GIST: an update

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Cell Culture

EM

IHC

Genomics

1950

1960

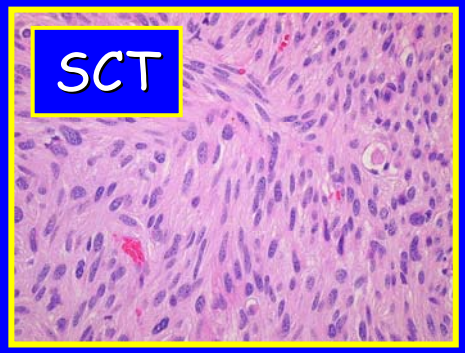
1970

1980

1990

2000

SCT



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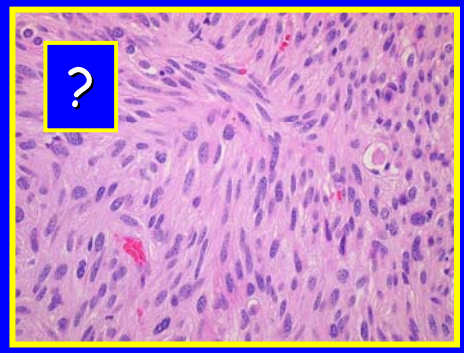
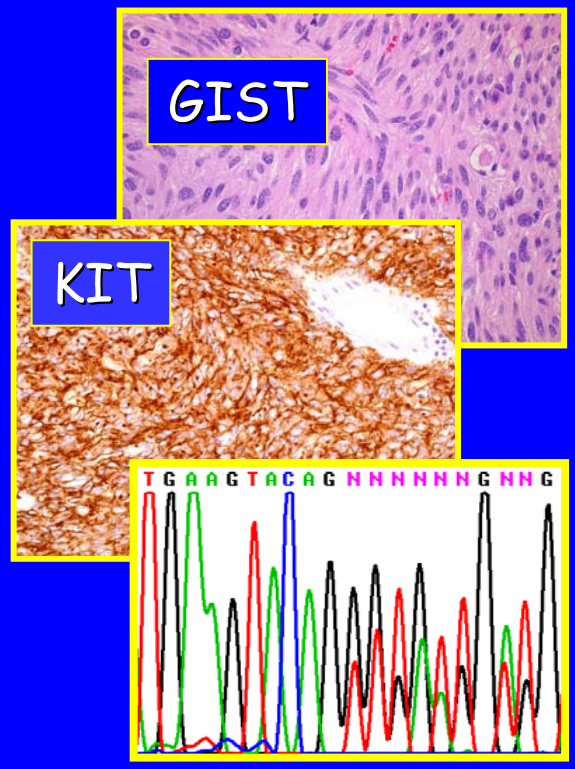


GIST

KIT



Targeted Therapy

- A paradigm shift
- A revolution
- A new era
- A long awaited breakthrough
- …

Ideal Target

- Oncogenetically relevant
- Present in most tumors to target
- Present in most tumor cells
- Low expression in normal cells
- Drugable

1: Science. 1998 Jan 23;279(5350):577-80.

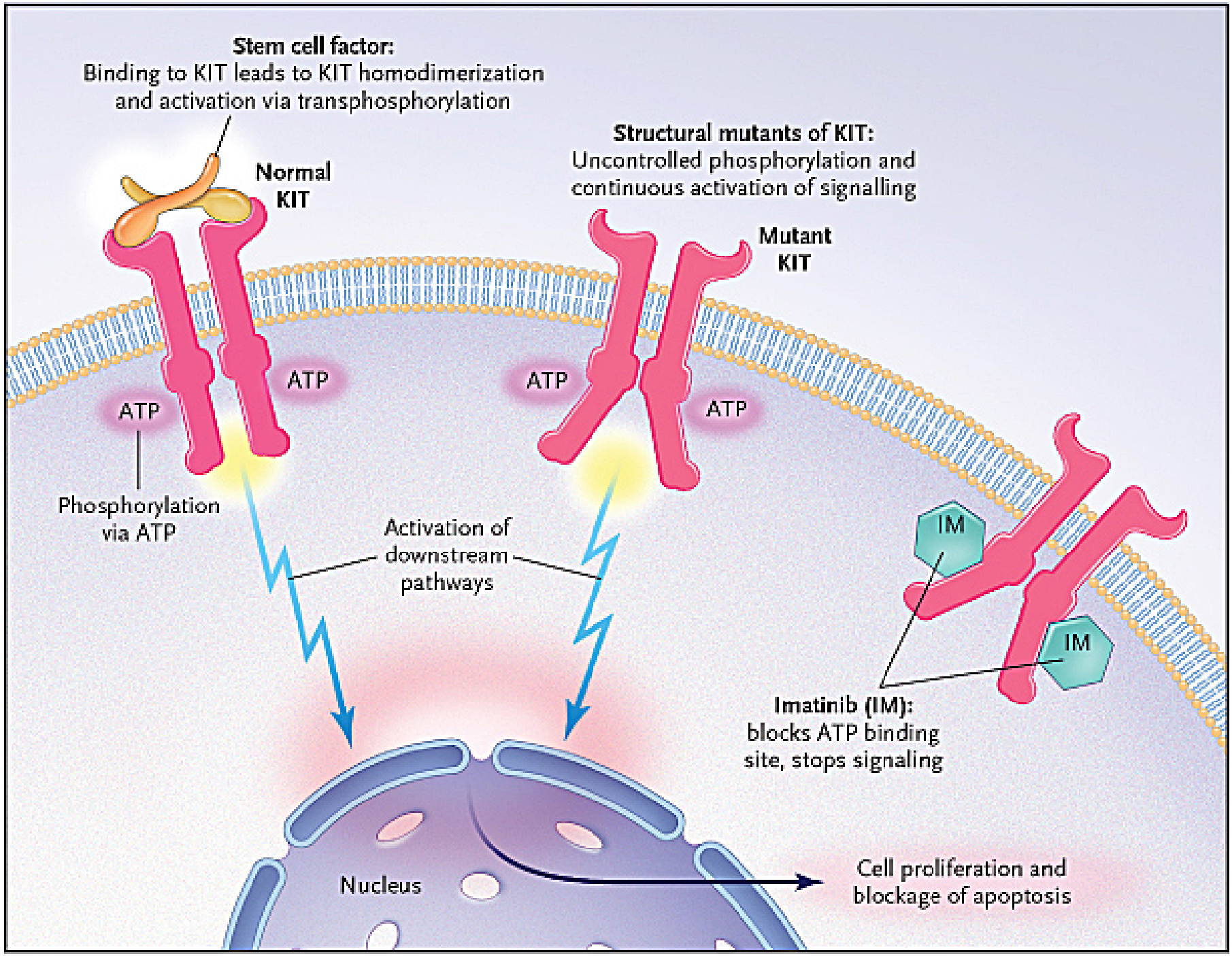
Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors.

Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y.

- 5 cases of GIST
- KIT activating mutations
- Relationships with ICC
  - Depndence of ICC on SCF-KIT interaction
  - Expression of KIT

KIT Mutations

- Found in most GISTs
- Irrespective of size/morphology/clinical behavior/neural differentiation
- 70%: juxtamembrane region
  - 20%: extracellular domain
  - 10%: other
- High level KIT activation/phosphorylation
- KIT activated also rare KIT wild- type cases

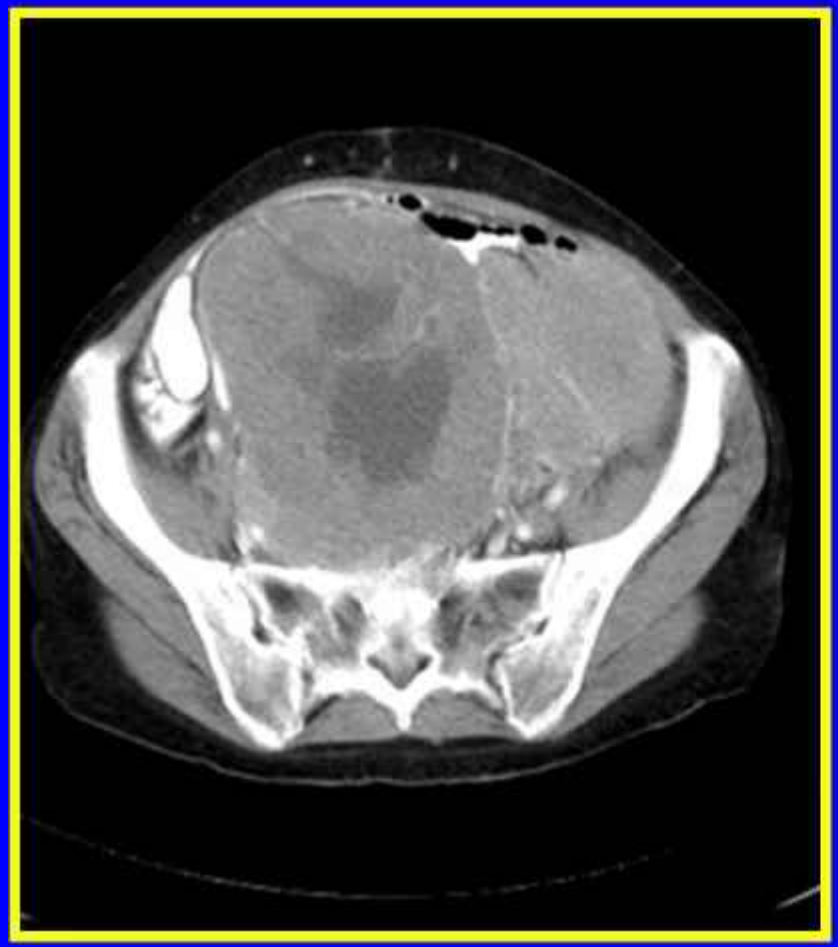

Stem cell factor:
Binding to KIT leads to KIT homodimerization and activation via transphosphorylation
Normal KIT
Structural mutants of KIT:
Uncontrolled phosphorylation and continuous activation of signalling
Mutant KIT
ATP
ATP
ATP
ATP
Phosphorylation via ATP
Activation of downstream pathways
IM
IM
Imatinib (IM):
blocks ATP binding site, stops signaling
Nucleus
Cell proliferation and blockage of apoptosis

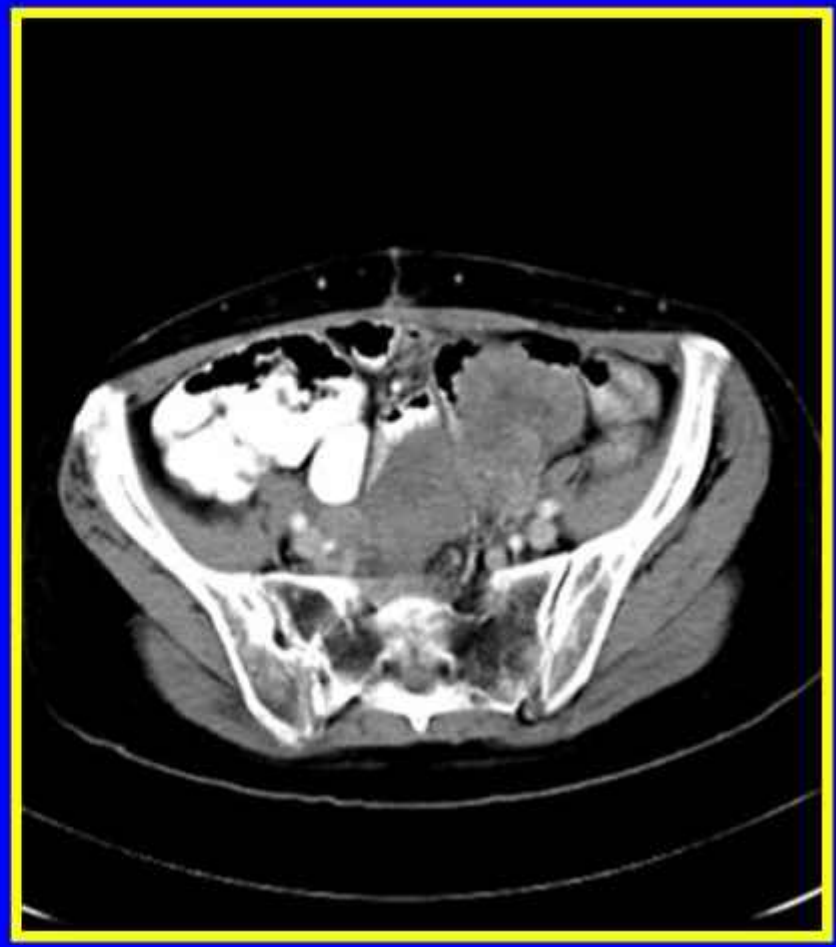
The New England Journal of Medicine

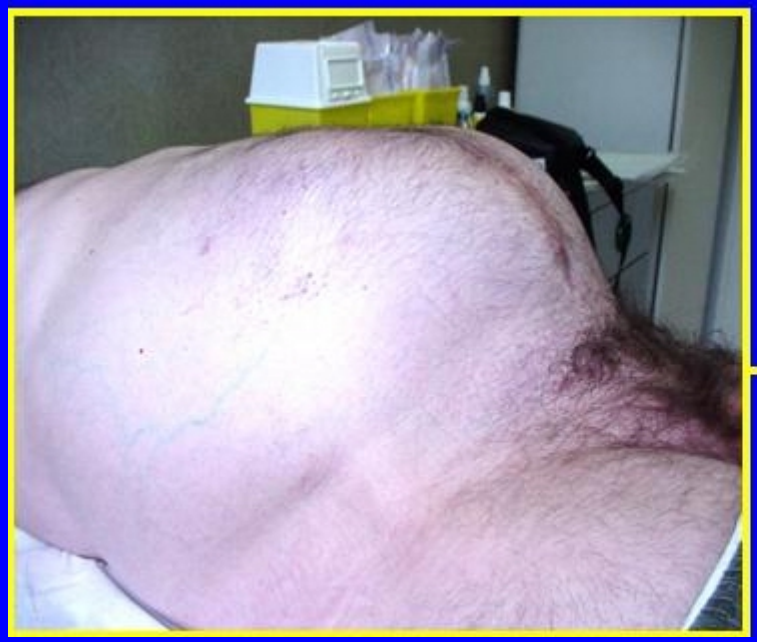
Established in 1812 as The New England Journal of Medicine and Surgery

VOLUME 344 APRIL 5, 2001 NUMBER 14

Effect of Imatinib on Advanced GIST



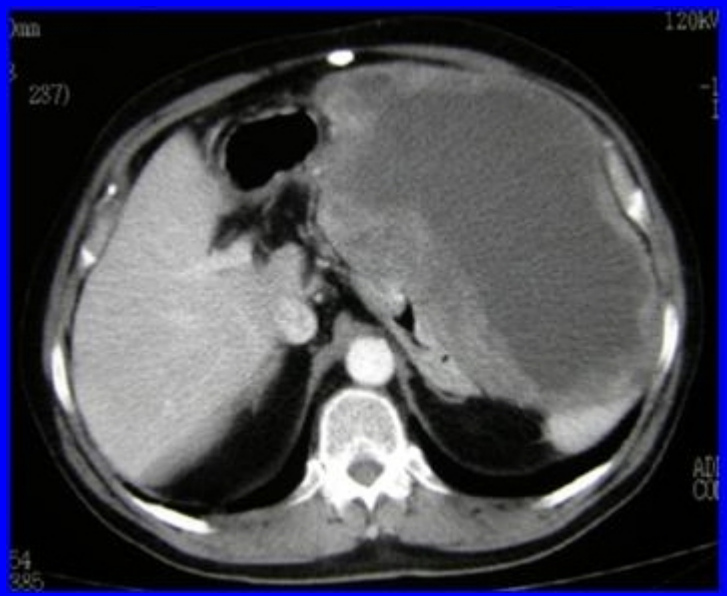


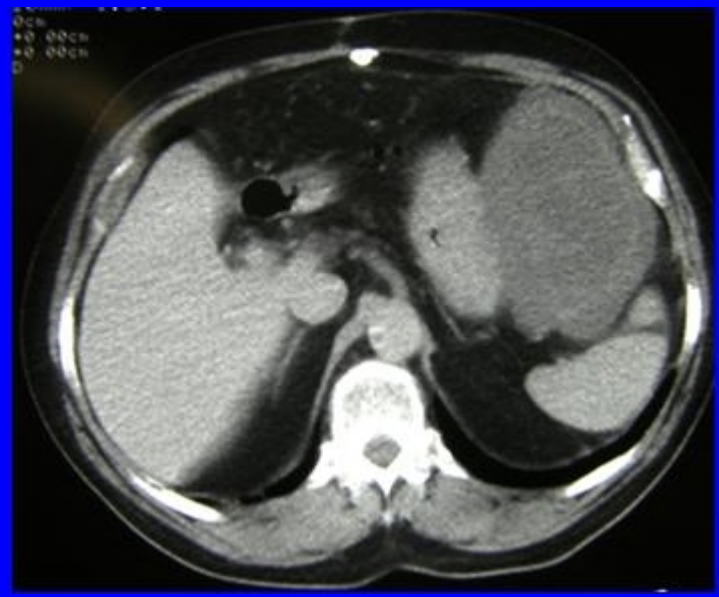


0

+2 wks

"Dimensional" tumor response …

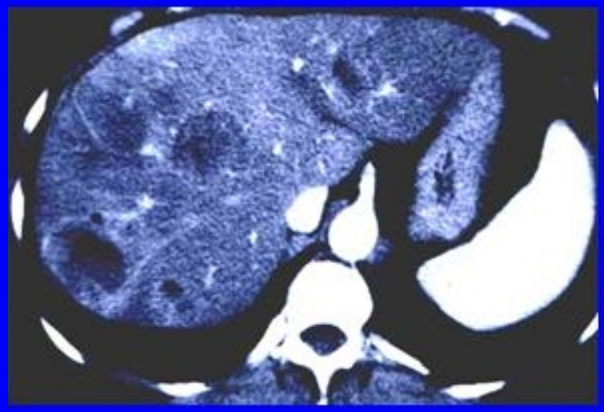


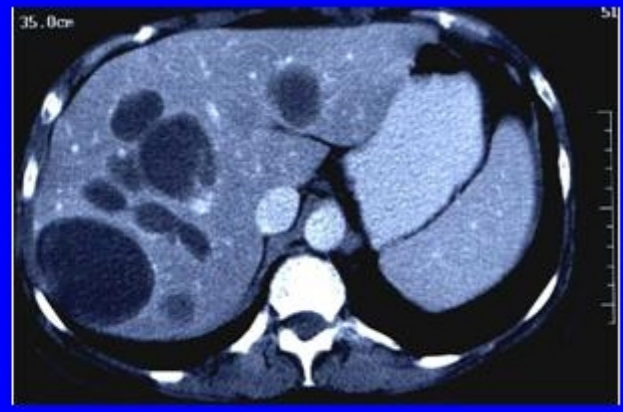


0

+11 mos

"Tissue" partial response…





VOLUME 25 · NUMBER 13 · MAY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Correlation of Computed Tomography and Positron Emission Tomography in Patients With Metastatic Gastrointestinal Stromal Tumor Treated at a Single Institution With Imatinib Mesylate: Proposal of New Computed Tomography Response Criteria

