CLEARING THE "MIST" AROUND GIST

Dr Sanjay De Bakshi
MS (Cal); FRCS(Eng); FRCS(Edin-ad eundem)

CLEARING THE "MIST" AROUND GIST

A BRIEF TRAVEL THROUGH TIME

Dr Sanjay De Bakshi

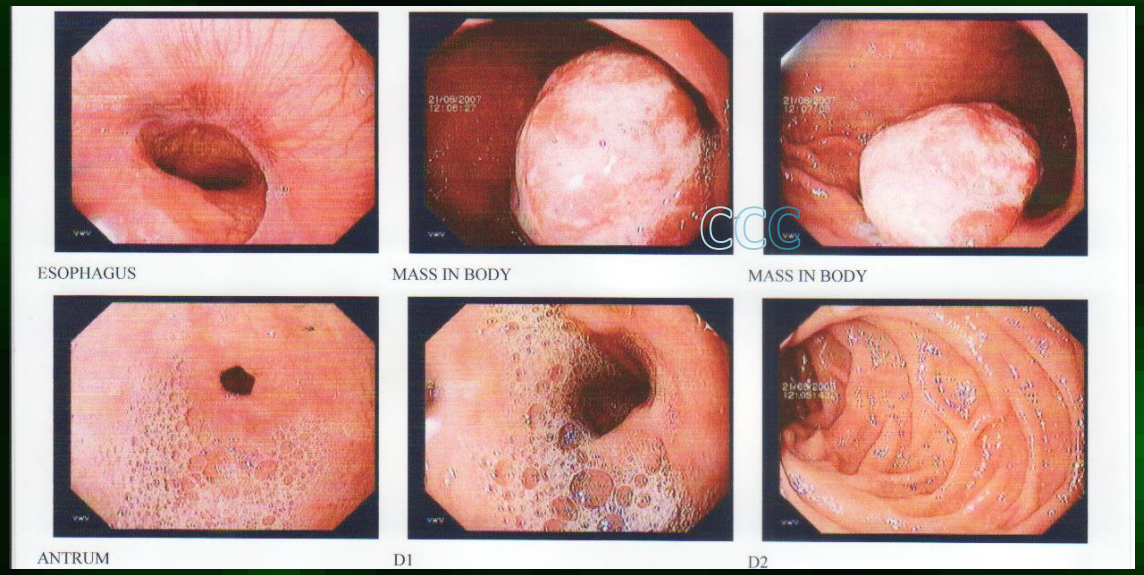
DIRECTOR ; CALCUTTA CHIRURGIAE COLLECTIVE.
DEPARTMENT OF GI SURGERY;
CMRI; CK BIRLA HOSPITAL
WOODLANDS MUTISPECIALTY HOSPITAL.
EXAMINER; ROYAL COLLEGE OF SURGEONS OF EDINBURGH.


The
Calcutta
Medical
Research
Institute
7/2


WOODLANDS
HOSPITAL

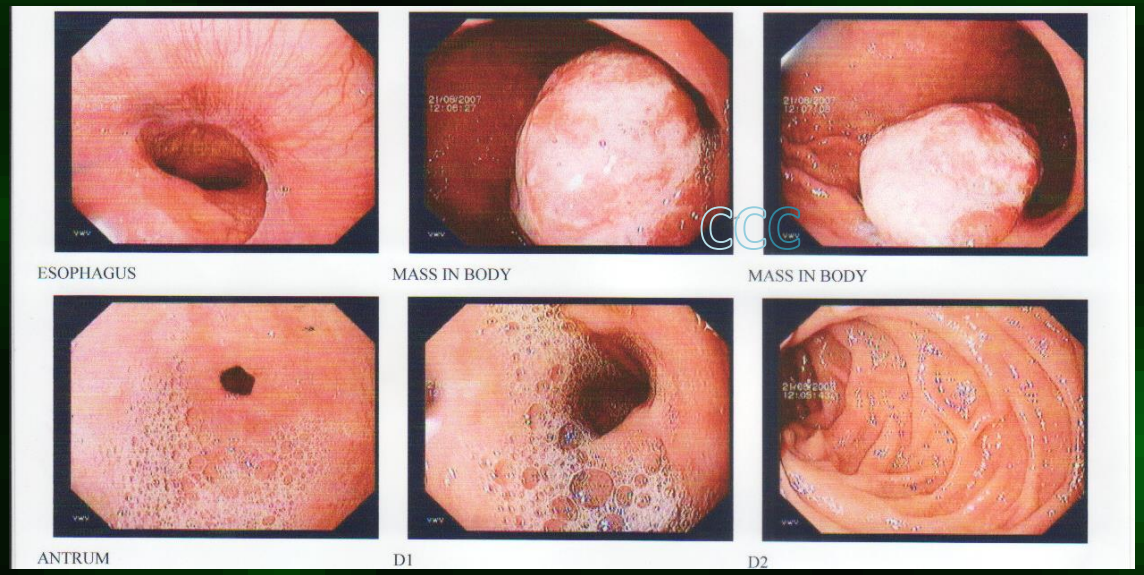
OSCE

- A 50 year old presents with melaena and anaemia.
- The endoscopic picture is presented.
- What is the finding and the likely diagnosis?
- How would one proceed?



