANT METASTASIS (M)	
❑ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
❑ M1	Distant metastasis	❑ M1
❑ M1a	Lung	❑ M1a
❑ M1b	Other distant sites	❑ M1b

ANATOMIC STAGE • PROGNOSTIC GROUPS – GASTRIC GIST

CLINICAL					PATHOLOGIC				
GROUP	T	N	M	Mitotic Rate	GROUP	T	N	M	Mitotic Rate
❑ IA	T1 or T2	N0	M0	Low	❑ IA	T1 or T2	N0	M0	Low
❑ IB	T3	N0	M0	Low	❑ IB	T3	N0	M0	Low
❑ II	T1	N0	M0	High	❑ II	T1	N0	M0	High
	T2	N0	M0	High		T2	N0	M0	High
	T4	N0	M0	Low		T4	N0	M0	Low
❑ IIIA	T3	N0	M0	High	❑ IIIA	T3	N0	M0	High
❑ IIIB	T4	N0	M0	High	❑ IIIB	T4	N0	M0	High
❑ IV	Any T	N1	M0	Any rate	❑ IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate		Any T	Any N	M1	Any rate
❑ Stage unknown					❑ Stage unknown				

ANATOMIC STAGE • PROGNOSTIC GROUPS – SMALL INTESTINAL GIST
(also to be used for esophagus, colorectal, and peritoneum)

CLINICAL					PATHOLOGIC				
GROUP	T	N	M	Mitotic Rate	GROUP	T	N	M	Mitotic Rate
❑ IA	T1 or T2	N0	M0	Low	❑ IA	T1 or T2	N0	M0	Low
❑ II	T3	N0	M0	Low	❑ II	T3	N0	M0	Low
❑ IIIA	T1	N0	M0	High	❑ IIIA	T1	N0	M0	High
	T4	N0	M0	Low		T4	N0	M0	Low
❑ IIIB	T2	N0	M0	High	❑ IIIB	T2	N0	M0	High
	T3	N0	M0	High		T3	N0	M0	High
	T4	N0	M0	High		T4	N0	M0	High
❑ IV	Any T	N1	M0	Any rate	❑ IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate		Any T	Any N	M1	Any rate
❑ Stage unknown					❑ Stage unknown				

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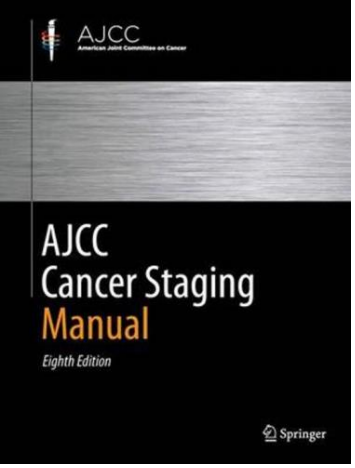

Gastric and Omental GIST

When T is…	And N is…	And M is…	And mitotic rate is…	Then the stage group is…
T1 or T2	N0	M0	Low	IA
T3	N0	M0	Low	IB
T1	N0	M0	High	II
T2	N0	M0	High	II
T4	N0	M0	Low	II
T3	N0	M0	High	IIIA
T4	N0	M0	High	IIIB
Any T	N1	M0	Any rate	IV
Any T	Any N	M1	Any rate	IV

Small Intestinal, Esophageal, Colorectal, Mesenteric, and Peritoneal GIST

When T is…	And N is…	And M is…	And mitotic rate is…	Then the stage group is…
T1 or T2	N0	M0	Low	I
T3	N0	M0	Low	II
T1	N0	M0	High	IIIA
T4	N0	M0	Low	IIIA
T2	N0	M0	High	IIIB
T3	N0	M0	High	IIIB
T4	N0	M0	High	IIIB
Any T	N1	M0	Any rate	IV
Any T	Any N	M1	Any rate	IV

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GASTROINTESTINAL STROMAL TUMOR STAGING FORM

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS) – FOR GIST AT ALL SITES

REQUIRED FOR STAGING: Mitotic rate

CLINICALLY SIGNIFICANT:

KIT Immunohistochemistry: _____

Mutational status of KIT, PDGFRA: _____

Histologic Grade (G) *(also known as overall grade)*

Histological grading, an ingredient in sarcoma staging, is not well suited to GISTs, because a majority of these tumors have low or relatively low mitotic rates below the thresholds used for grading of soft tissue tumors, and because GISTs often manifest aggressive features with mitotic rates below the thresholds used for soft tissue tumor grading (the lowest tier of mitotic rates for soft tissue sarcomas being 10 mitoses per 10 HPFs). In GIST staging, the grade is replaced by mitotic activity.