Haesun Choi, Chuslip Charnsangavej, Silvana C. Faria, Homer A. Macapinlac, Michael A. Burgess, Shreyaskumar R. Patel, Lei L. Chen, Donald A. Podoloff, and Robert S. Benjamin

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

We Should Desist Using RECIST, at Least in GIST

Robert S. Benjamin, Haesun Choi, Homer A. Macapinlac, Michael A. Burgess, Shreyaskumar R. Patel, Lei L. Chen, Donald A. Podoloff, and Chuslip Charnsangavej

Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial

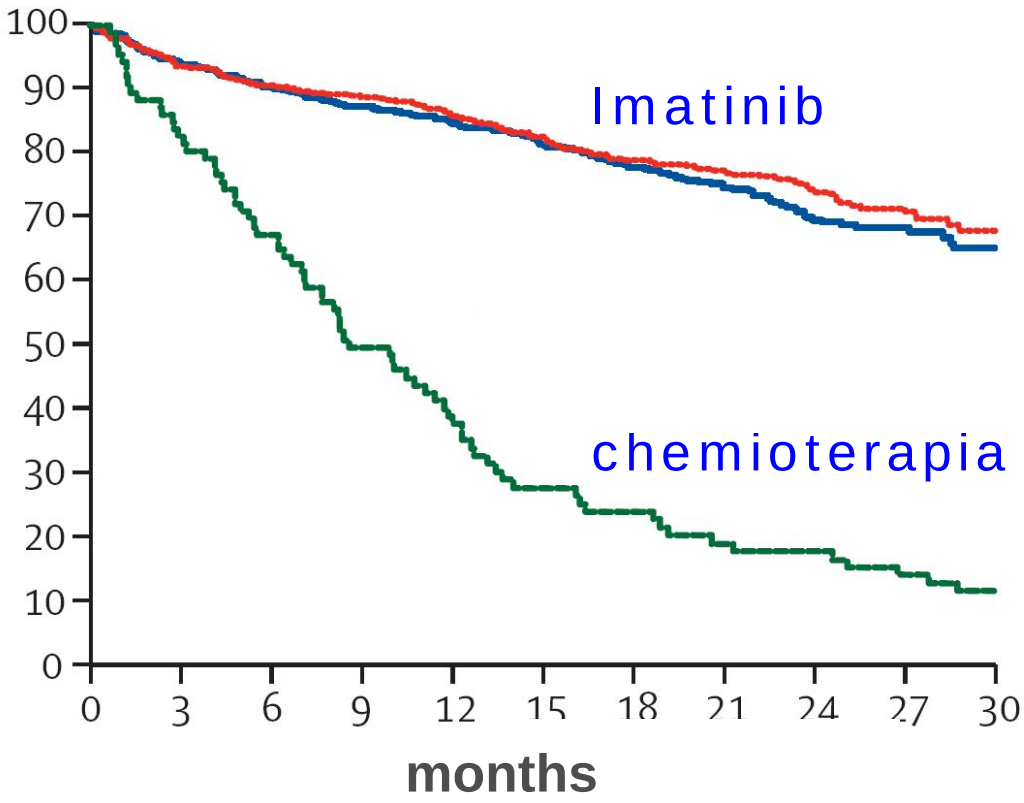
*Jaap Verweij, Paolo G Casali, John Zalcberg, Axel LeCesne, Peter Reichardt, Jean-Yves Blay, Rolf Issels, Allan van Oosterom, Pancras C W Hogendoorn, Martine Van Glabbeke, Rossella Bertulli, Ian Judson, for the EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group**

Lancet 2004; 364: 1127–134

See **Comment** page 1101

*Study investigators listed at end f report

OS



Impact of "the model"

- Epidemiology
- Pathology
- Determination of prognostic/predictive factors
- Determination of response

Epidemiology

- Old
  - $1.5/10^6$ people
- New
  - $16/10^6$ people
- About 1,000 cases/year in Italy

Arthur Purdy Stout

Historical Perspective

- 1940, Arthur Purdy Stout
- Smooth muscle neoplasms
- 1960-70, Electron Microscopy
  - few showed EM features of SM differentiation
- 1980, IHC
  - many lacked IHC features of SM differentiation
- 1983, Mazur and Clark : "stromal tumor"
- 1984, Herrera: Plexosarcoma/"GANT"
  - S-100/NSE +/EM: Schwannian or neuro-axonal differentiation

What was a GIST?

- All mesenchymal tumors of GI tract
  - including true leiomyomas and schwannomas
- A group of mesenchymal tumors with certain common histopathologic properties
  - excluding true leiomyomas and schwannomas

The KIT revolution

- Activating *KIT* mutations
- Expression of KIT protein (CD117)
- Reliable phenotypic marker

The KIT revolution

- Interstitial cells of Cajal
  - Gastrointestinal pacemaker cells
  - Peristalsis regulation
- Interface between the autonomic innervation and smooth muscle
- IHC/ EM features of smooth muscle and neuronal differentiation


AYUNTAMIENTO
DE CÓRDOBA
PLAZA DE
RAMÓN Y CAJAL

- Exon 11
  - Juxtamembrane domain
  - Frequency = 66%
  - Disruption of an amphipatic alpha loop regulatory domain
  - Spontaneous dimerization
- Exon 9
  - Extracellular domain
  - Frequency = 10%
  - Small intestine (95%)
  - Disruption of a dimerization motif in the extracellular domain

- Exon 13
  - Kinase I domain
  - Frequency = 1.2 %
  - Ligand independent activation
  - Mechanism unclear
- Exon 17
  - Activation loop
  - Frequency = 0.6%
  - N822K and D820Y
  - Nearby codon in exon 17 (Asp816) involved in mast cell disease, seminoma, AML, sinonasal NK/T cell NHL
  - Mechanism of activation unclear

All we need is KIT?

- Greater complexity
- KIT alone may be not sufficient
- Other oncogenetic mechanisms involved

KIT vs. PDGFRA

- Science 2003, 299:708-710.
- 40 GISTS lacking KIT mutations
- 35% activating mutations of PDGFRA
- KT and PDGFRA aberration mutually exclusive
- Identical activation of downstream signalling pathways

GIST in NF1 patients

- NF1 cases = no mutations (J Pathol 2004; 202:80)
- Incidence: 7%
- Multifocality frequent

Paediatric GIST

- Majority Wild type
- Female predominance
- Multifocality frequent

Familial GIST

- Japanese family
  - Deletion of 559/560 on exon 11
  - Multiple GIST and disorder of pigmentation
  - Knock-in mice (murine $KIT^{\Delta 558}$)
    - KIT + GIST in caecum
- Other families with V559A
  - Multiple GIST
  - ICC hyperplasia
  - Disorder of pigmentation
  - Urticaria pigmentosa

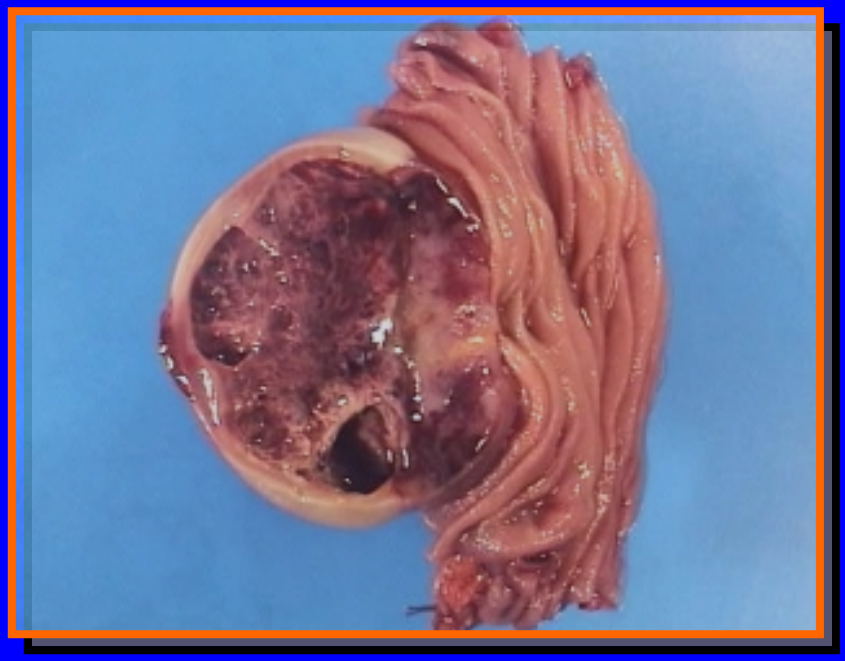
Carney's Complex

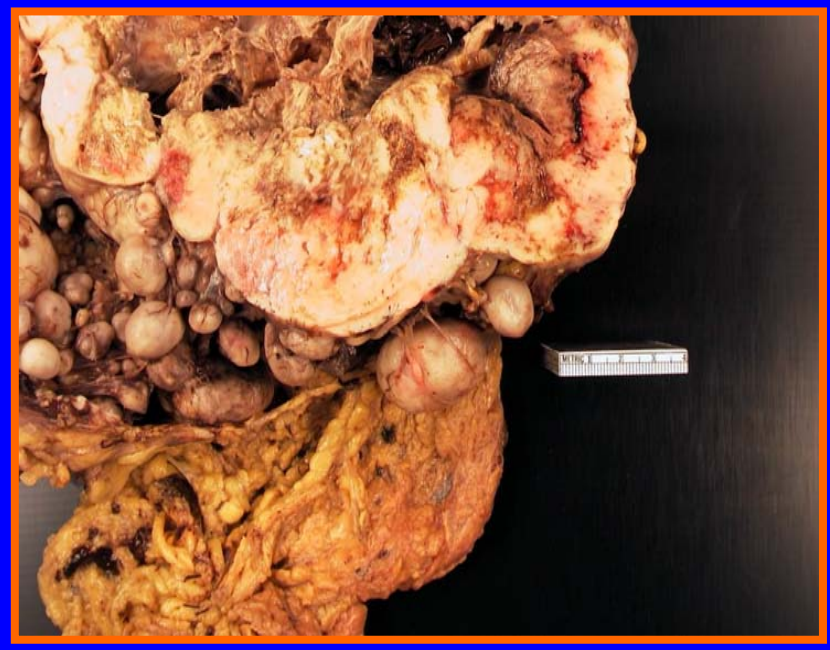
- GIST, paraganglioma, pulmonary chondromas
  - KIT/PDGFRA wild type
  - Sporadic
- Carney and Stratakis
  - Multiple parangliomas and multiple gastric GISTs
  - Familial autosomal dominant

Tumor Progression and Cytogenetic Mechanisms

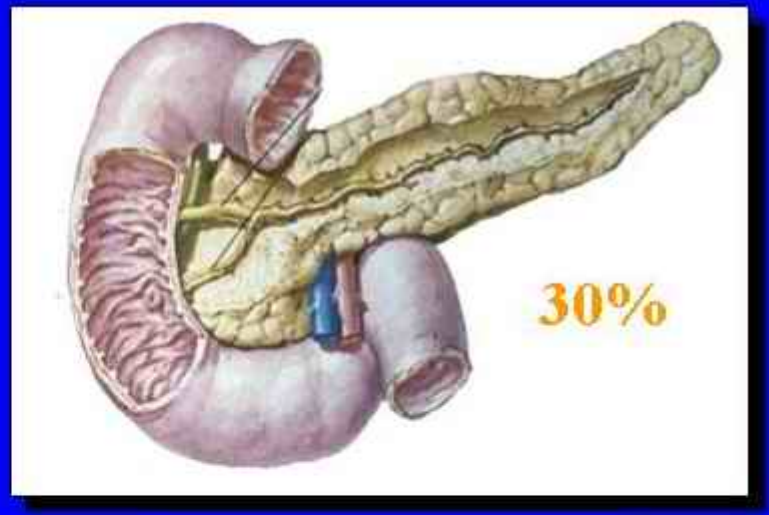
- Kit mutation = early event
- Tumor progression associated with:
  - Loss of chromosome 14, 1p, 9p, 11p, 22q
- 4q12 (kit locus) almost never amplified or rearranged