OSCE

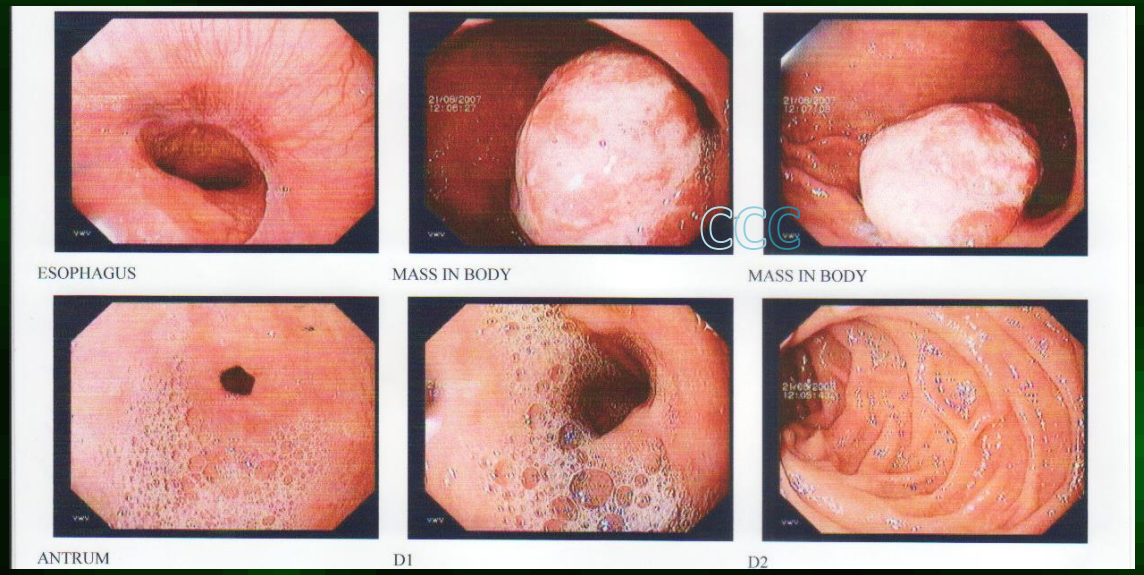
- This rounded lesion could be
  - A GIST
  - A leiomyoma
  - A leiomyosarcoma
  - A lipoma
- Superficial endoscopic biopsy is often non- contributory .
  - So strip and biopsy – to access deeper tissues.
  - EUS & FNAC & IHC
  - EUS – needle biopsy & IHC
  - EUS criteria of poorer prognosis?



OSCE

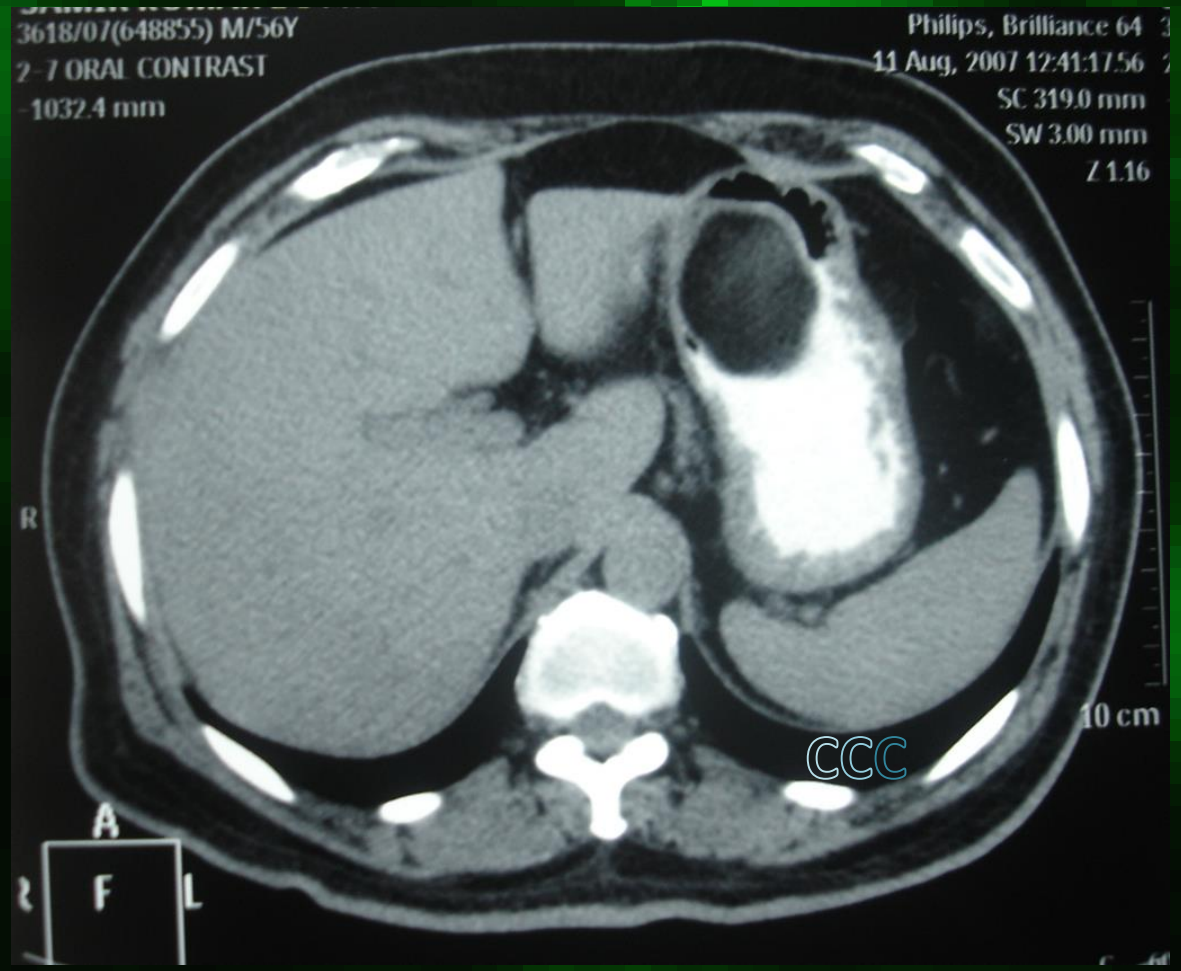
- EUS criteria for poorer prognosis
- 1. size > 2cm
- 2. irregular borders
- 3. heterogenous echopattern
- 4. anechoic spaces
- 5. echogenic foci
- 6. rapid growth on follow-up

- WHAT NEXT?