- ❑ GX Grade cannot be assessed
- ❑ G1 Low grade; mitotic rate <5/50 HPF
- ❑ G2 High grade, mitotic rate >5/50 HPF

ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

- ❑ Lymph-Vascular Invasion Not Present (absent)/Not Identified
- ❑ Lymph-Vascular Invasion Present/Identified
- ❑ Not Applicable
- ❑ Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

- ❑ RX Presence of residual tumor cannot be assessed
- ❑ R0 No residual tumor
- ❑ R1 Microscopic residual tumor
- ❑ R2 Macroscopic residual tumor

General Notes:

For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

❑ Clinical stage was used in treatment planning (describe): _____

❑ National guidelines were used in treatment planning ❑ NCCN ❑ Other (describe): _____

_____

_____

Physician signature Date/Time

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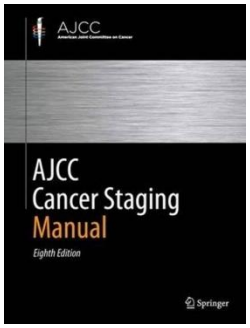

Tabella dei fattori prognostici – Sarcoma dei tessuti molli e GIST

Fattori prognostici per sarcomi dei tessuti molli

Fattori prognostici	Correlati al tumore	Correlati al paziente	Correlati all'ambiente
Essenziali	Sede anatomica Tipo istologico Dimensione del tumore: – in generale: <5 o >5 cm – per GIST: ≤2, 2-≤5, 5-≤10 e >10 cm Profondità di invasione Grado (da ben differenziato a scarsamente differenziato) Classe M Indice mitotico per GIST (<5 e ≥5 mitosi/50 HPF)		
Addizionali	Presenza di mutazione *c-Kit* per GIST Sito di mutazione in *c-Kit* o nel gene *PDGFRA* per GIST Trascritto di fusione di *EWS-FL11* per sarcoma di Ewing Trascritto di fusione *SYT-SSX* per sarcoma sinoviale Traslocazione *FOXO1* per rabdomiosarcoma alveolare Margini di resezione chirurgica Stato alla presentazione (primitivo *vs* recidiva)	Neurofibromatosi (NF1) Sarcomi radioindotti Età	Qualità della chirurgia e della radioterapia
Innovativi e promettenti	*TP53* Ki-67 Ipossia tumorale		

Fonte: *UICC Manual of Clinical Oncology*, Ninth Edition. Edited by Brian O'Sullivan, James D. Brierley, Amil K. D'Cruz, Martin F. Fey, Raphael Pollock, Jan B. Vermorken and Shao Hui Huang. © 2015 UICC. Published 2015 by John Wiley & Sons, Ltd.

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Template for Reporting Results of Biomarker Testing of Specimens From Patients With Gastrointestinal Stromal Tumors

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METHODS

Dissection Method(s) (select all that apply) (note G)

___ Laser capture microdissection
___ Manual under microscopic observation
___ Manual without microscopic observation
___ Cored from block
___ Whole tissue section (no tumor enrichment procedure employed)

***KIT* Mutational Analysis**

Exons Assessed (select all that apply)

___ Exon 9
___ Exon 11
___ Exon 13
___ Exon 14
___ Exon 17
___ Other (specify): _____

Testing Method(s)†

Specify name of method used and exons tested:

_____

† *Please specify if different testing methods are used for different exons.*

***PDGFRA* Mutational Analysis**

Exons Assessed (select all that apply)

___ Exon 12
___ Exon 14
___ Exon 18
___ Other (specify): _____

RESULTS

Immunohistochemical Studies (note A)

___ KIT (CD117)†
  ___ Positive
  ___ Negative
___ DOG1 (ANO1)†
  ___ Positive
  ___ Negative
___ SDHB
  ___ Intact
  ___ Deficient
___ SDHA
  ___ Intact
  ___ Deficient
___ Other (specify): _____
  ___ Positive
  ___ Negative

***KIT* Mutational Analysis (note B)**

___ No mutation detected
___ Mutation identified (specify:) _____
___ Cannot be determined (explain):
_____

***PDGFRA* Mutational Analysis (note C)**

___ No mutation detected
___ Mutation identified (specify): _____
___ Cannot be determined (explain):
_____

***BRAF* Mutational Analysis (note D)**

___ No *BRAF* mutation detected
___ *BRAF* V600E (c.1799T>A) mutation
___ Other *BRAF* mutation (specify): _____
___ Cannot be determined (explain):
_____

***SDHA/B/C/D* Mutational Analysis (note E)**

___ No mutation detected
___ Mutation identified (specify): _____
___ Cannot be determined (explain):
_____

***NF1* Mutational Analysis (note F)**

___ No mutation detected
___ Mutation identified (specify): _____
___ Cannot be determined (explain):
_____