Pathology of GIST



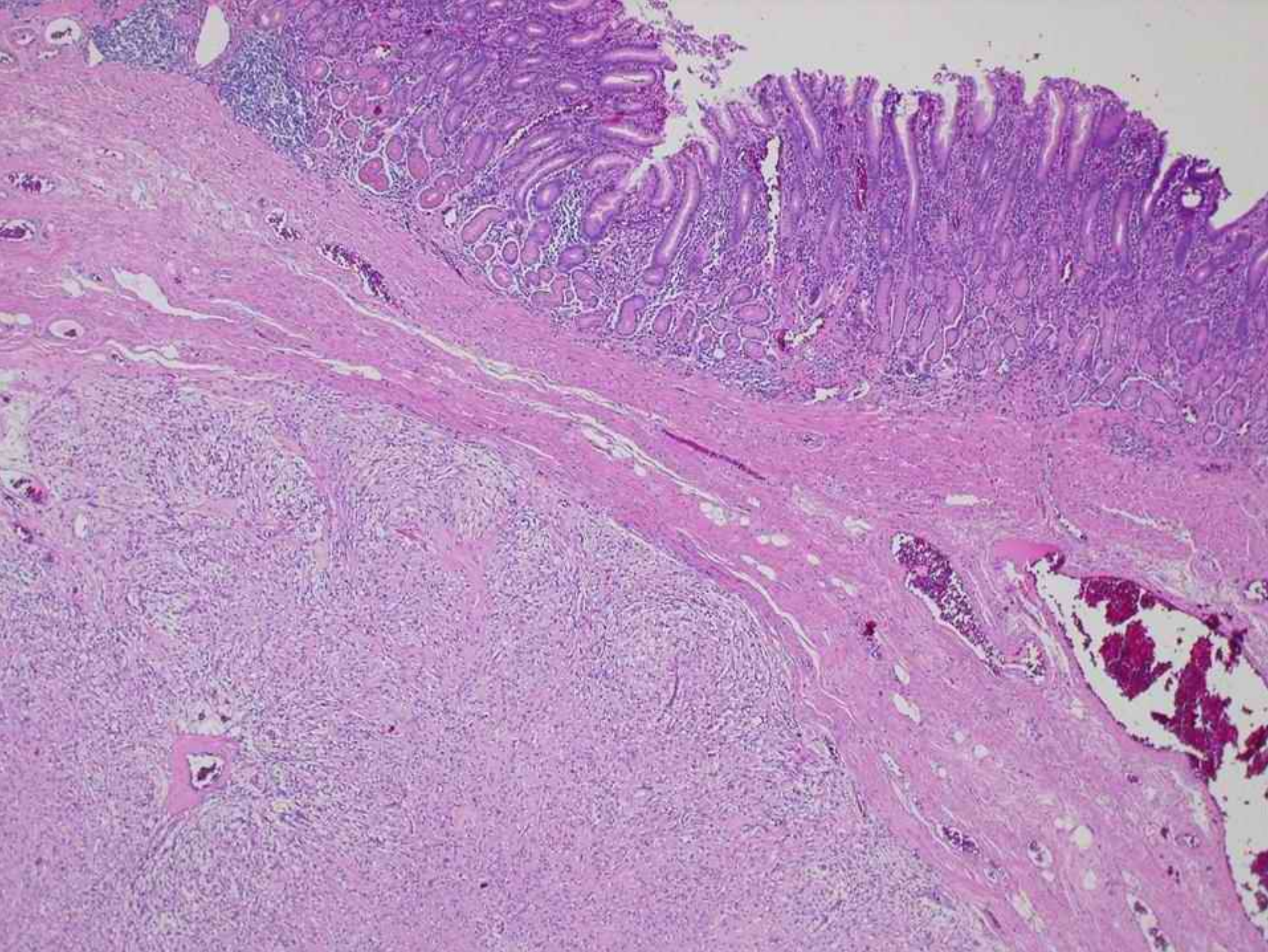


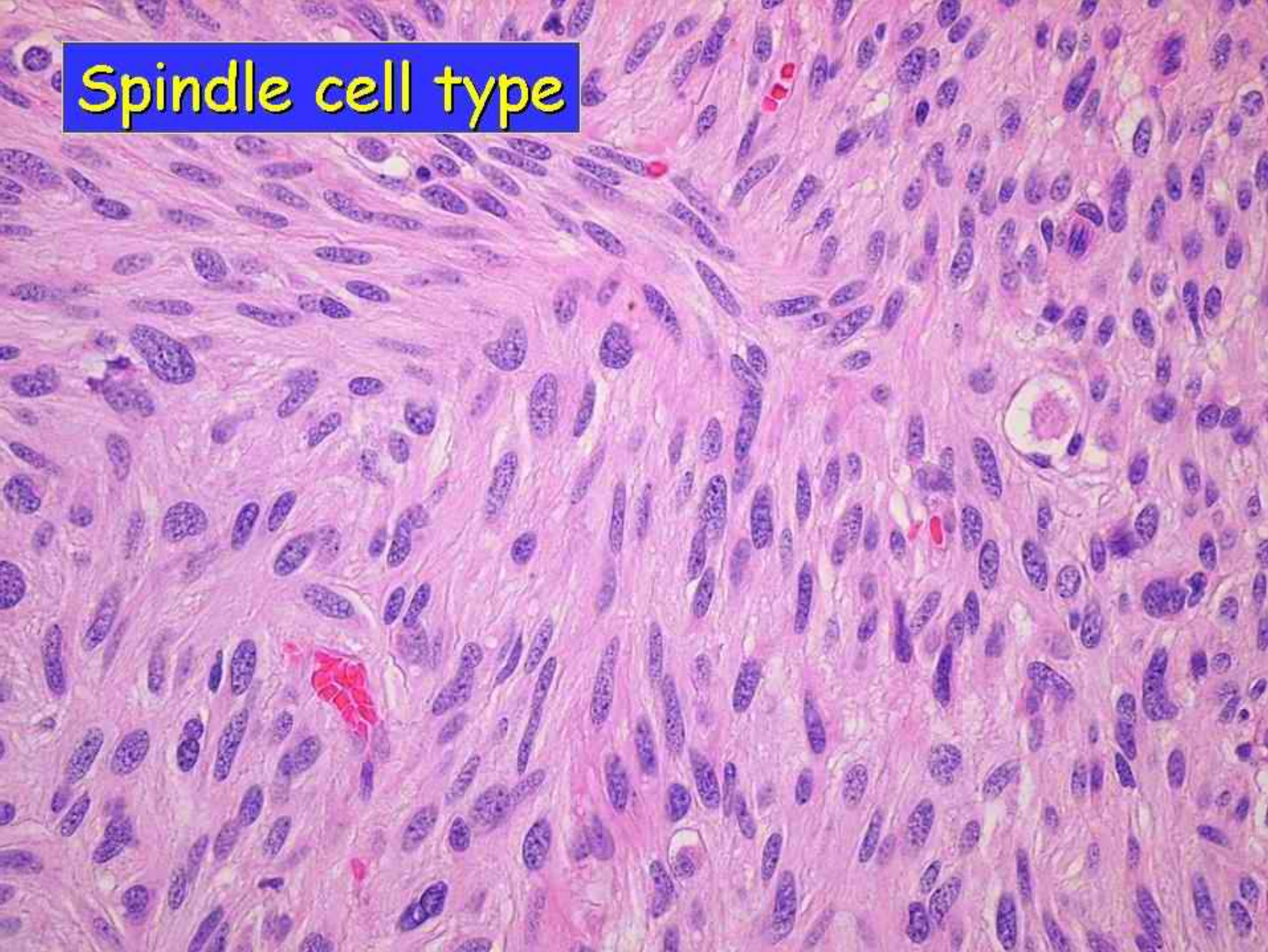
GIST: anatomic sites

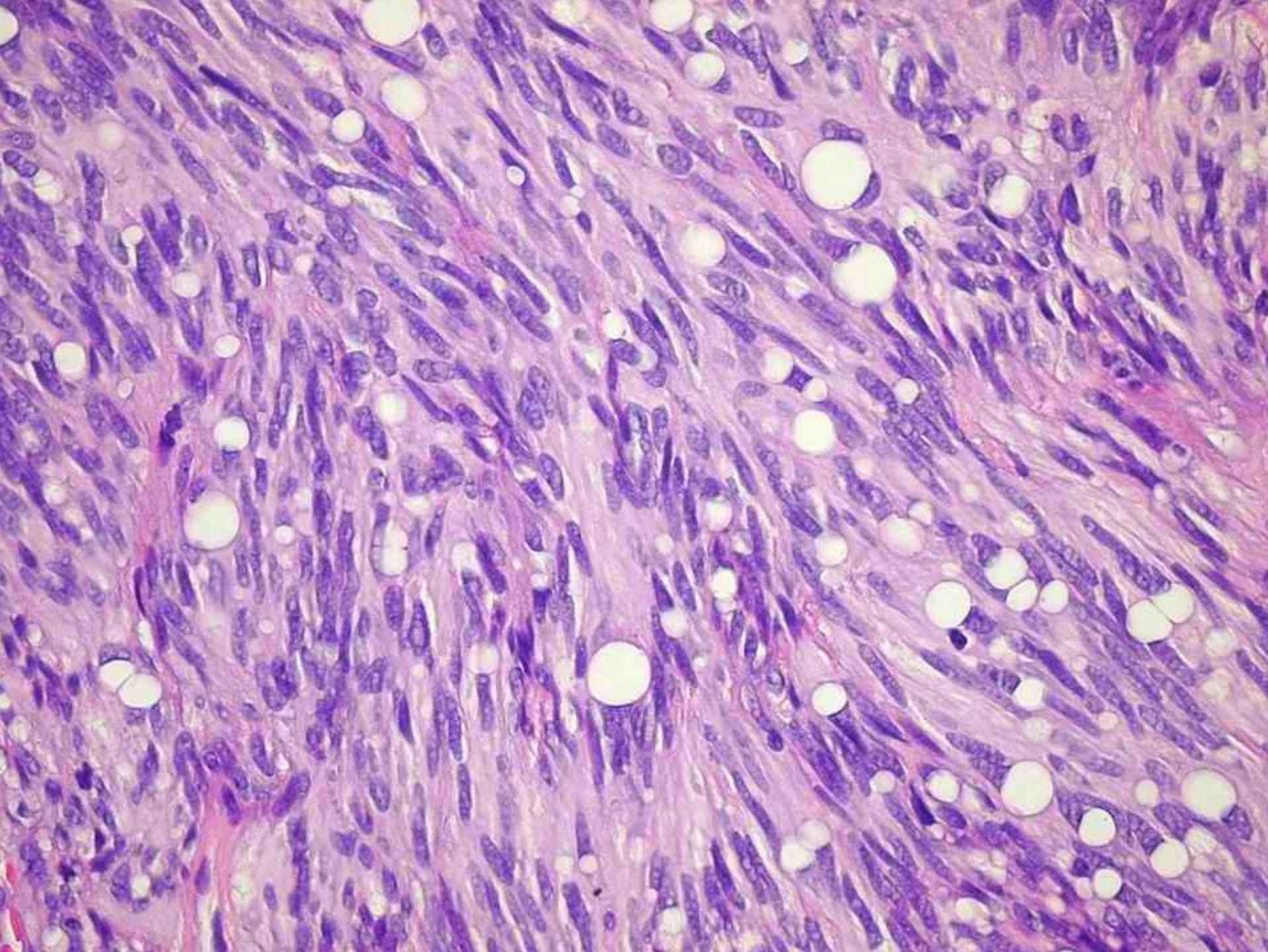


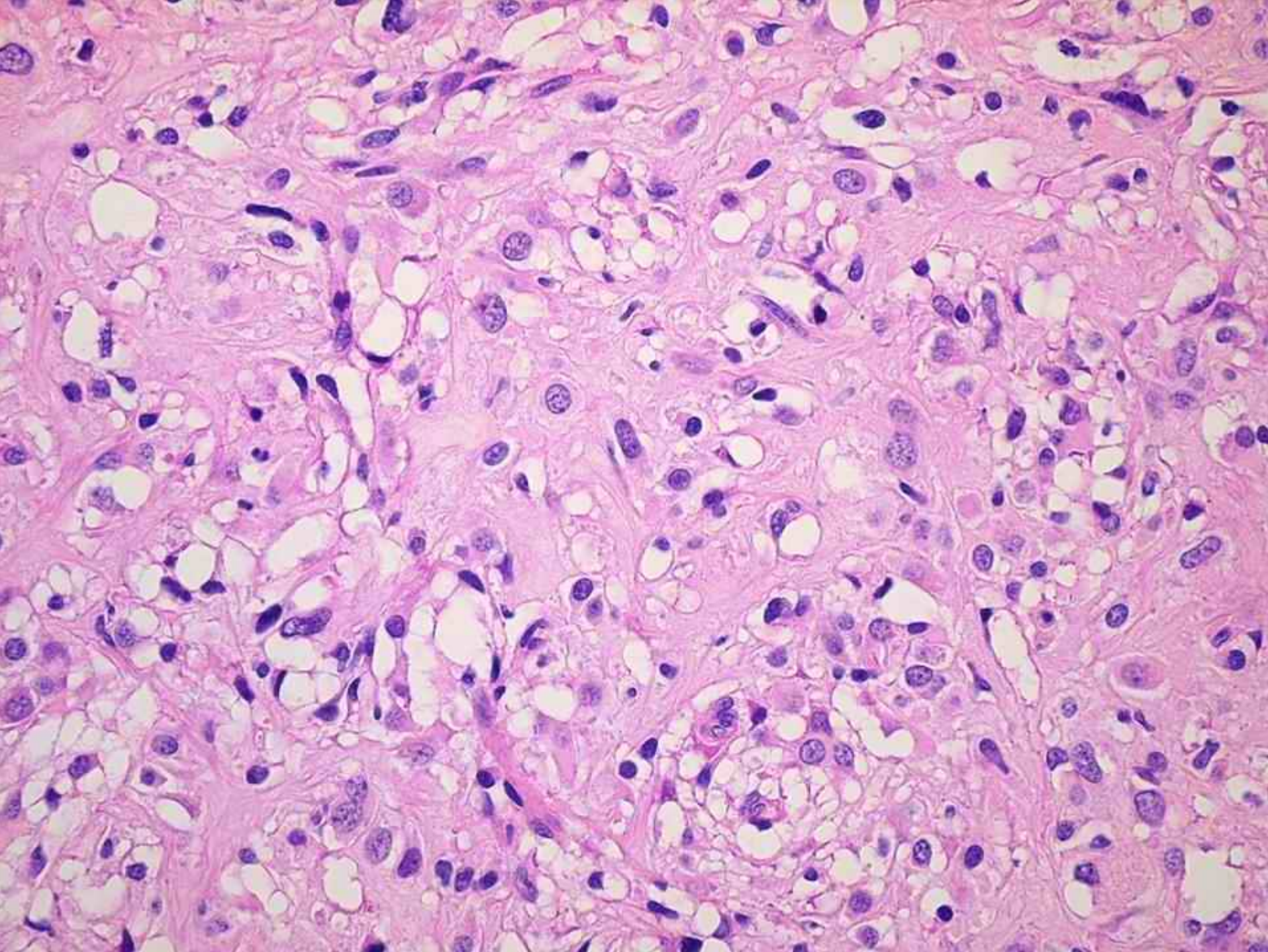
GIST

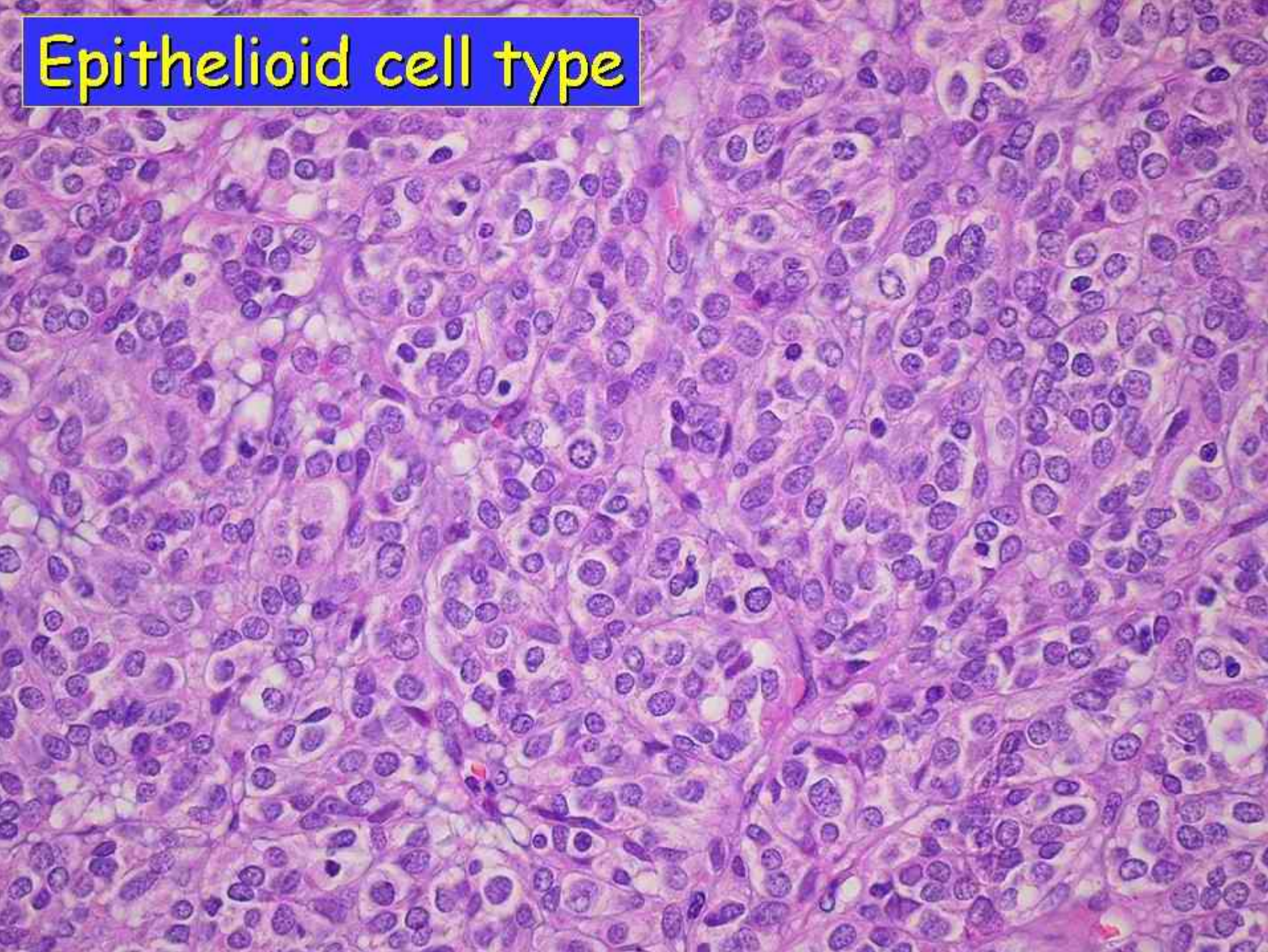
- Spindle cell type (70%)
- Epithelioid type (20%)
- Mixed type (10%).
  - prominent myxoid stroma (5%)
  - a nested paraganglioma-like (small intestine)
  - carcinoid-like growth pattern
  - pleomorphism (< 2-3%)