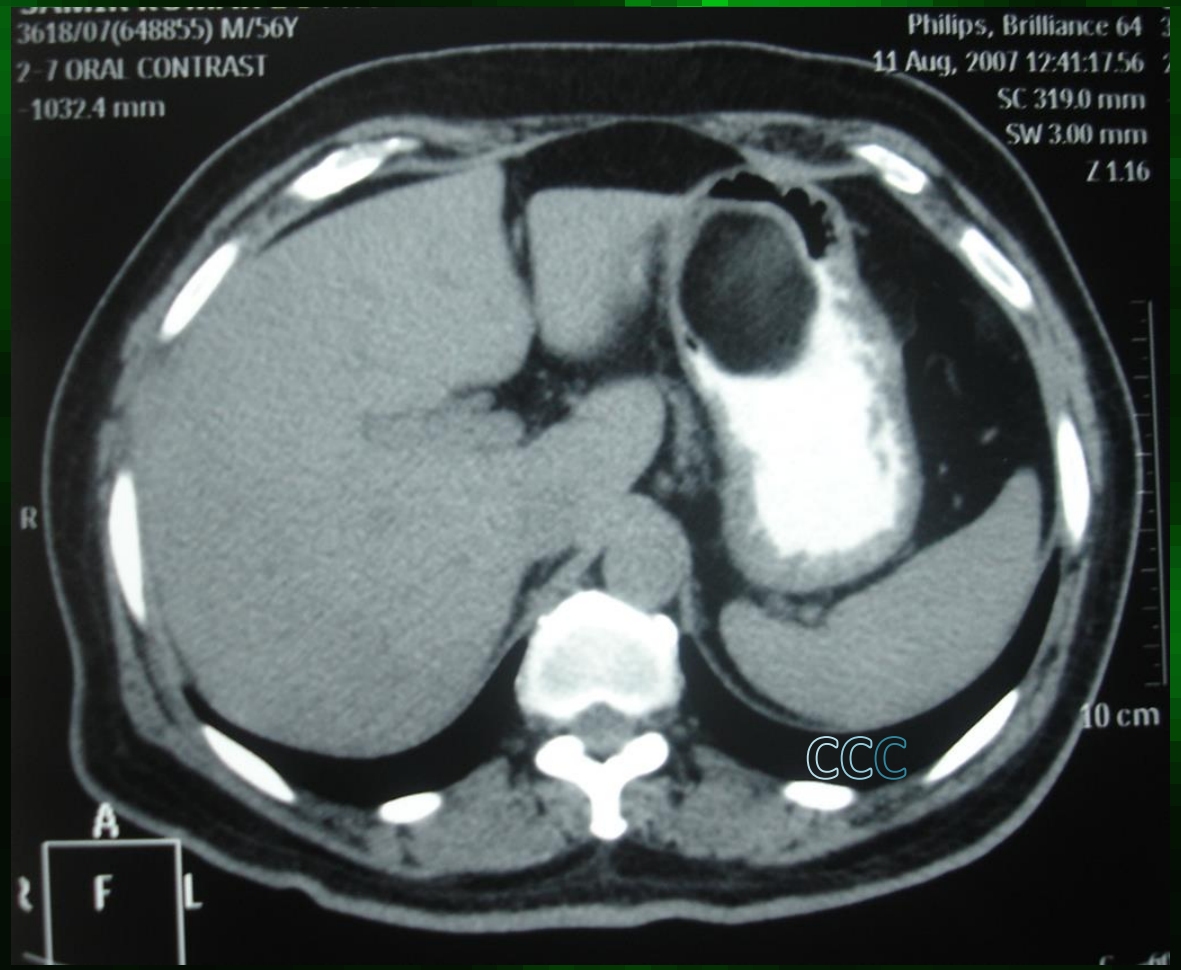
OSCE

- What is shown on the CT scan?
- How would one proceed?
- Biopsy was inconclusive –WHAT NEXT?

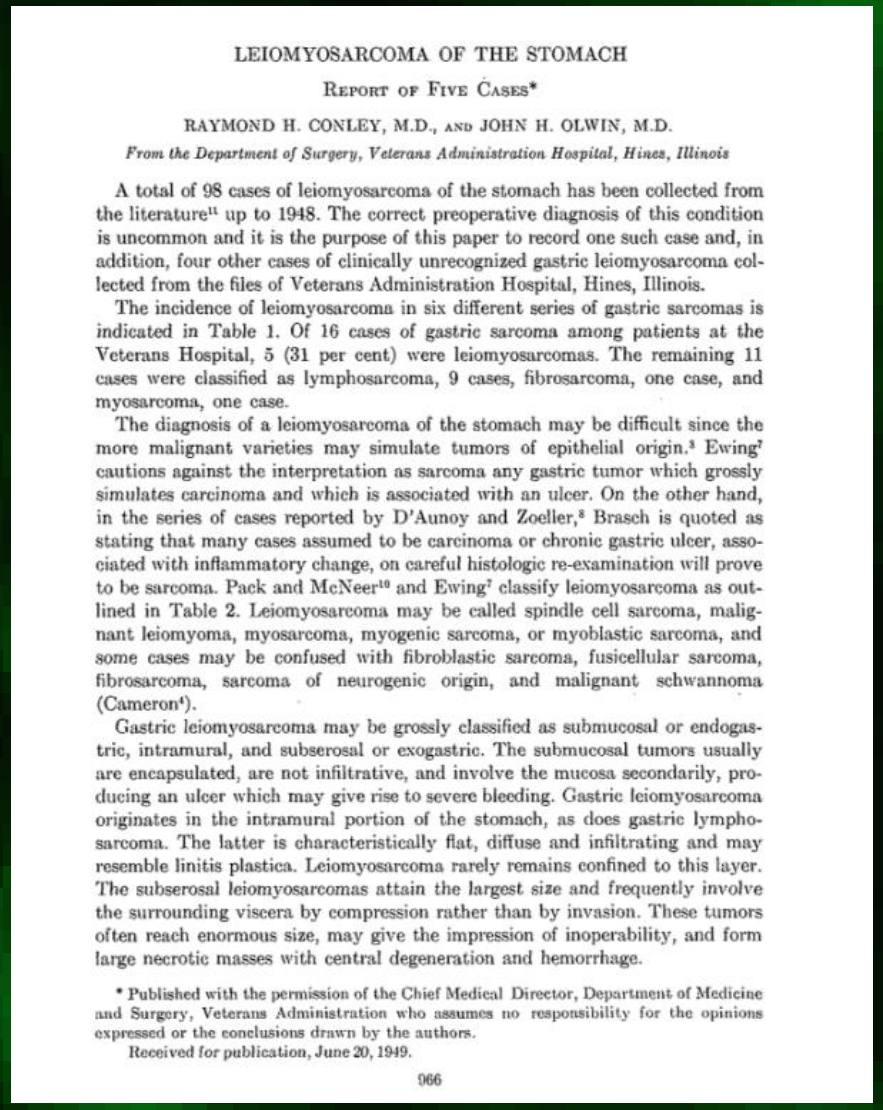


OSCE

- The CT Scan shows a rounded endophytic uniform lesion arising from the medial wall of the stomach.
- Measurement shows it to be 4 cm.
- The lesion is uniform.
- So gastric lesion < 5cm, uniform consistency in CT scan – so merits a gastrectomy lap/open to excise the lesion IN ITS ENTIRETY, keeping the vagal nerves of Laterjet intact.
- Histology and the mitotic index will guide further treatment.
- T2 MR-low = Stage IA follow up
- Ts MR – high = Stage II prudent to advise adjuvant therapy.