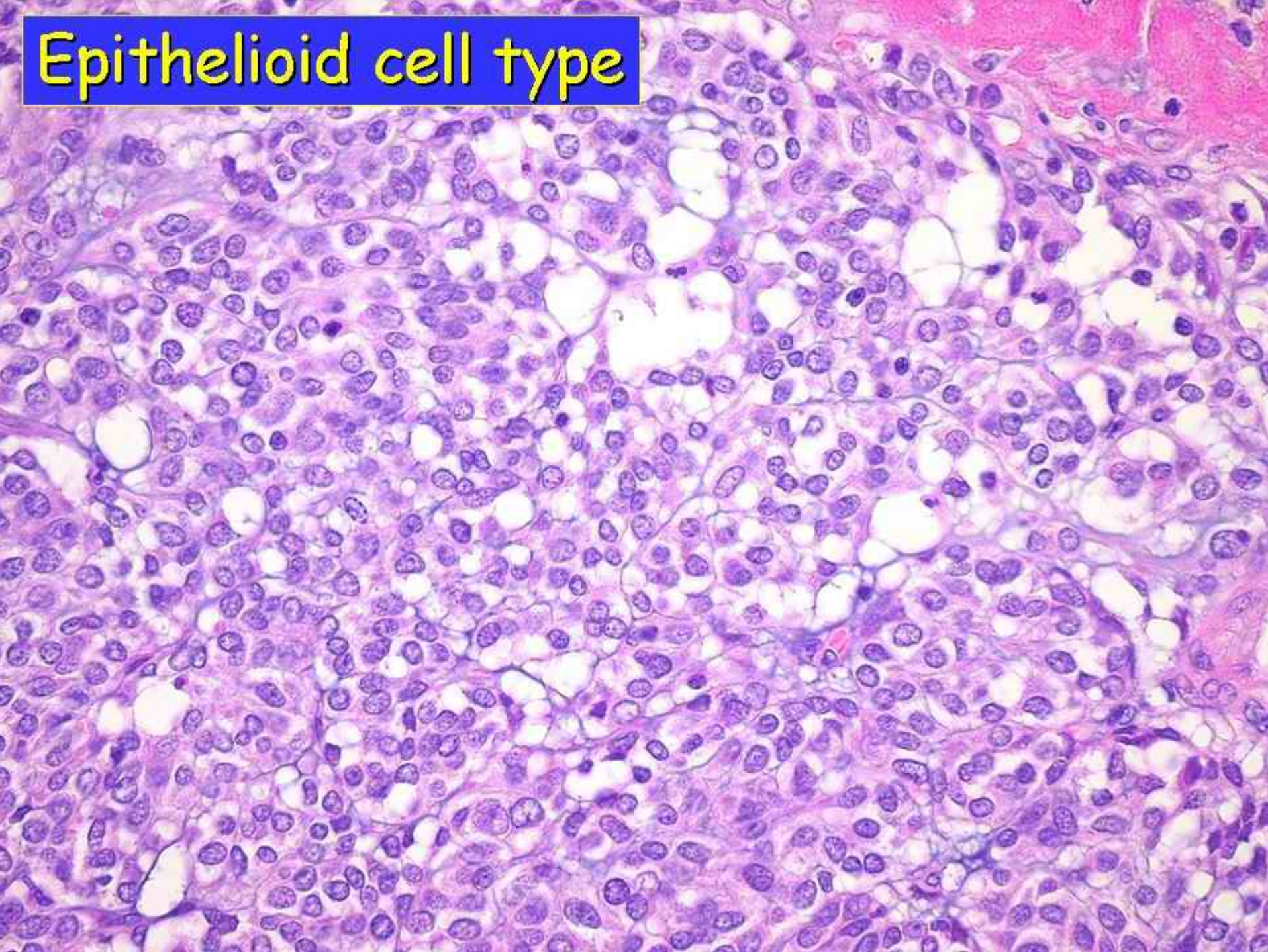


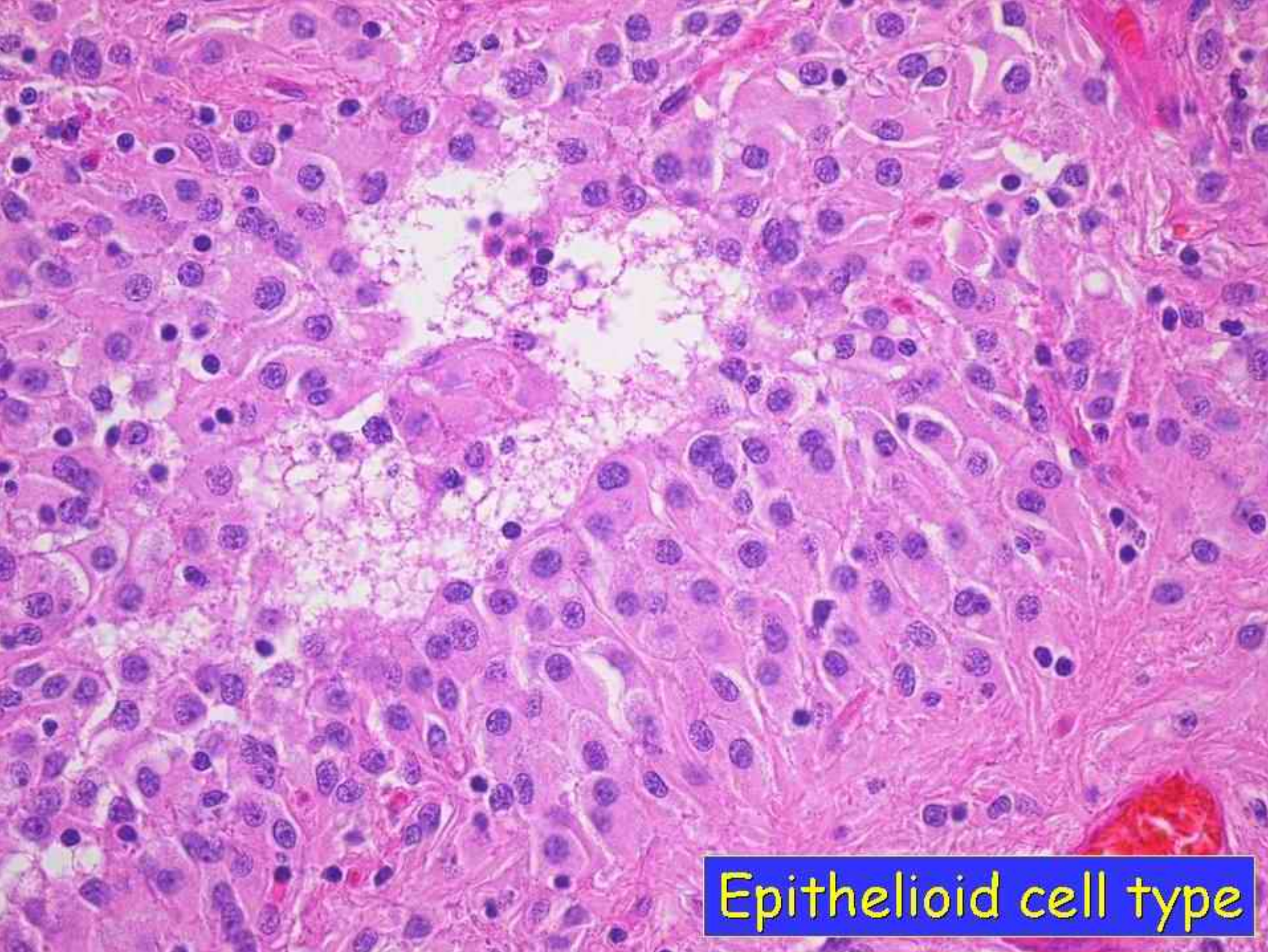

Spindle cell type

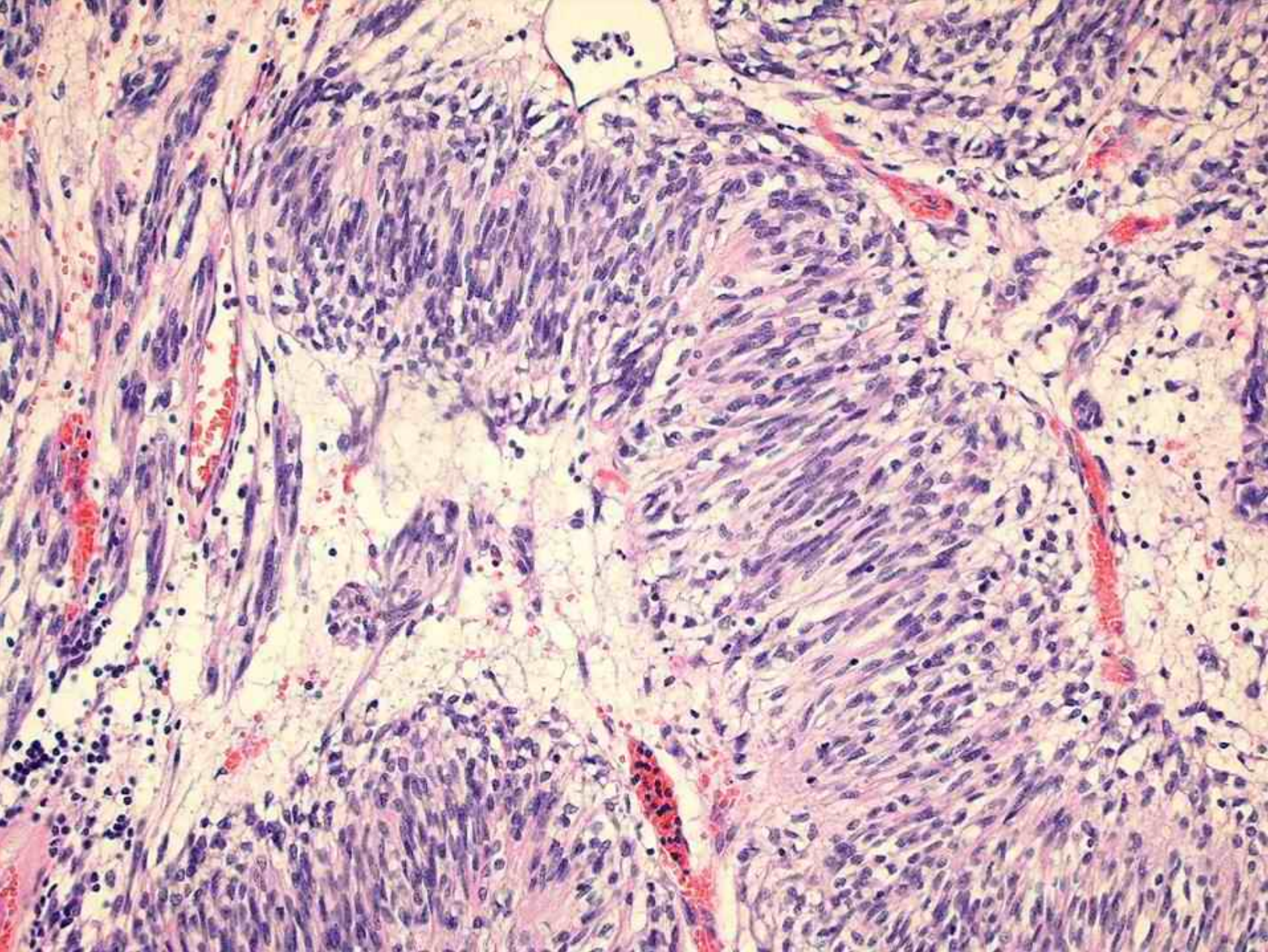


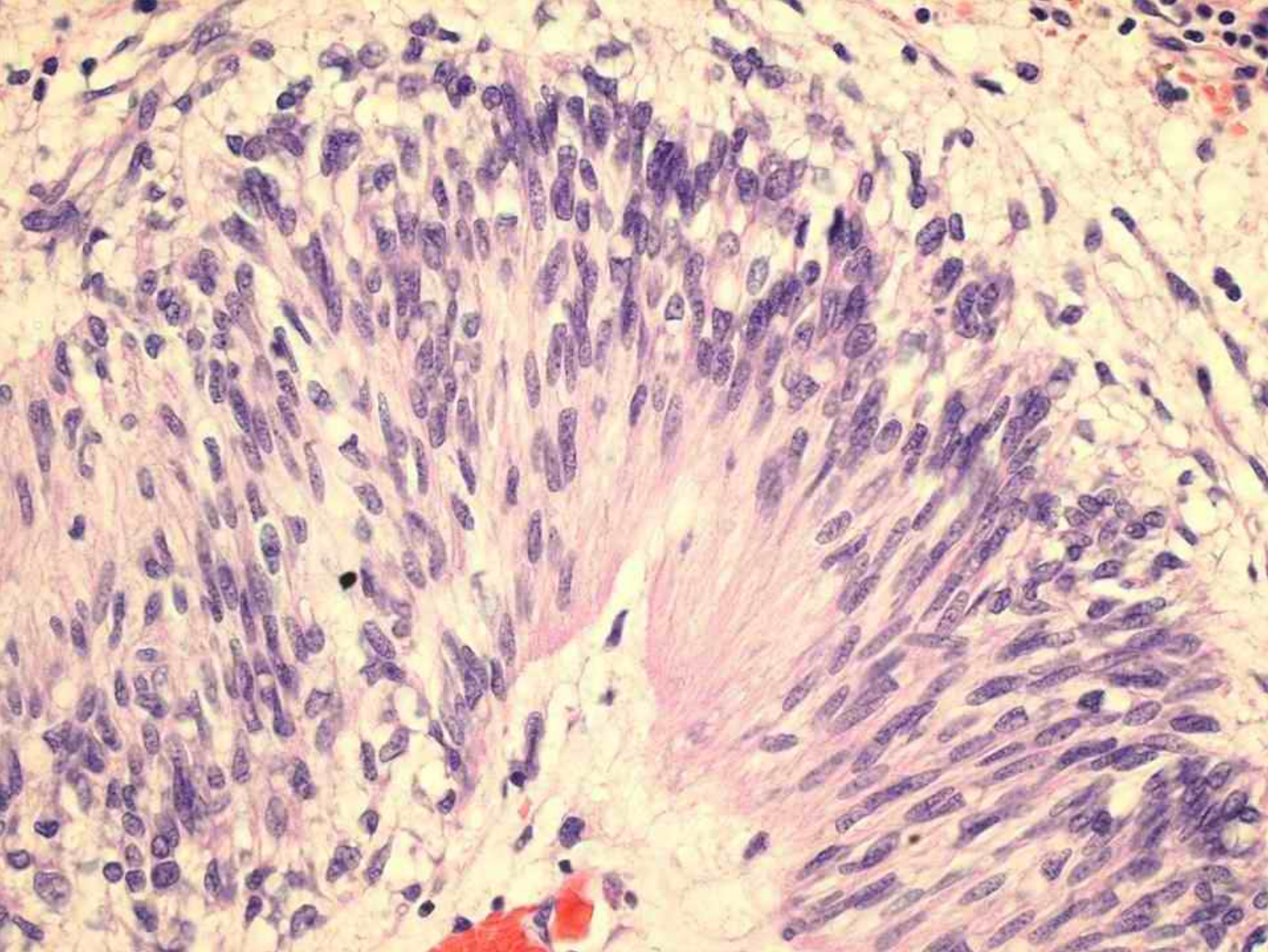


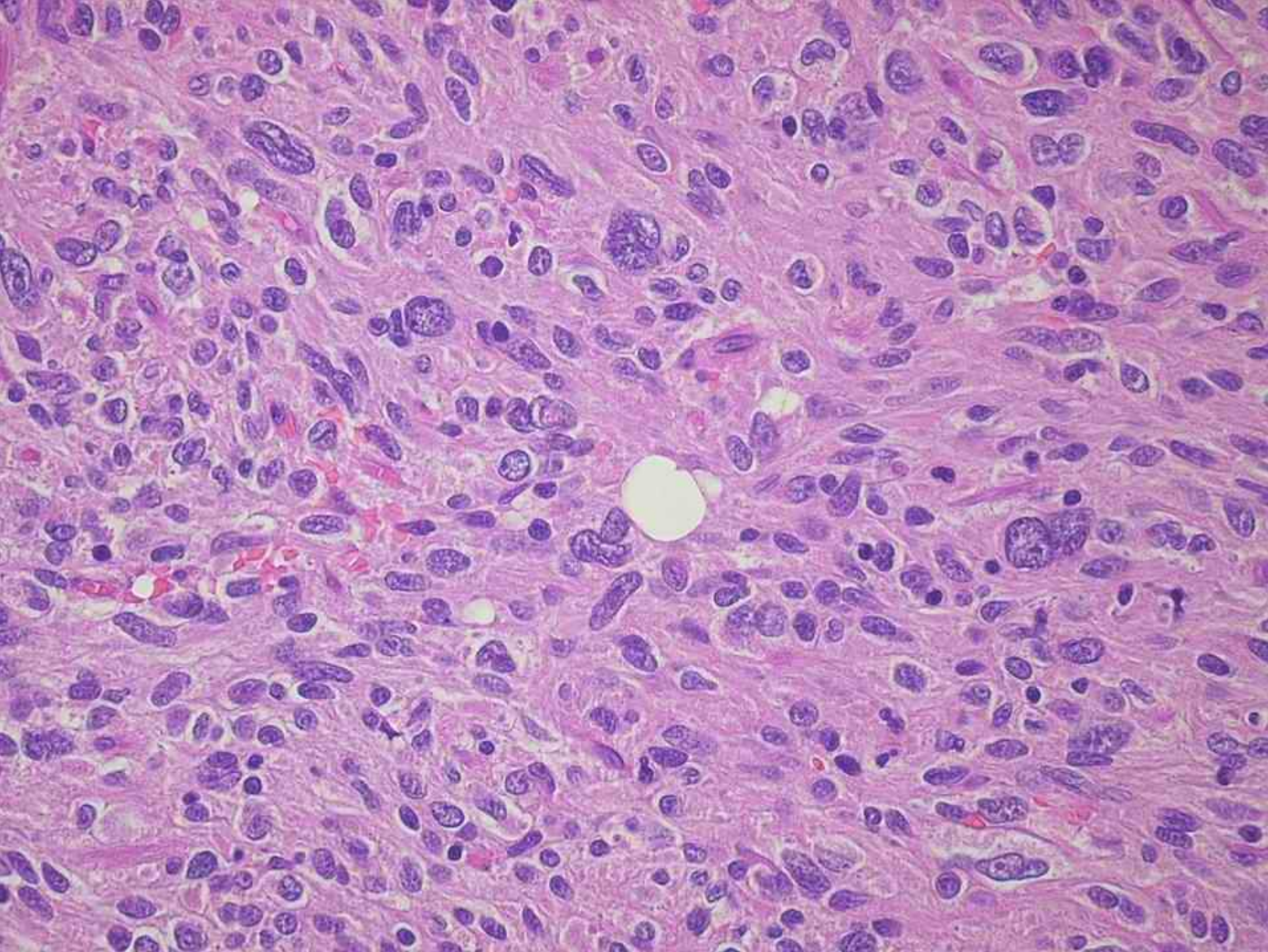

Epithelioid cell type

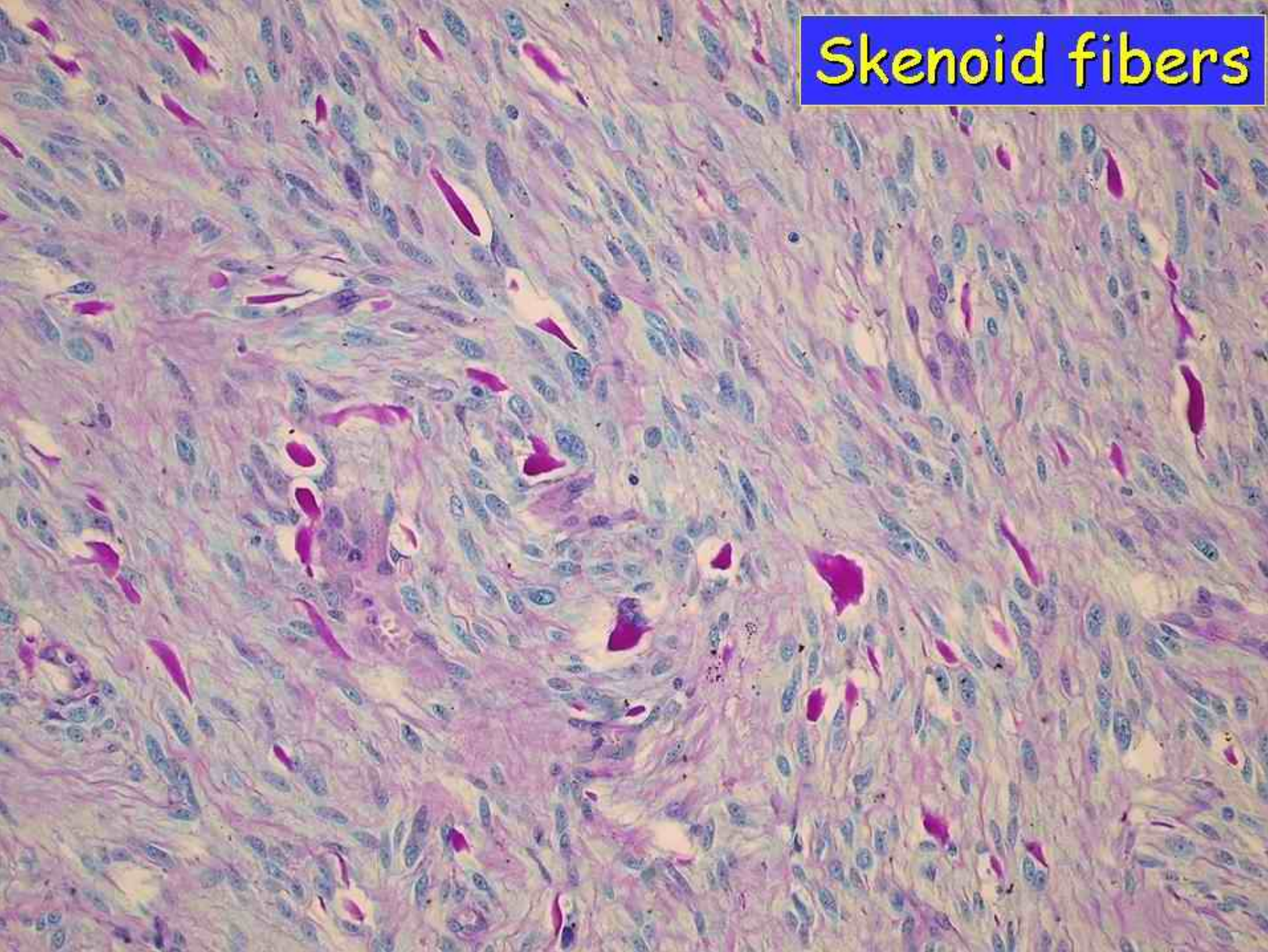

Epithelioid cell type

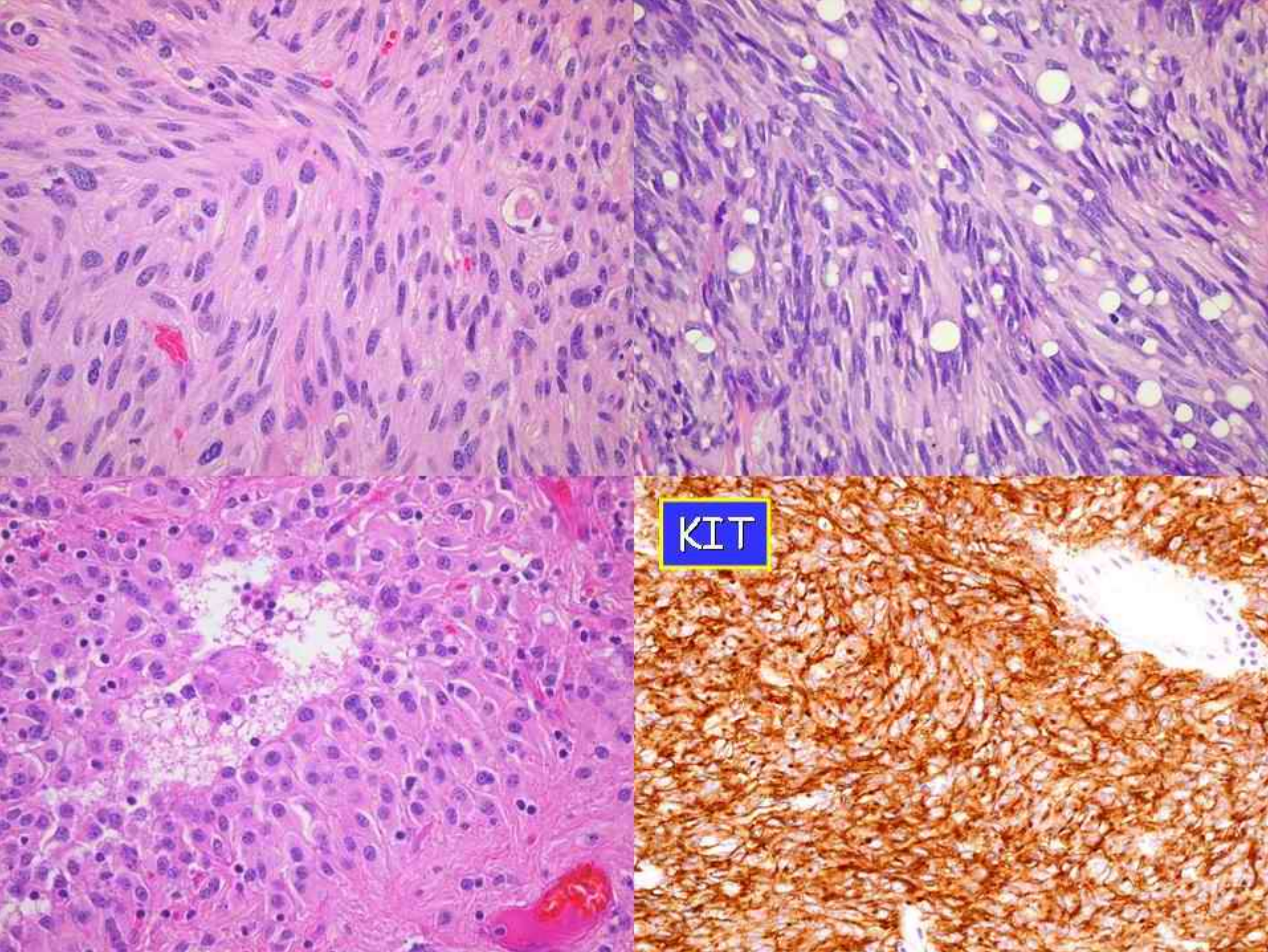

Epithelioid cell type

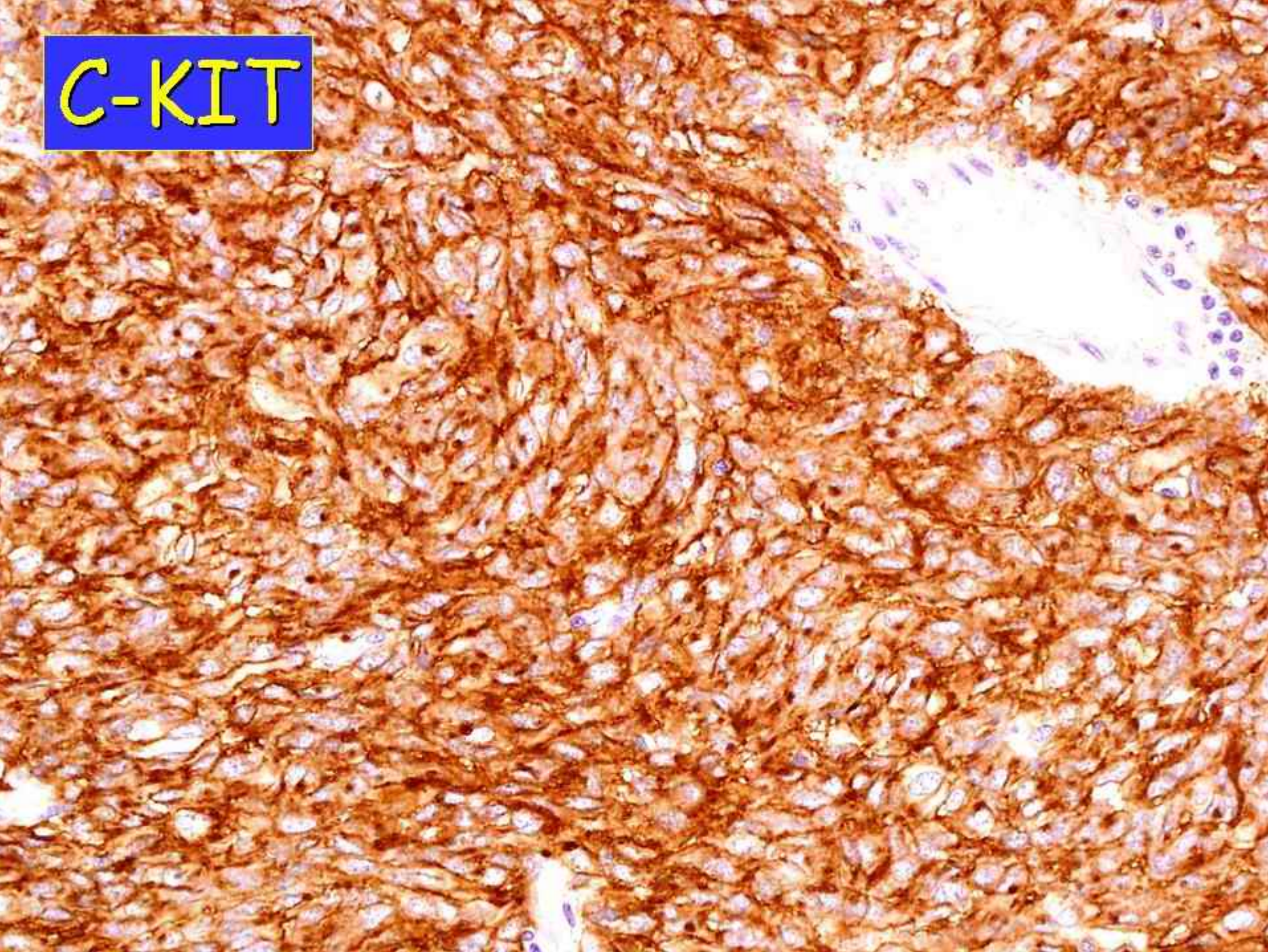







Skenoid fibers


KIT


C-KIT


May I call GIST a KIT-ve lesion?

KIT- GIST

- Medeiros et al, AJSP 2004
- Approximately 5%
- Epithelioid morphology
- PDGFR-alpha mutations

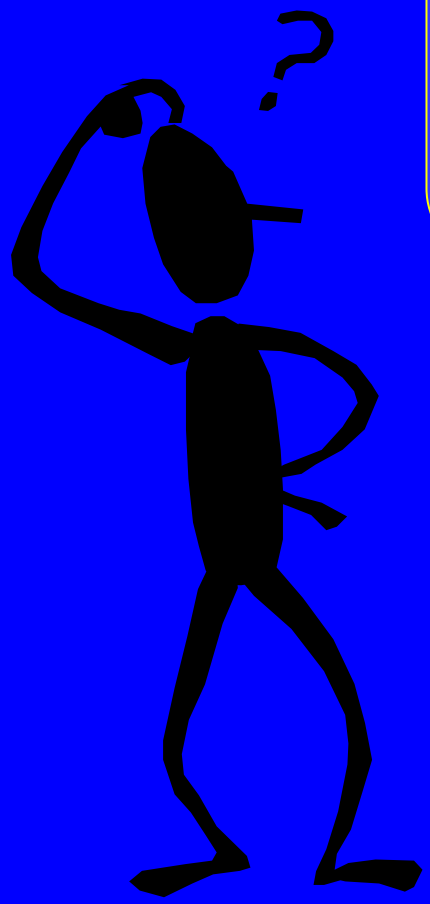
C-kit immunohistochemistry: to cook or not to cook?

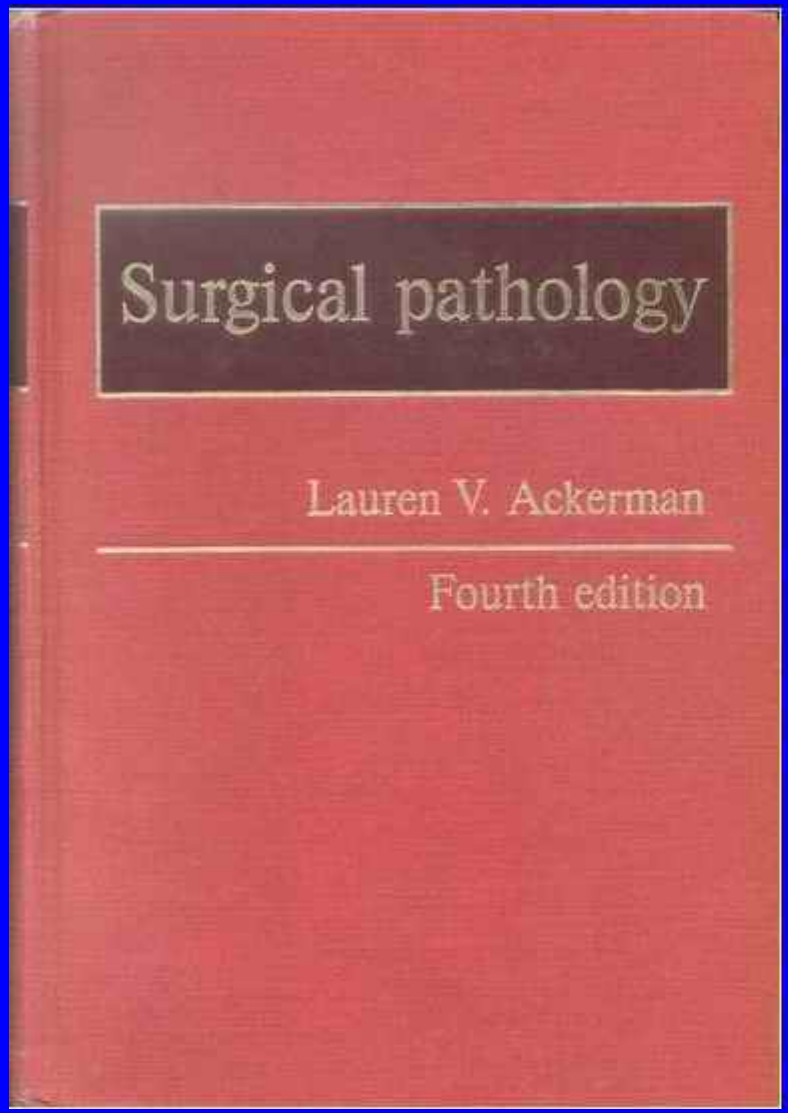
- Kit immunostaining = very easy
- Antigen retrieval
  - Higher sensitivity
  - Lower specificity
- Sensitivity = technical artifact

Differential Diagnosis

- Smooth muscle tumors
  - Desmin/Caldesmin +
- Neural tumors
  - S-100 +
- Intraabdominal fibromatosis
  - Beta catenin +
- Inflammatory myofibroblastic tumor
  - Alk-1 +
- Sarcomatoid carcinoma
  - CK/EMA+ (SMA+)
- FDC sarcoma
  - CD21/CD35+

May I call a GIST benign?




Surgical pathology
Lauren V. Ackerman
Fourth edition

Smooth Muscle Tumors of the GI tract

"However, smooth muscle tumors of the GI tract have been known to appear perfectly benign under the microscope and behave as malignant neoplasms clinically"

(Ackerman, 1968)

Prognostic parameters

- Size
- Mitotic Rate
- Site
  - Mucosal invasion
  - Tumor necrosis
  - High cellularity
  - Cell proliferation markers
  - …
- Type of KIT mutations

Risk Assessment