A Tumour which often started life as a leiomyoma or a leiomyosarcoma



LEIOMYOSARCOMA OF THE STOMACH

REPORT OF FIVE CASES*

RAYMOND H. CONLEY, M.D., AND JOHN H. OLWIN, M.D.

From the Department of Surgery, Veterans Administration Hospital, Hines, Illinois

A total of 98 cases of leiomyosarcoma of the stomach has been collected from the literature[11] up to 1948. The correct preoperative diagnosis of this condition is uncommon and it is the purpose of this paper to record one such case and, in addition, four other cases of clinically unrecognized gastric leiomyosarcoma collected from the files of Veterans Administration Hospital, Hines, Illinois.

The incidence of leiomyosarcoma in six different series of gastric sarcomas is indicated in Table 1. Of 16 cases of gastric sarcoma among patients at the Veterans Hospital, 5 (31 per cent) were leiomyosarcomas. The remaining 11 cases were classified as lymphosarcoma, 9 cases, fibrosarcoma, one case, and myosarcoma, one case.

The diagnosis of a leiomyosarcoma of the stomach may be difficult since the more malignant varieties may simulate tumors of epithelial origin.[3] Ewing[7] cautions against the interpretation as sarcoma any gastric tumor which grossly simulates carcinoma and which is associated with an ulcer. On the other hand, in the series of cases reported by D'Aunoy and Zoeller,[3] Brasch is quoted as stating that many cases assumed to be carcinoma or chronic gastric ulcer, associated with inflammatory change, on careful histologic re-examination will prove to be sarcoma. Pack and McNeer[10] and Ewing[7] classify leiomyosarcoma as outlined in Table 2. Leiomyosarcoma may be called spindle cell sarcoma, malignant leiomyoma, myosarcoma, myogenic sarcoma, or myoblastic sarcoma, and some cases may be confused with fibroblastic sarcoma, fusicellular sarcoma, fibrosarcoma, sarcoma of neurogenic origin, and malignant schwannoma (Cameron[4]).

Gastric leiomyosarcoma may be grossly classified as submucosal or endogastric, intramural, and subserosal or exogastric. The submucosal tumors usually are encapsulated, are not infiltrative, and involve the mucosa secondarily, producing an ulcer which may give rise to severe bleeding. Gastric leiomyosarcoma originates in the intramural portion of the stomach, as does gastric lymphosarcoma. The latter is characteristically flat, diffuse and infiltrating and may resemble linitis plastica. Leiomyosarcoma rarely remains confined to this layer. The subserosal leiomyosarcomas attain the largest size and frequently involve the surrounding viscera by compression rather than by invasion. These tumors often reach enormous size, may give the impression of inoperability, and form large necrotic masses with central degeneration and hemorrhage.

* Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

Received for publication, June 20, 1949.

- Conley and Owen from the Veterans Admin. Hospital, Hines, Illinois 1949.
- 16 sarcomas of stomach
  - 5 – leiomyosarcomas
  - 9 – lymphosarcomas
  - 1 – fibrosarcoma
  - 1 – myosarcoma.

1949

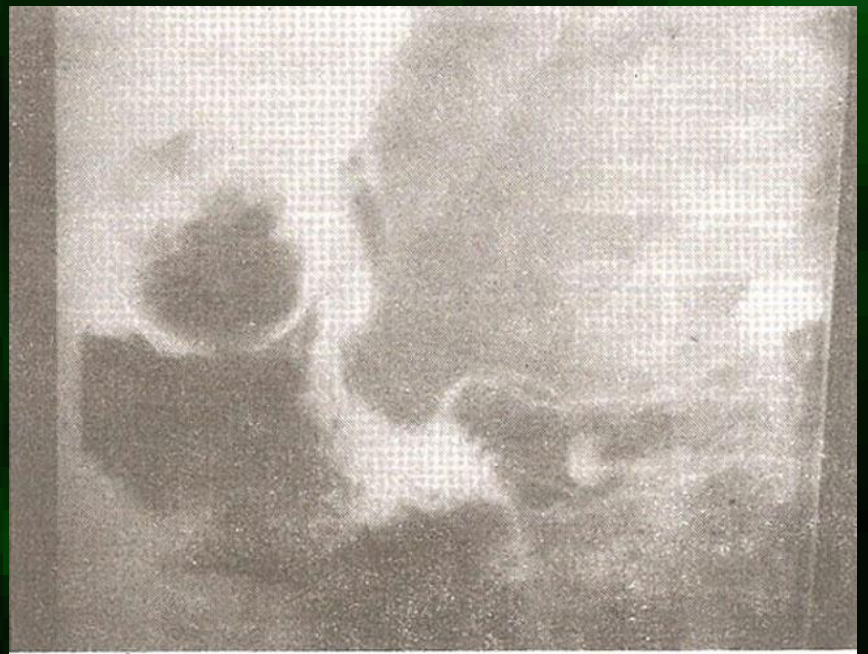


Figure 1 Barium Meal film of case 2 showing a roundish filling defect in the mid-lesser curve of the stomach which at laparotomy was a leimoyoma.

- Gastric leiomyomas and its manifestations in Nigerians. A series of 10 patients from -
- University of Benin Teaching hospital , Benin City, Nigeria in **1986**.

SEMINAL PAPER (1983)

- Twenty-eight gastric wall tumours classified by light microscopy as leiomyomas or leiomyosarcomas were reevaluated for histogenesis.
- The results of this study indicate that many gastric wall tumours are not derived from smooth muscle. The presence of S-100 protein suggests a nerve sheath origin in some cases.