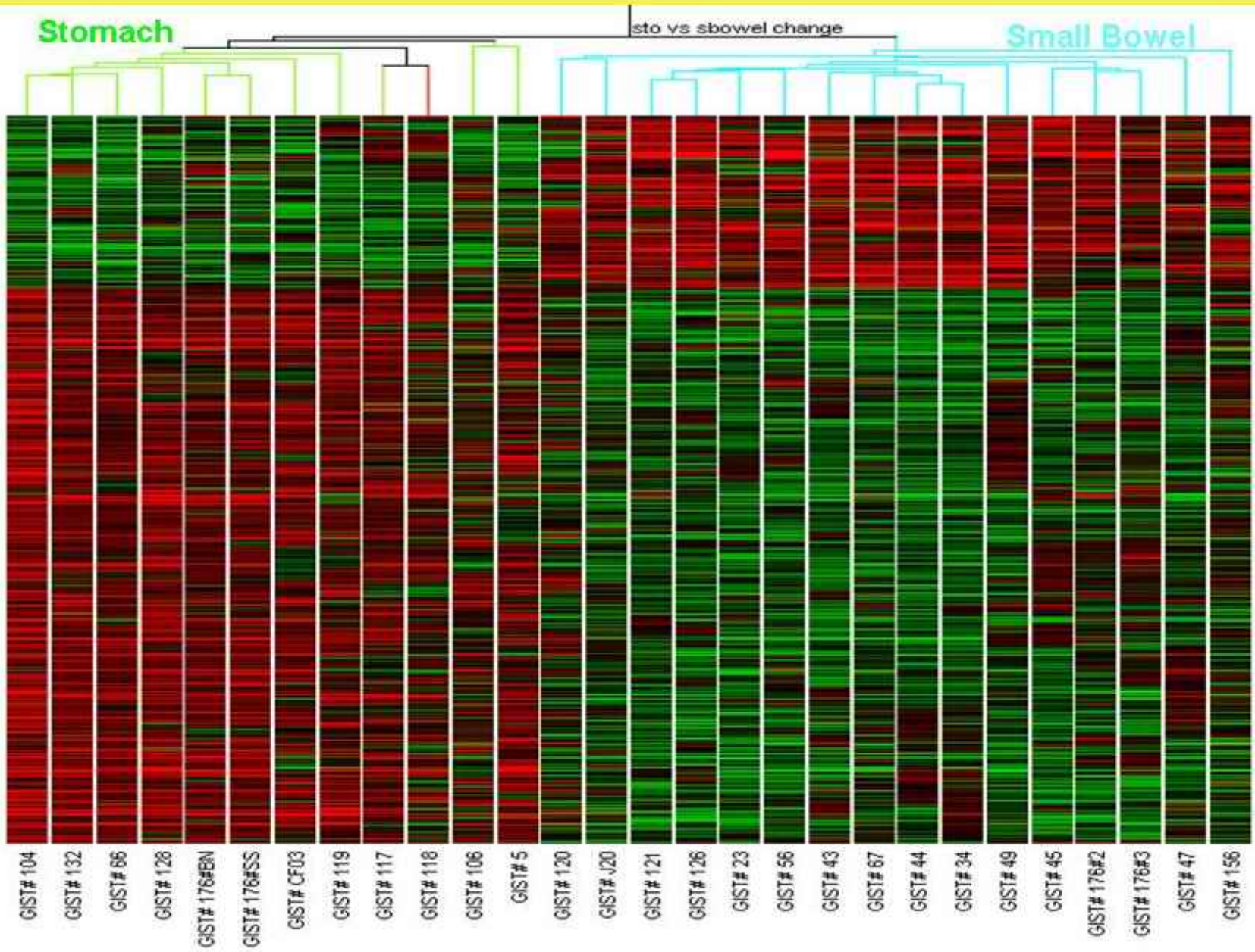
NIH Consensus Conference

	Size (cm)	Mitoses
Very Low Risk	< 2	< 5/50HPF
Low Risk	2-5	≤ 5/50HPF
Interm'te Risk	≤ 5 6-10	6-10/50HPF ≤5/50HPF
High Risk	> 5 > 10 Any size	> 5/50HPF Any MR > 10/50HPF

New Risk Classification

Size (cm)	*Mitotic Index*	Stomach	Duodenum	jejumun/ileum	rectum
≤2	≤5	none	none	none	none
>2≤5		Very low	low	low	low
>5≤10		low	intermediate	No data	No data
>10		intermediate	high	high	high
≤2	>5	none	high	No data	high
>2≤5		intermediate	high	high	high
>5≤10		high	high	high	high
>10		high	high	high	high

Modified from Miettinen & Lasota, 2006


Stomach
sto vs sbowel change
Small Bowel
GIST# 104
GIST# 132
GIST# 65
GIST# 128
GIST# 176#BN
GIST# 176#SS
GIST# CF03
GIST# 119
GIST# 117
GIST# 118
GIST# 106
GIST# 5
GIST# 120
GIST# J20
GIST# 121
GIST# 126
GIST# 23
GIST# 56
GIST# 43
GIST# 67
GIST# 44
GIST# 34
GIST# 49
GIST# 45
GIST# 176#2
GIST# 176#3
GIST# 47
GIST# 156

Molecular Classification

	Frequency	IV sensitivity	Objctive Response	Progressive Disease
KIT Ex 8	< 1%	Yes	-	-
KIT Ex 9	10%	Yes	34-40%	17%
KIT Ex 11	67%	Yes	65-67%	3%
KIT Ex 13	1%	Yes	Rr	-
KIT Ex 14	1%	Yes	Rr	-
PDGFRA 12	1%	Yes	Rr	-
PDGFRA 14	< 1%	Yes	-	-
PDGFRA 18	5%	D842V No	Rr	D842V
Wild Type	12-15%	Yes	23-40%	19%

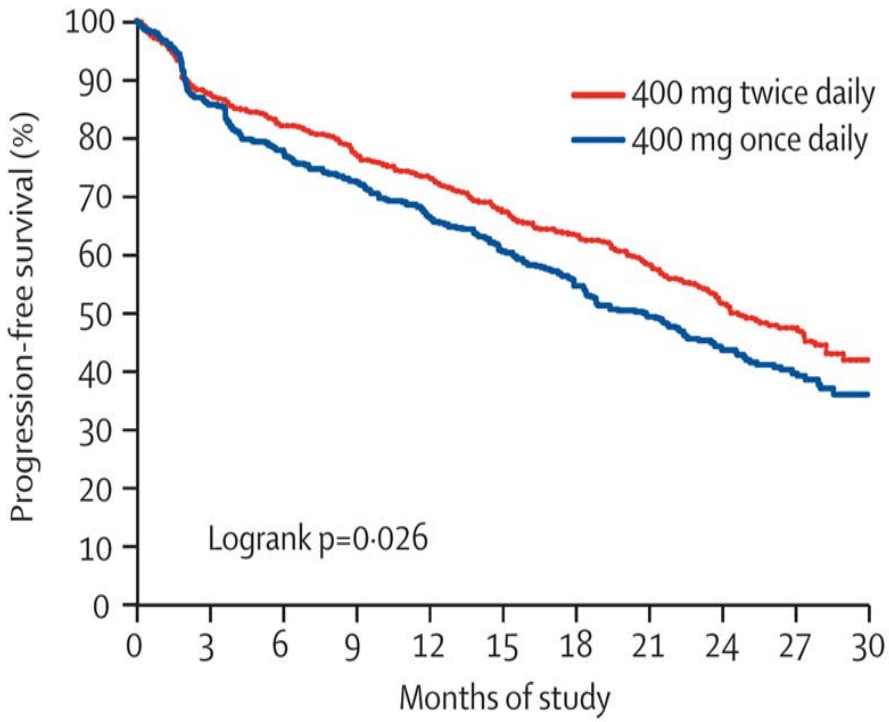
Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial

*Jaap Verweij, Paolo G Casali, John Zalcberg, Axel LeCesne, Peter Reichardt, Jean-Yves Blay, Rolf Issels, Allan van Oosterom, Pancras C W Hogendoorn, Martine Van Glabbeke, Rossella Bertulli, Ian Judson, for the EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group**

Lancet 2004; 364: 1127–134

See Comment page 1101

*Study investigators listed at end of report



EUROPEAN JOURNAL OF CANCER 42 (2006) 1093–1103

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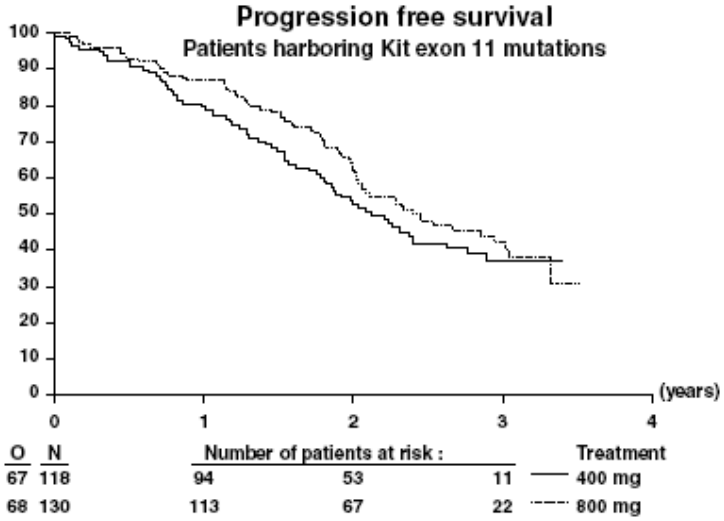
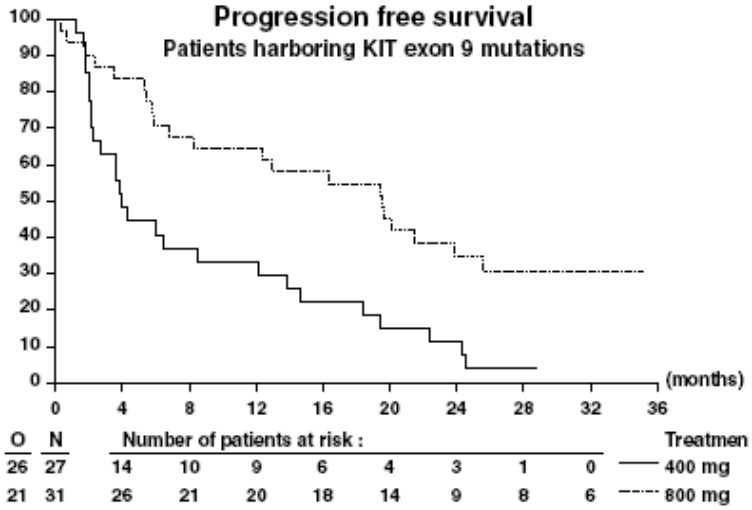
journal homepage: www.ejconline.com

KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours

Maria Debiec-Rychter[a,*], *Raf Sciot*[b], *Axel Le Cesne*[d], *Marcus Schlemmer*[e], *Peter Hohenberger*[f], *Allan T. van Oosterom*[c], *Jean-Yves Blay*[g], *Serge Leyvraz*[h], *Michel Stul*[a], *Paolo G. Casali*[i], *John Zalcberg*[j], *Jaap Verweij*[k], *Martine Van Glabbeke*[l], *Anne Hagemeijer*[a], *Ian Judson*[m], *On behalf of the EORTC Soft Tissue and Bone Sarcoma Group, The Italian Sarcoma Group and the Australasian GastroIntestinal Trials Group*





Predictive Role of KIT/PDGFRA Sequencing

- Imatininb vs Sunitinib
- Dosage (400 vs 800)
- Important in the metastatic settings
- Mandatory in the adjuvant setting

Gastrointestinal Stromal Tumors: The Incidence, Prevalence, Clinical Course, and Prognostication in the Preimatinib Mesylate Era

A Population-Based Study in Western Sweden

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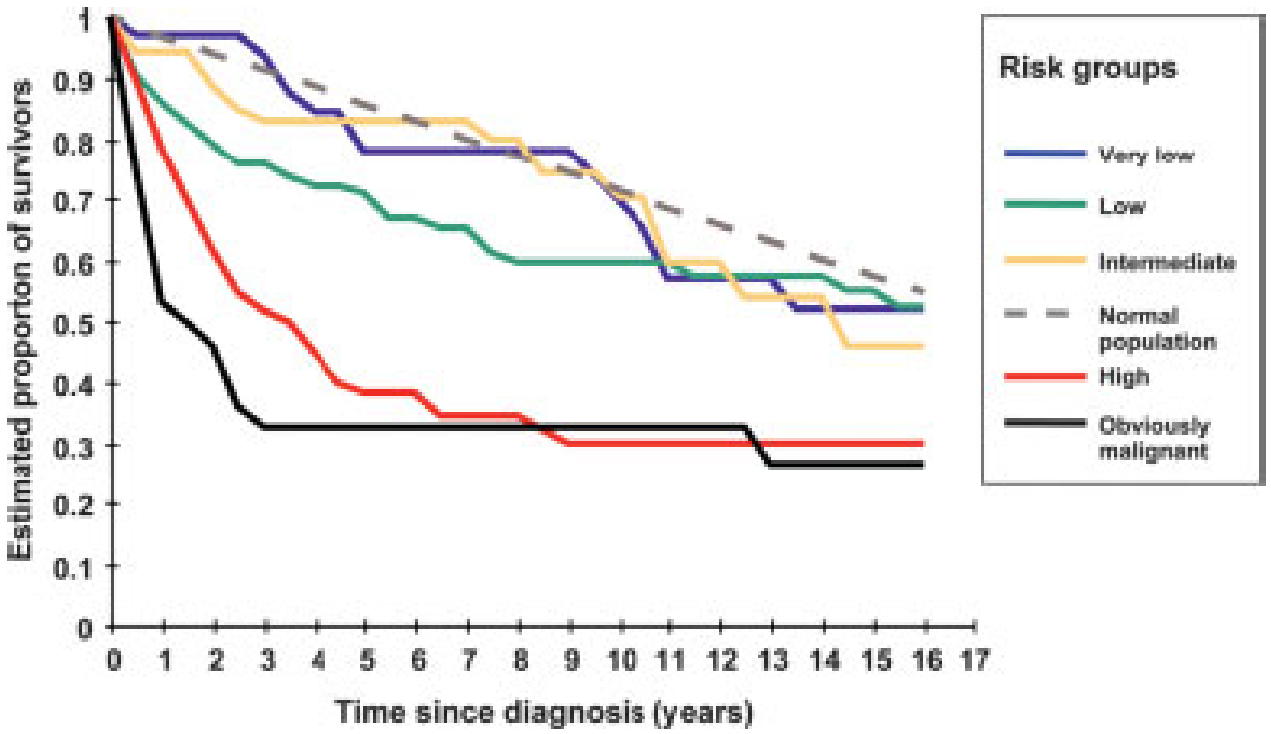

FIGURE 1. The estimated overall survival in 259 patients with clinically detected gastrointestinal stromal tumors is compared according to risk group with an age-matched and gender-matched, normal population.

Is low risk really that low?

- 58/170 pts (VLR, LR and IR) = incidental findings
- A proportion of pts in the low risk category died for other malignancies

1021 patients

Molecular pathology of Resistance

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Molecular Correlates of Imatinib Resistance in Gastrointestinal Stromal Tumors

Michael C. Heinrich, Christopher L. Corless, Charles D. Blanke, George D. Demetri, Heikki Joensuu, Peter J. Roberts, Burton L. Eisenberg, Margaret von Mehren, Christopher D.M. Fletcher, Katrin Sandau, Karen McDougall, Wen-bin Ou, Chang-Jie Chen, and Jonathan A. Fletcher

Molecular genetics and resistance

- Primary resistance different from secondary resistance
- In PR intracellular signalling identical to untreated GISTs
- Persistent KIT phophorilation and activation of downstream AKT and MAPK pathways
- Exon 9 and PDGFRA D842V mutations overrepresented in PR

Molecular genetics and resistance

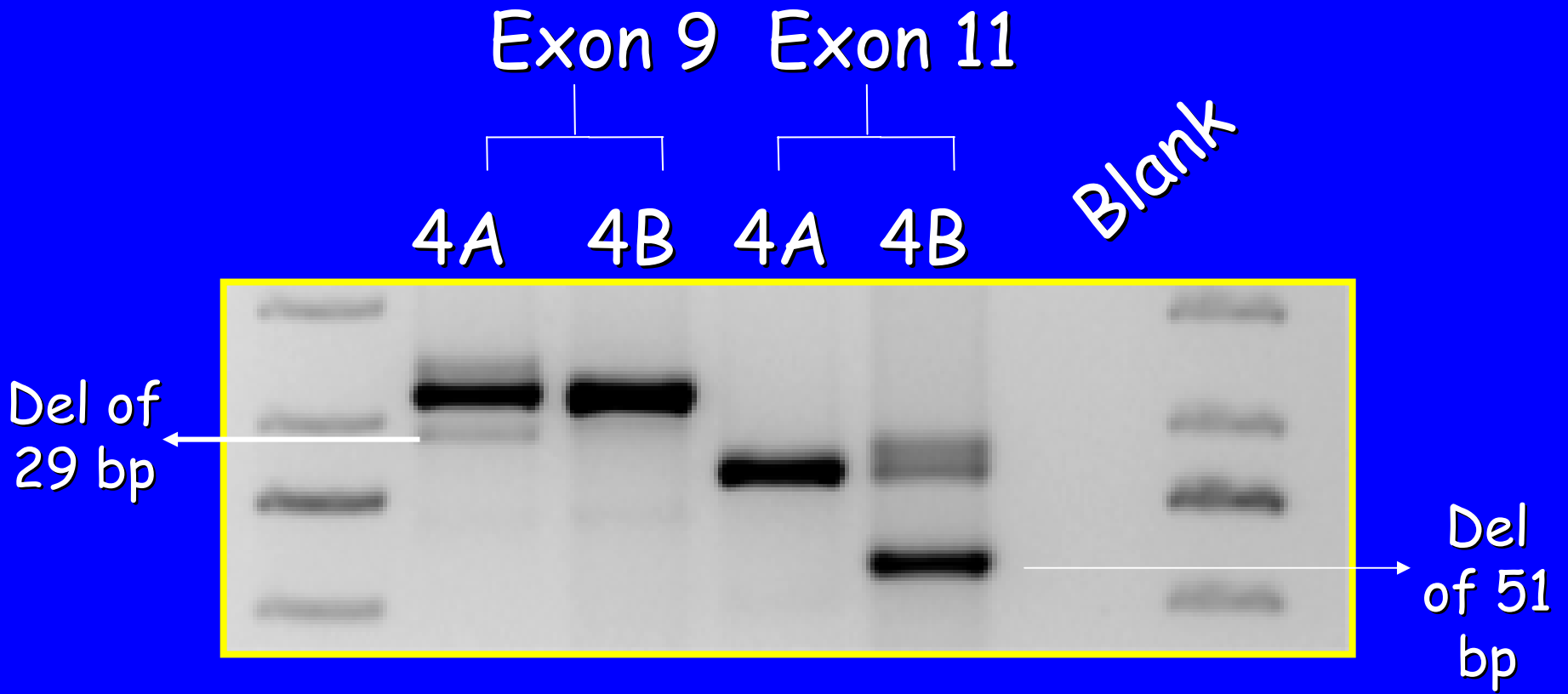
- Secondary kinase mutations are common in secondary but not primary resistance: 67% vs 10%
- SR $\Rightarrow$ reactivation of KIT and KIT-dependent signalling
- Secondary KIT mutations involve the ATP binding pocket domain or the kinase activation loop

Molecular genetics and resistance: open questions

- Mechanism of PR not clear
- Activation of KIT-independent pathways
- Is SR really an acquired phenomenon?
- Gene amplification very uncommon

Molecular genetics and clonality

- Sinchronous primaries vs. metastatic
- Different treatment
- KIT/PDGFRA sequencing

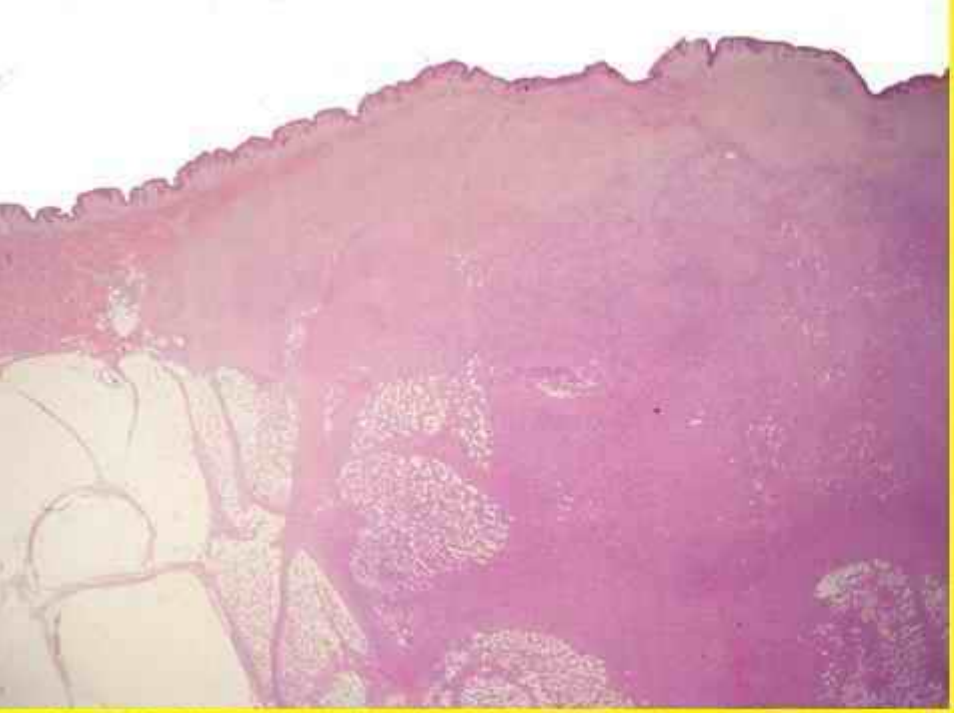
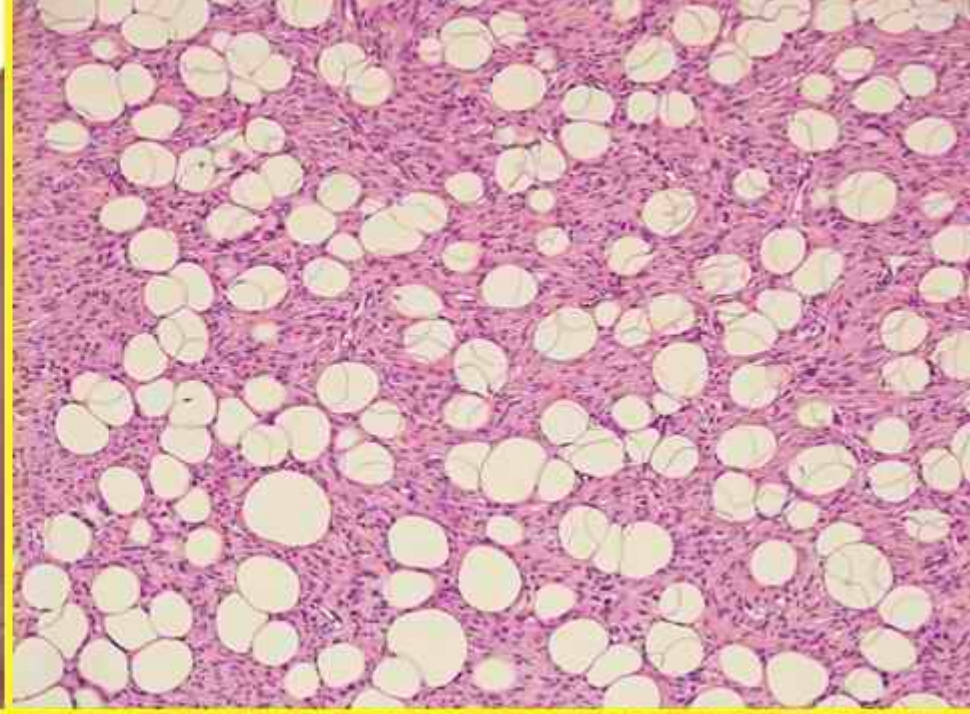
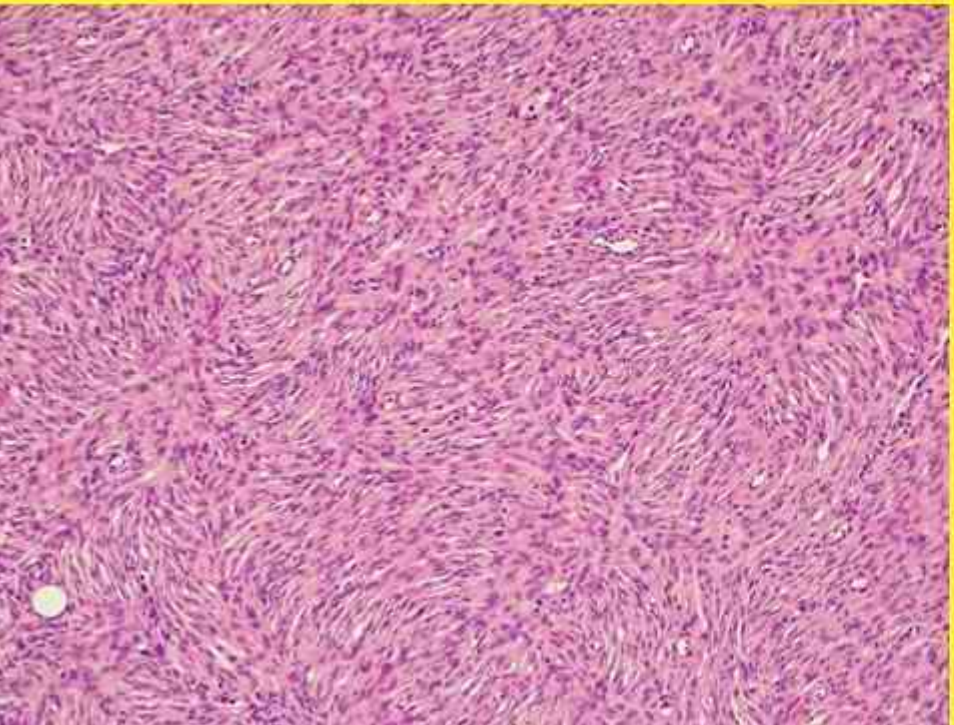
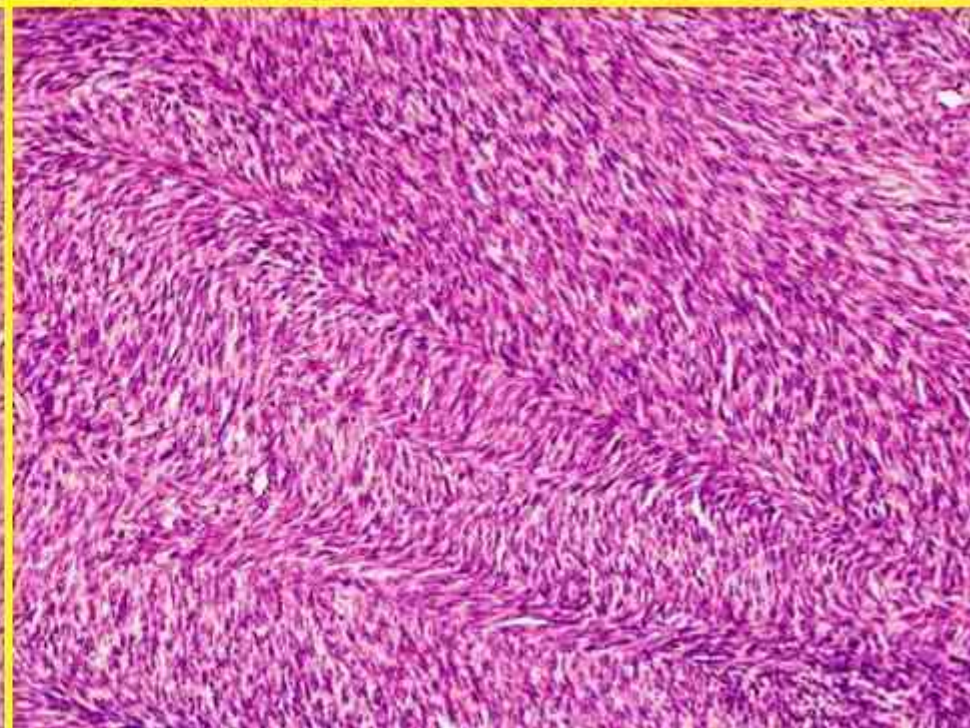