- Gastric stromal tumors. Reappraisal of histogenesis.
- *Mazur MT, Clark HB. Am J Surg Pathol. 1983 Sep;7(6):507-19.*
- *Institution*
- *University of Minnesota Twin Cities*

Preamble

- Since the term Gastrointestinal Stromal Tumour (GIST) was introduced by Mazur and Clark in 1983, laboratory investigations aimed at the subcellular and molecular levels demonstrated that GISTs DO NOT possess the ultrastructural and immunohistochemical features characteristic of smooth muscle differentiation, as are seen in leiomyomas and leiomyosarcomas.

Preamble

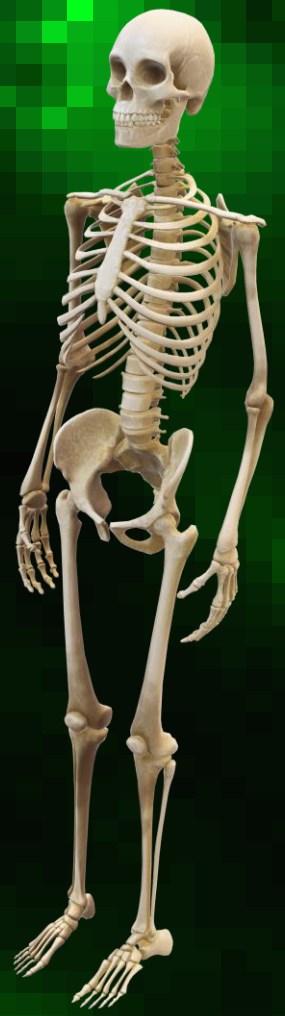
- Realisation came, that GISTs do not arise from smooth muscle cells, but from another mesenchymal derivative which were programmed to form spindle and epithelioid cells.
- Kindblom and associates reported in 1998, that the actual cell of origin of GISTs is a pluripotential mesenchymal stem cell programmed to differentiate into the **“pacemaker” interstitial cell of Cajal**. This finding led Kindblom and coworkers to suggest the term GI pacemaker cell tumors.

1998

THE WORLD
WONDERED.....

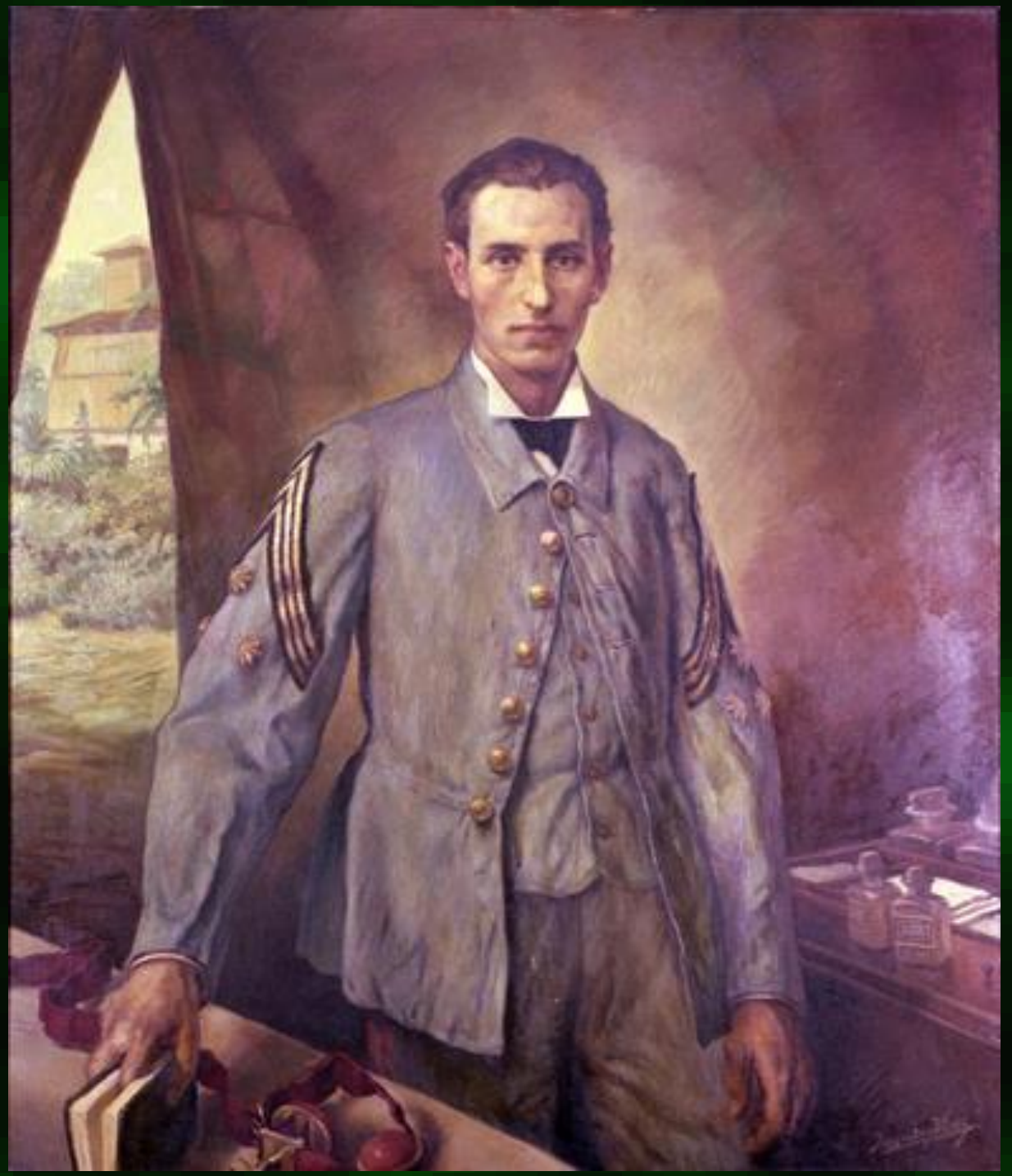
WHO WAS CAJAL?