Exon 9
Exon 11
4A
4B
4A
4B
Blank
Del of 29 bp
Del of 51 bp

Dermatofibrosarcoma Protuberans

- Young adults
- Trunk
- Clear margins difficult to obtain
- Repeated local recurrences
- Tumor progression (FS-DFSP)
- t(17;22)(q22;q13)
- fusion genes COL1A1 e PDGFB

Dermatofibrosarcoma Protuberans

- t(17;22) ⇒ places PDGFB under the control of the collagen 1A1 promoter
- Transcriptionl upregulation of the PDGFB gene
- COL 1A1/PDGFB fusion postranslationally processed ⇒ functional PDGFB
- Activation of PDGFRB by autocrine and paracrine production of a functional ligand

VOLUME 23 · NUMBER 4 · FEBRUARY 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Molecular and Clinical Analysis of Locally Advanced Dermatofibrosarcoma Protuberans Treated With Imatinib: Imatinib Target Exploration Consortium Study B2225

Grant A. McArthur, George D. Demetri, Allan van Oosterom, Michael C. Heinrich, Maria Debiec-Rychter, Christopher L. Corless, Zariana Nikolova, Sasa Dimitrijevic, and Jonathan A. Fletcher

- All patients responded to Imatinib
- 4/8 pts = CR
- 1 metastatic = PR

DFSP and Imatinib

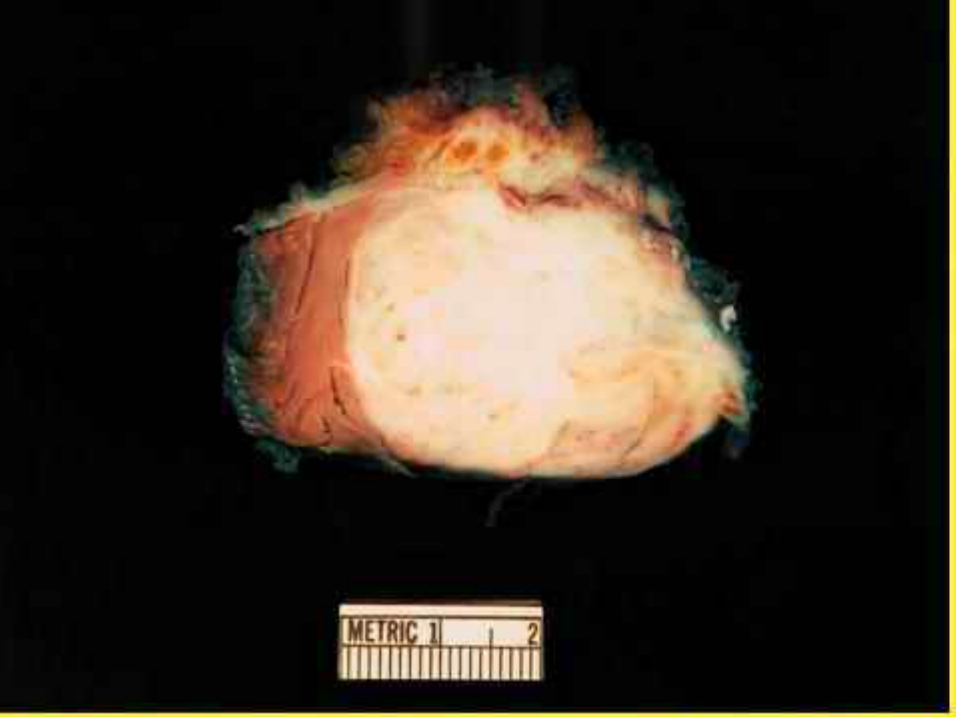
- High respose rate $\Rightarrow$ dependance on aberrant activation of PDGFRB for proliferation and survival
- Surprising low levels of PDGFRB activation
  - Stark contrast with PDGFRA in GIST
- Neither high levels of RTK activation nor RTK overexpression required for response to imatinib

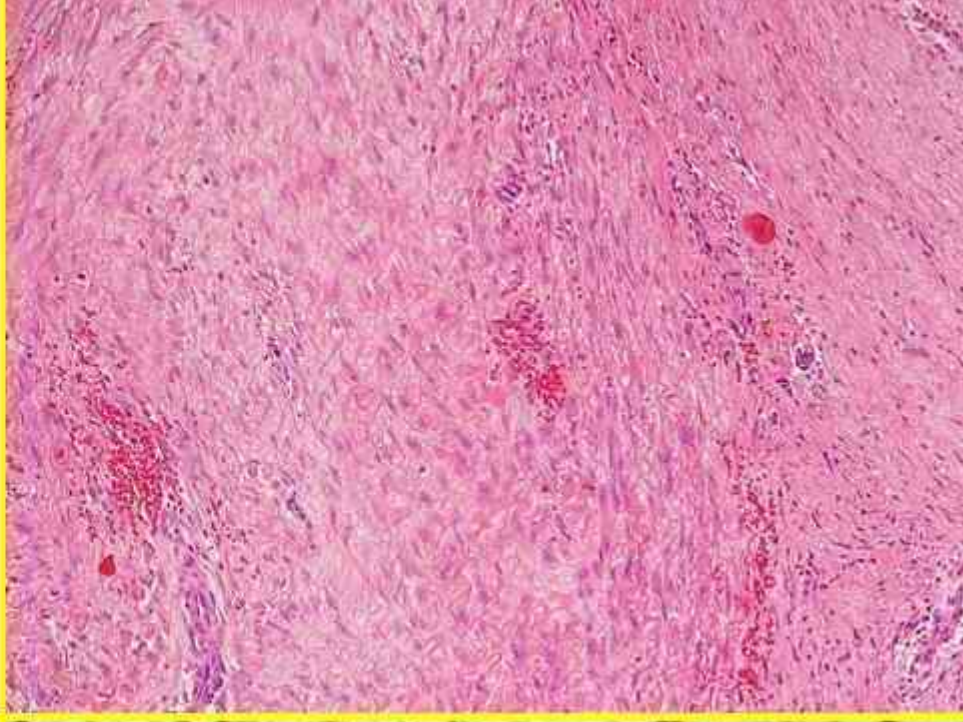
Deep-seated (desmoid type) Fibromatoses

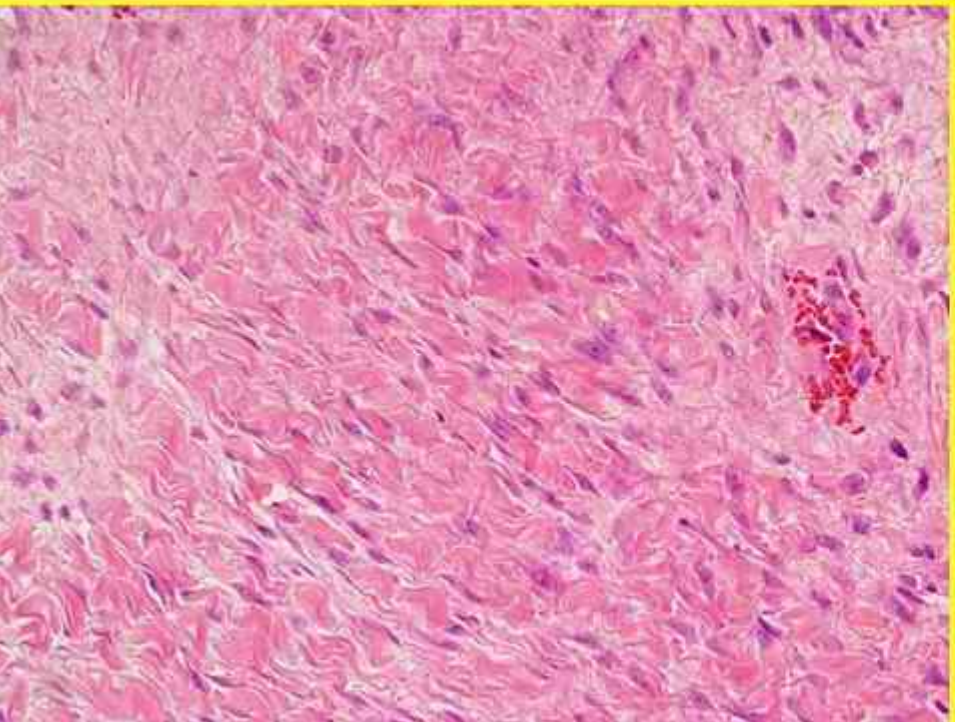
- Sporadic
  - Most often extra-abdominal
- Associated with Familial Adenomatous Polyposis (Gardner's Syndrome)
  - Mesentery
- Multicentric familial non-FAP

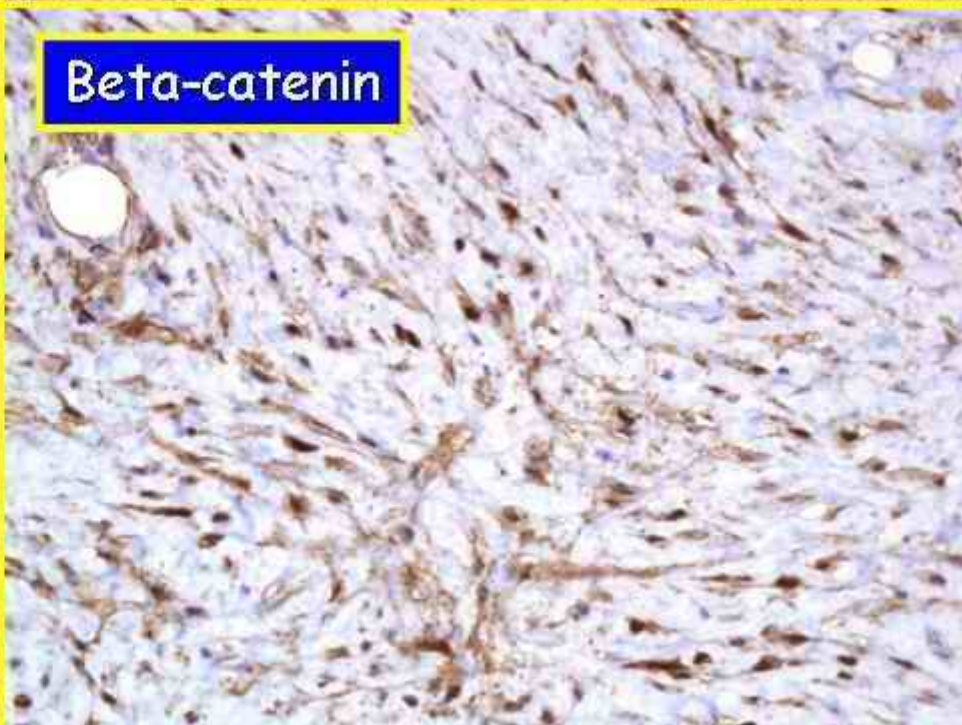
Deep-seated (desmoid type) Fibromatoses

- Second-Fourth decade
- F > M 2:1
- High recurrence rate (extra-abdominal
- Repeated surgery may lead to severe morbidity
- Local aggressive behavior may prove fatal


METRIC 1
2



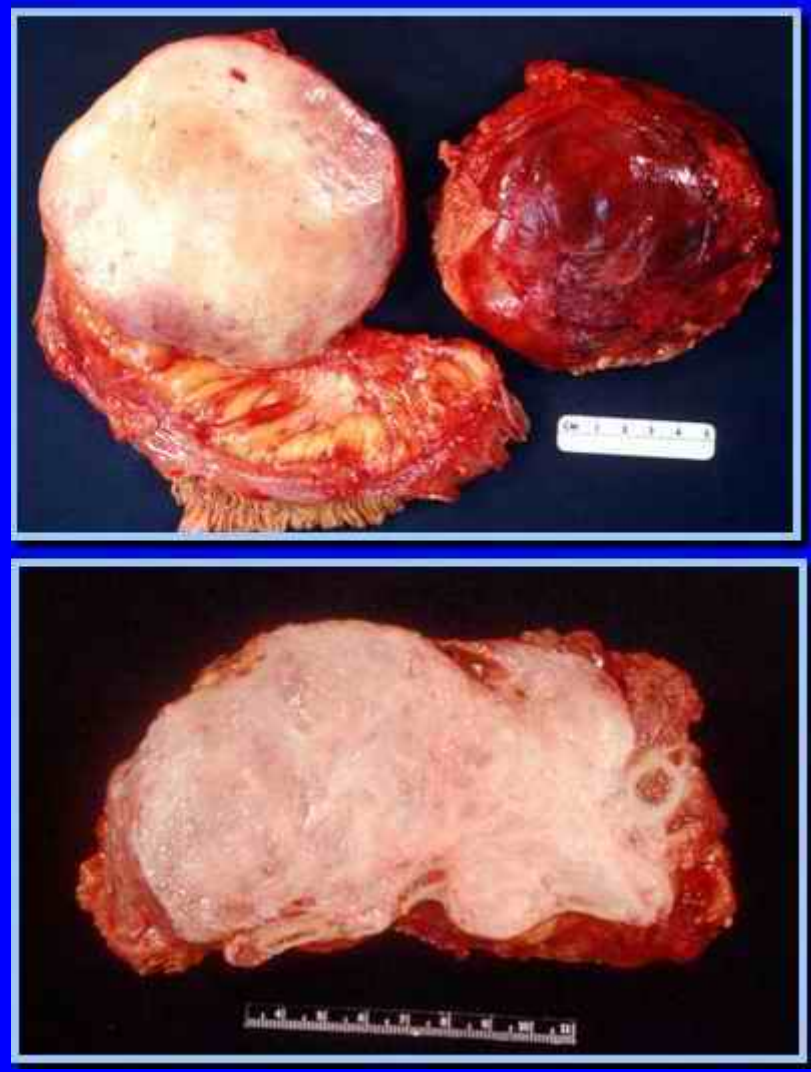



Beta-catenin

APC Gene Mutations
Gardner's Syndrome

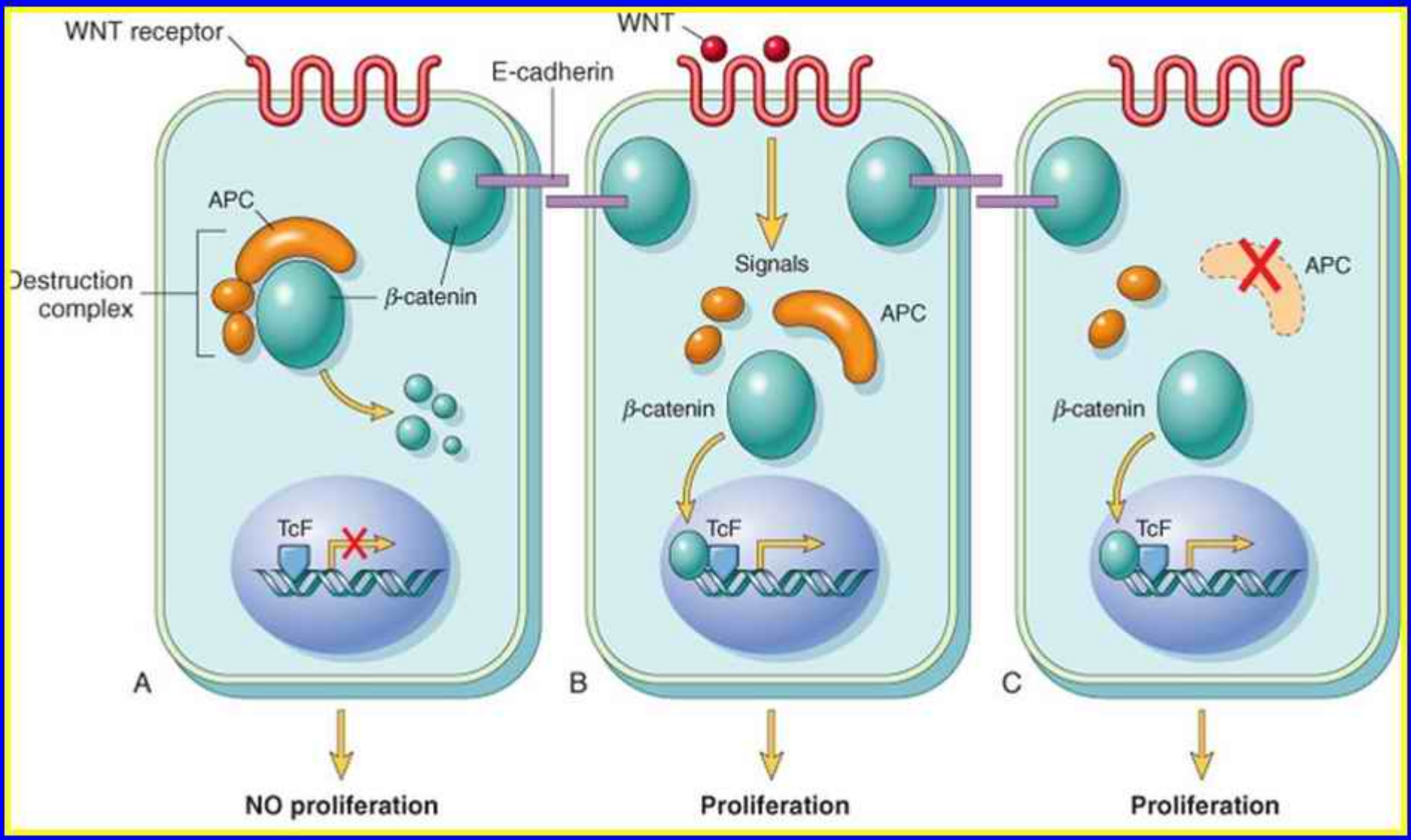
Defects in chromosome 5

- Desmoid tumors
- Colorectal adenocarcinoma
- Carcinoma in familial polyposis



APC ß-catenin complex

- APC regulates intracellular level of ß-catenin
- ß-catenin can translocate to the nucleus and activate proliferation


WNT receptor
WNT
E-cadherin
APC
Destruction complex
β-catenin
Signals
APC
APC
β-catenin
β-catenin
TcF
TcF
TcF
A
B
C
NO proliferation
Proliferation
Proliferation

Deep-seated (desmoid type) Fibromatoses

- Mutation of *APC* gene on 5q.
- Gain of function mutations of beta catenin (CTNNB1)

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JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Desmoid Tumors Respond to Chemotherapy: Defying the Dogma in Oncology

Shreyaskumar R. Patel and Robert S. Benjamin, *The University of Texas M.D. Anderson Cancer Center, Houston, TX*

VOLUME 24 · NUMBER 7 · MARCH 1 2006

JOURNAL OF CLINICAL ONCOLOGY

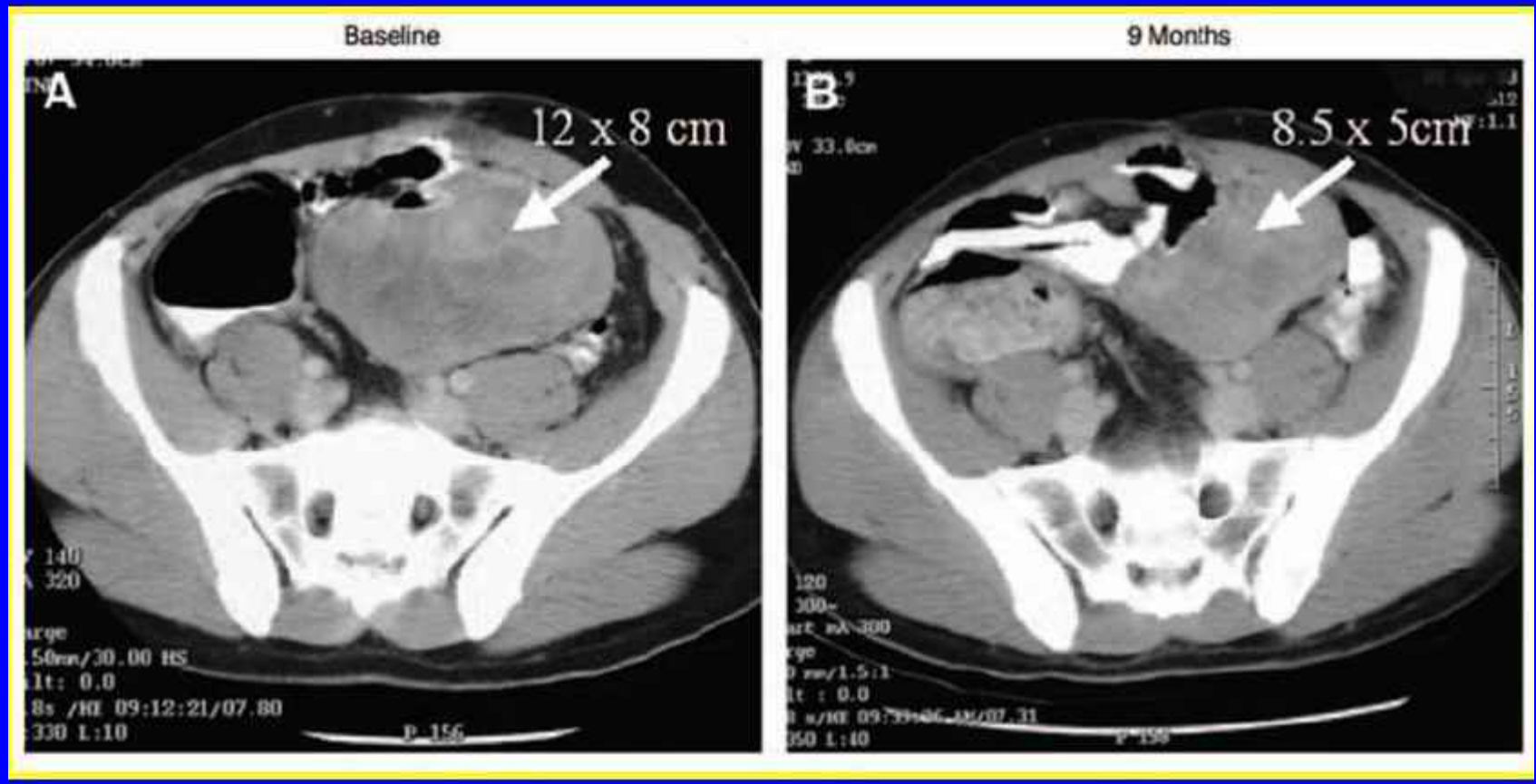
ORIGINAL REPORT

Clinical and Molecular Studies of the Effect of Imatinib on Advanced Aggressive Fibromatosis (desmoid tumor)

Michael C. Heinrich, Grant A. McArthur, George D. Demetri, Heikki Joensuu, Petri Bono, Richard Herrmann, Hal Hirte, Sara Cresta, D. Bradley Koslin, Christopher L. Corless, Stephan Dirnhofer, Allan T. van Oosterom, Zariana Nikolova, Sasa Dimitrijevic, and Jonathan A. Fletcher

Deep-seated (desmoid type) Fibromatoses

- Desmoid fatal in 11% of FAP patients
- Tamoxifen
  - 15% response rate
- Doxorubicin and dacarbazine
  - Complete response in three pts and PR in four pts
- Imatinib
  - 15% partial response rate


Baseline
9 Months
A
12 x 8 cm
B
8.5 x 5cm

Deep-seated (desmoid type) Fibromatoses

- No KIT, PDGFRA or PDGFRB mutations
- Beta catenin gain of function mutations or APC germline/somatic mutations = 84%
- No correlation between different WNT aberration and response
- Increased expression of PDGFRB
- Reduced expression after imatinib

Imatinib Mesylate in Chordoma

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Antonella Messina, M.D.[2]
Silvia Stacchiotti, M.D.[1]
Elena Tamborini, Ph.D.[3]
Flavio Crippa, M.D.[4]
Alessandro Gronchi, M.D.[5]
Rosaria Orlandi, Ph.D.[6]
Carla Ripamonti, M.D.[7]
Carlo Spreafico, M.D.[8]
Raffaello Bertieri, M.D.[9]
Rossella Bertulli, M.D.[10]
Maurizio Colecchia, M.D.[11]
Elena Fumagalli, M.D.[1]
Angela Greco, Ph.D.[12]
Federica Grosso, M.D.[1]
Patrizia Olmi, M.D.[10]
Marco A. Pierotti, Ph.D.[12,13]
Silvana Pilotti, M.D.[3]

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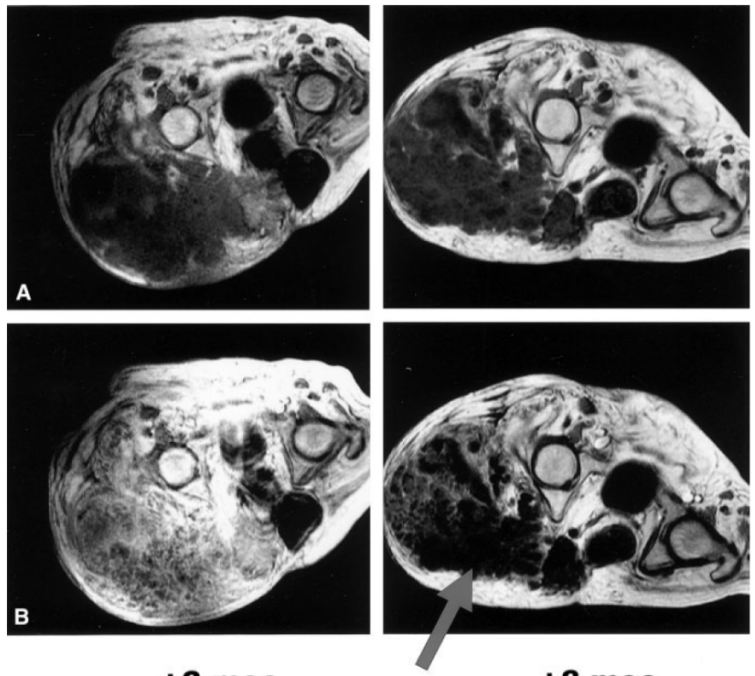
[2] Radiodiagnostic Unit 1, Department of Diagnostic Imaging and Radiotherapy, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.

[3] Pathology Unit C, Department of Pathology, Isti-

BACKGROUND. To the authors' knowledge, no effective medical therapy currently is available for advanced chordoma. Imatinib mesylate is a tyrosine kinase inhibitor targeting platelet-derived growth factor receptor-β (PDGFRB), BCR-ABL, and KIT.
METHODS. Six patients with advanced chordoma were treated with imatinib mesylate at a dose of 800 mg daily. In all patients, the tumor was found to be positive for PDGFRB, and in four patients PDGFRB was shown to be phosphorylated/expressed.
RESULTS. After a treatment period of $\geq$ 1 year, overt tumor liquefaction was evident on computed tomography (CT) scan in the first patient. In previous months, a decrease in contrast enhancement on magnetic resonance imaging (MRI) and a decrease in glucose uptake on positron emission tomography (PET) were detected. Similar signs on MRI and PET were observed in subsequent patients, who had a shorter treatment period. One of these patients initially was removed from therapy and then was readmitted to therapy because of difficulties with regard to tumor response assessment; 1 month after the reinitiation of therapy, an overt decrease in tumor density was visible on CT scan in this patient. In four of five symptomatic patients, a subjective improvement was observed early in the course of treatment. The first patient died after 17 months, with a sizeable, mostly liquefied mass. Another patient died early, apparently of unrelated causes. The remaining patients were on therapy at the time of last follow-up.

CONCLUSIONS. Imatinib mesylate has been found to have antitumor activity in patients with chordoma. This activity might be mediated by inactivation of PDGFRB. Tumor response manifests through patterns that are similar to those observed in patients with gastrointestinal stromal tumors who respond to molecular-targeted therapy, but evolves more slowly. The benefit to the patient entailed by this pattern of tumor response in chordoma needs to be elucidated, but may be limited in the presence of significant local disease. *Cancer* 2004;101:2086–97.

KEYWORDS: chordoma, imatinib mesylate, tyrosine kinase inhibitor, platelet-derived growth factor receptor-β (PDGFRB), response.



Casali PG et al. Cancer 2004; 101: 2086

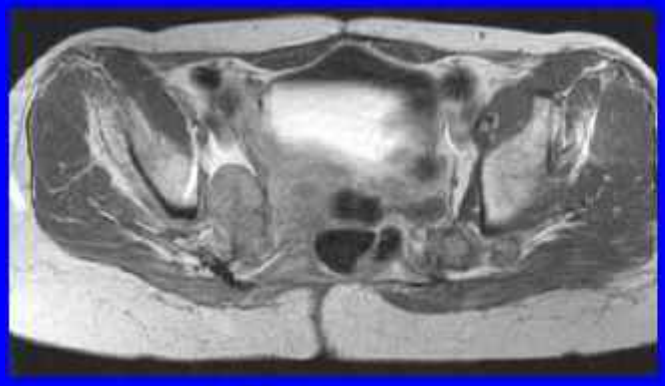
Response rate

RECIST
PD = 20%
SD = 80%

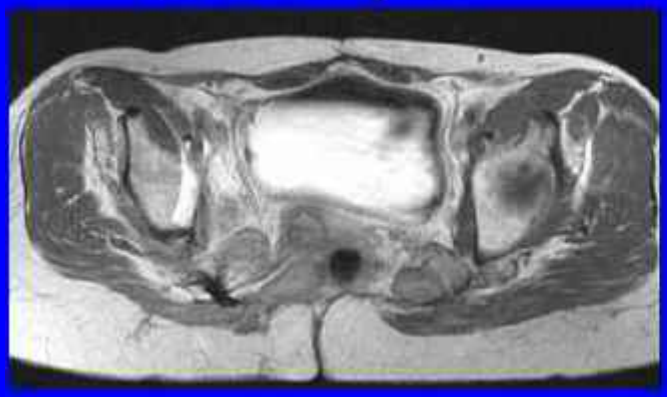
Clinical benefit (CR+PR+SD≥6mos)	71%
Minor responses	16%
PET response (SUVmax decrease ≥10%)	12/22

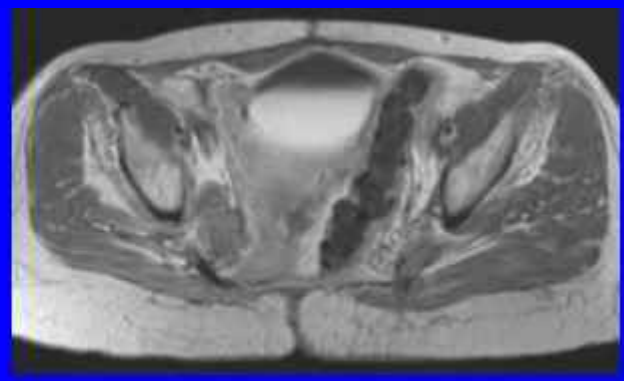
[investigator's assessment – Review ongoing]

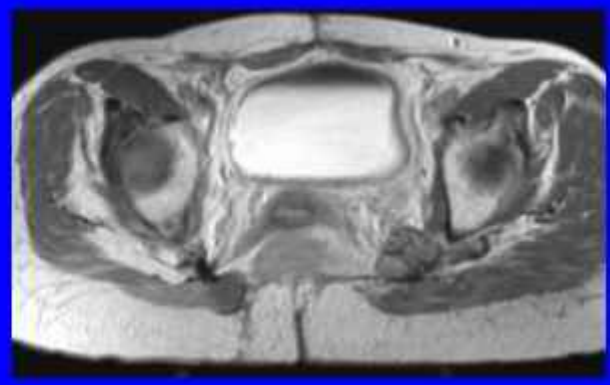
"Tissue response"



MRI T1w post







0

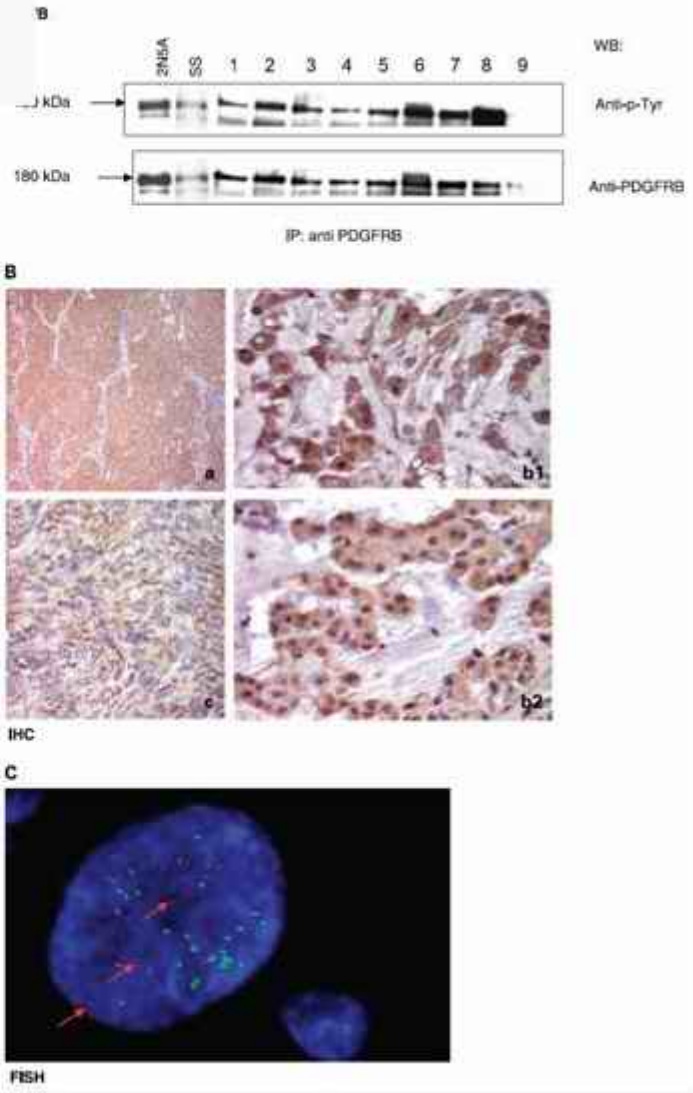
+ 6 mos

- Antitumor activity observed in the compassionate setting confirmed by this study, in terms of:
  - patterns of tumor responses
  - frequency of tumor responses
  - clinical benefit (>70%) and PFS (median = 9 mos – 35% at 1 year)
  - pain improvement in responsive patients
- Efficacy amenable to improvement by combining medical therapy with surgery and/or radiation therapy?
- Antitumor activity amenable to improvement by combining imatinib with cisplatin?

Molecular and Biochemical Analyses of Platelet-Derived Growth Factor Receptor (PDGFR) B, PDGFRA, and KIT Receptors in Chordomas

Elena Tamborini,[1] Francesca Miselli,[1] Tiziana Negri,[1] M. Stefania Lagonigro,[1] Samantha Staurengo,[1] Gian Paolo Dagrada,[1] Silvia Stacchiotti,[2] Elisa Pastore,[1] Alessandro Gronchi,[2] Federica Perrone,[1] Antonino Carbone,[1] Marco A. Pierotti,[3] Paolo G. Casali,[2] and Silvana Pilotti[1]

Case	Sex	Age	Site	Sample type	Material	Type
1	M	61	Sacrum	Primary	Frozen	Surgical specimen
2	M	25	Sacrum	Primary	Frozen	Surgical specimen
3	M	58	Sacrum	Primary	Frozen	Biopsy
4	F	64	Vertebrae	Primary	Frozen	Surgical specimen
5	F	65	Vertebrae	Primary	Frozen	Surgical specimen
6	F	66	Sacrum	Recurrent	Frozen	Biopsy
7	M	52	Sacrum	Primary	Frozen	Biopsy
8	M	61	Sacrum	Primary	Frozen	Biopsy
9	F	73	Sacrum	Primary	Frozen	Surgical specimen
10	M	57	Clivus	Primary	Frozen	Biopsy
11	F	28	Clivus	Primary	Frozen	Surgical specimen
12	F	60	Vertebrae	Primary	Frozen	Biopsy
13	M	58	Sacrum	Primary	Frozen	Surgical specimen
14	M	56	Sacrum	Primary	Frozen	Surgical specimen
15	M	70	Sacrum	Recurrent	Frozen	Biopsy
16	M	24	Clivus	Recurrent	Frozen	Surgical specimen
17	M	41	Sacrum	Recurrent	Frozen	Surgical specimen
18	M	49	Sacrum	Primary	Frozen	Surgical specimen
19	F	47	Sacrum	Recurrent	Frozen	Surgical specimen
20	M	66	Sacrum	Primary	Frozen	Surgical specimen
21	M	77	Sacrum	Primary	Frozen	Surgical specimen
22	M	59	Sacrum	Primary	Frozen	Surgical specimen
23	M	66	Sacrum	Primary	Frozen	Surgical specimen
24	F	65	Sacrum	Recurrent	Frozen	Surgical specimen
25	F	60	Sacrum	Primary	Frozen	Surgical specimen
26	M	75	Sacrum	Primary	Frozen	Surgical specimen
27	F	41	Sacrum	Recurrent	Frozen	Biopsy
28	M	69	Vertebrae	Primary	Frozen	Surgical specimen
29	F	59	Sacrum	Primary	Paraffin	—
30	M	51	Vertebrae	Recurrent	Paraffin	—
31	F	66	Sacrum	Primary	Paraffin	—



Tamborini E et al. Clin Cancer Res 2006; 12: 6920

RTKs and Chordoma

- High expression and activation of PDGFRB
- Low expression but activation of KIT and PDGFRA
- No mutations
- Autocrine/paracrine loop
- Imatinib $\Rightarrow$ switching off of all three RTKs

GIST
Conclusions

- GIST is a distinct entity and has specific clinical implications
- Molecular genetics increasingly relevant both in prediction of response and resistance
- Downstream signalling represents potential target to override resistance
- Other enttites can be potentially targeted


THE
END