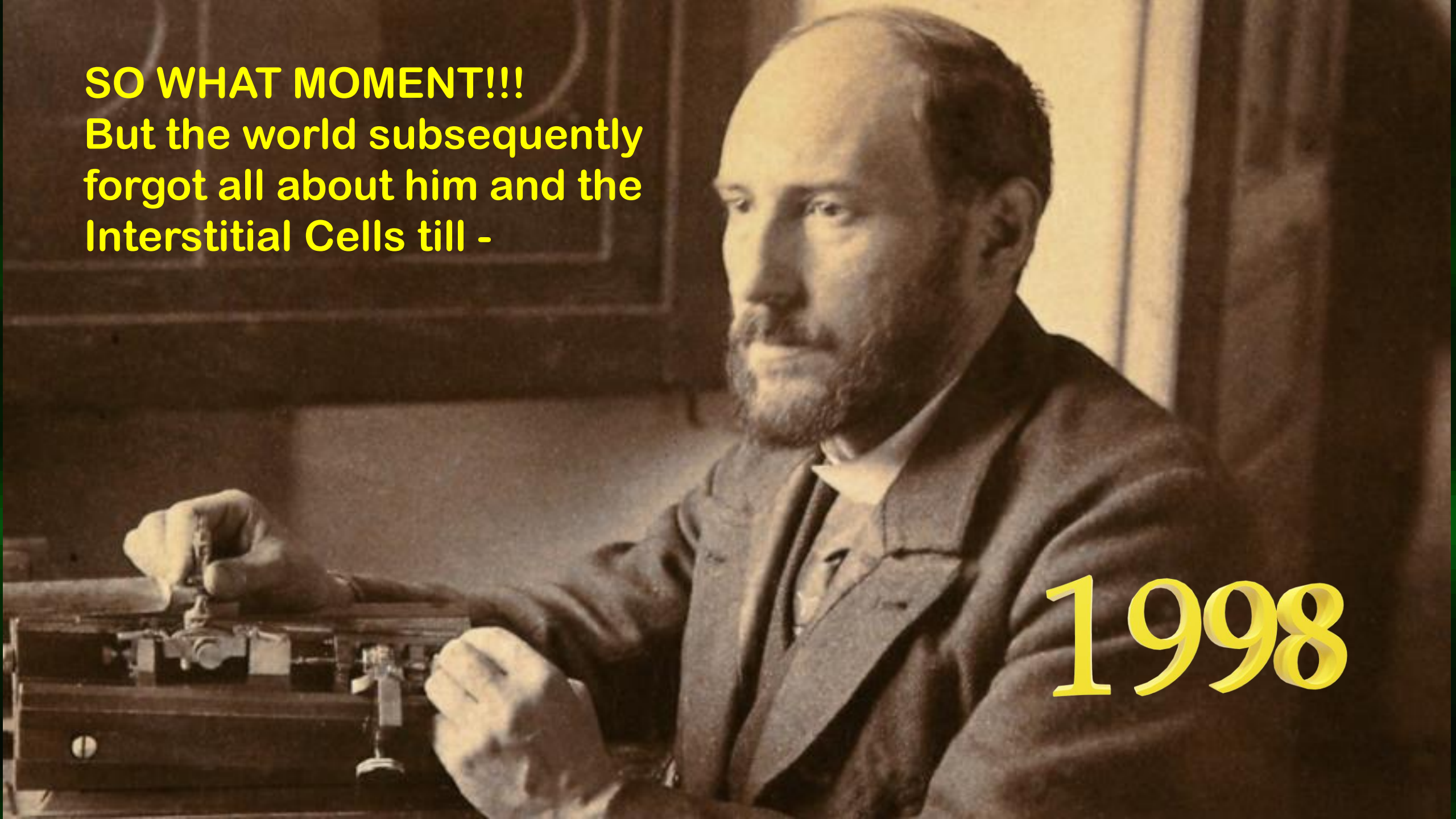
- Santiago Ramón y Cajal was born on the 1st of May 1852 in the town of Petilla de Aragón, Navarre, Spain. He was extremely rebellious and anti-authoritarian.
- Though a keen painter and artist, his father, an anatomist, apprenticed him to a shoemaker.
- In 1868, he discovered human bones in a graveyard where his father had taken him for a study in anatomy.
- That influenced him to study medicine.

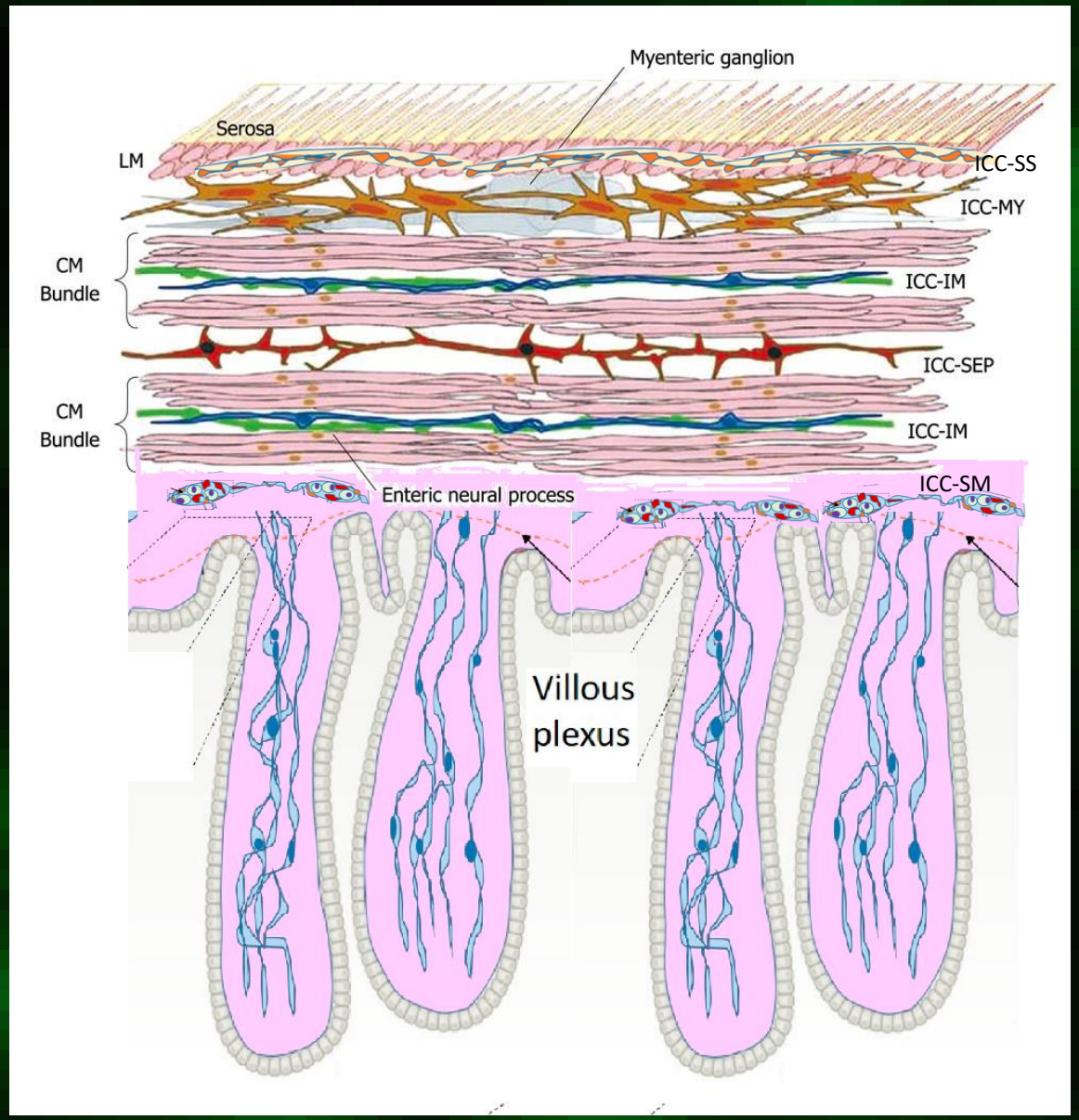


WHO WAS CAJAL?

- After graduation, he joined the Spanish army.
- Eventually, a Professor at Madrid in Neurosciences, **he** and **Camilo Golgi** received the Nobel Prize in Physiology and Medicine in **1906**.
- He also described the ubiquitous **Interstitial Cells**.




SO WHAT MOMENT!!!
But the world subsequently forgot all about him and the Interstitial Cells till -
1998

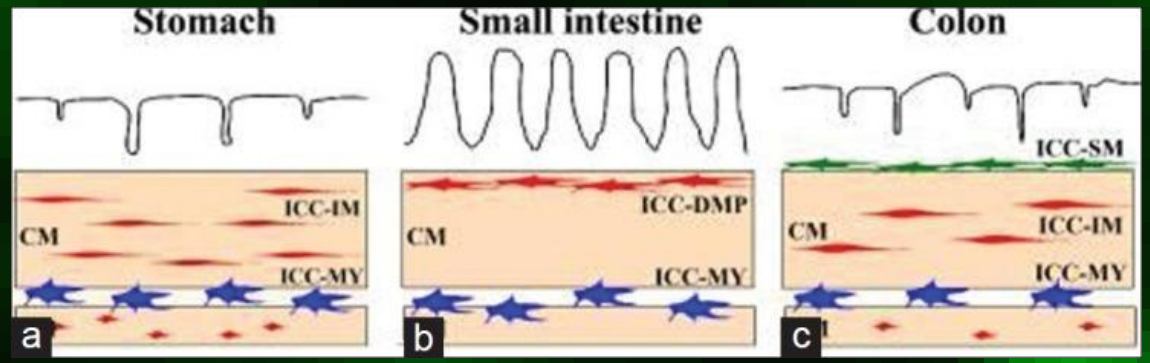


- After spending over a 100 years in obscurity, the Interstitial Cells of Cajal burst into prominence.
- It was discovered that GISTs originate for the these cells or their precursors.

Mostafa RM, Moustafa YM, Hamdy H. Interstitial cells of Cajal, the Maestro in health and disease. World J Gastroenterol 2010; 16(26): 3239-3248 [PMID: 20614479 DOI: 10.3748/wjg.v16.i26.3239]

2010

- ICC-IM – Intramuscular(circular muscle)
- ICC-MY – Myenteric plexus
- ICC-SM – Submucosal
- ICC- DMP – Deep muscular plexus



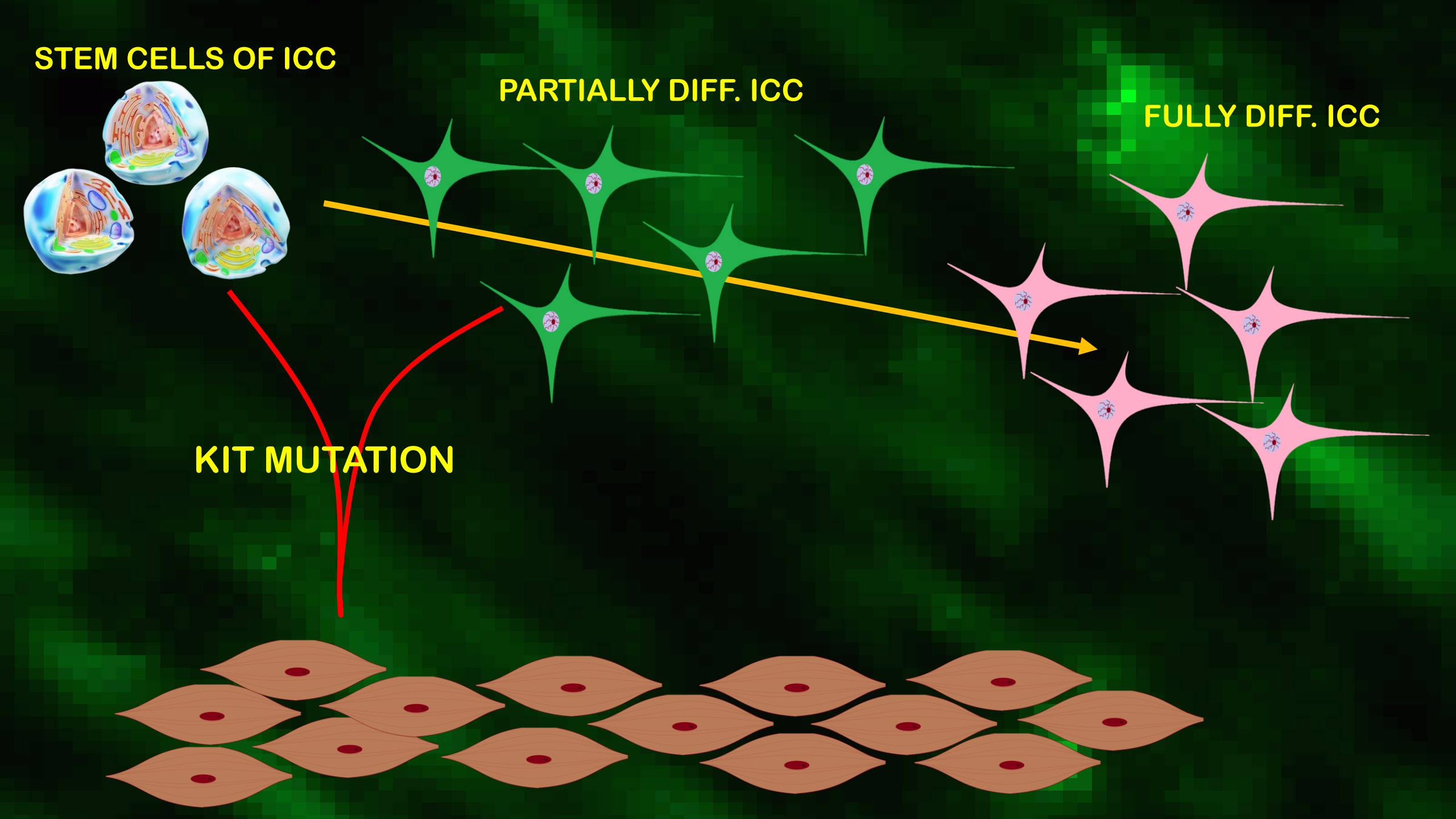
Al-Shboul OA. The importance of interstitial cells of cajal in the gastrointestinal tract. Saudi J Gastroenterol. 2013 Jan-Feb;19(1):3-15. doi: 10.4103/1319-3767.105909. PMID: 23319032; PMCID: PMC3603487.

2013

LOCATIONS OF ICC IN THE GI TRACT

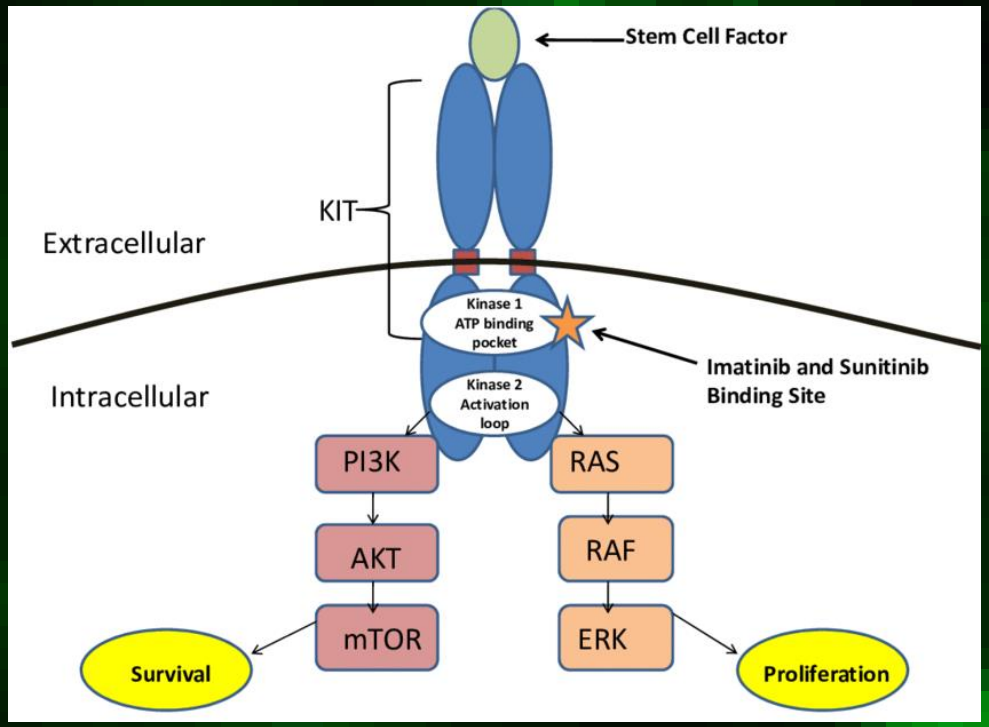
SITE	LOCATION
OESOPHAGUS	ICC-IM
STOMACH	{CORPUS/ANTRUM> FUNDUS} ANTRUM = ICC-MY & ICC-IM; FUNDUS = ICC-M PYLORUS = ICC-SM
DUODENUM	FIRST PART DUODENUM = ICC-MY & ICC-IM;
SMALL INTESTINE	REST OF INTESTINE ICC-DMP & ICC-MY (ILEUM>JEJUNUM)
LARGE INTESTINE	ICC-SMP {NO ICC-MP/ICC-SMP IN CAECUM (PAEDIATRIC)} HIGHEST IN DESCENDING COLON
PANCREAS	PANCREATIC ICC
EXTRA-INRESTINAL	UPPER URINARY TRACT, URETHRA, MYOMETRIUM, MYOCARDIUM, UTERUS, FALLOPIAN TUBE, HUMAN PLACENTA

2013


STEM CELLS OF ICC
PARTIALLY DIFF. ICC
FULLY DIFF. ICC
KIT MUTATION

WHAT IS KIT?

- This is a transmembrane kinase discovered by Hirohito and colleagues in 1998.
- It binds to a stem cell factor outside the cell membrane
- This activates ATP inside the cell
- In sequence this activates kinases
- Important for
  - Survival &
  - Proliferation.



Gastrointestinal Stromal Tumor. April 2012 DOI: 10.5772/1892.
Edition: 1stPublisher: InTech, Chapters published April 27, 2012 under CC BY 3.0 license.Editor: Raimundas LuneviciusISBN: ISBN 978-953-51-0580-0.
Roberta ZappacostaBarbara ZappacostaBarbara ZappacostaSerena Capanna

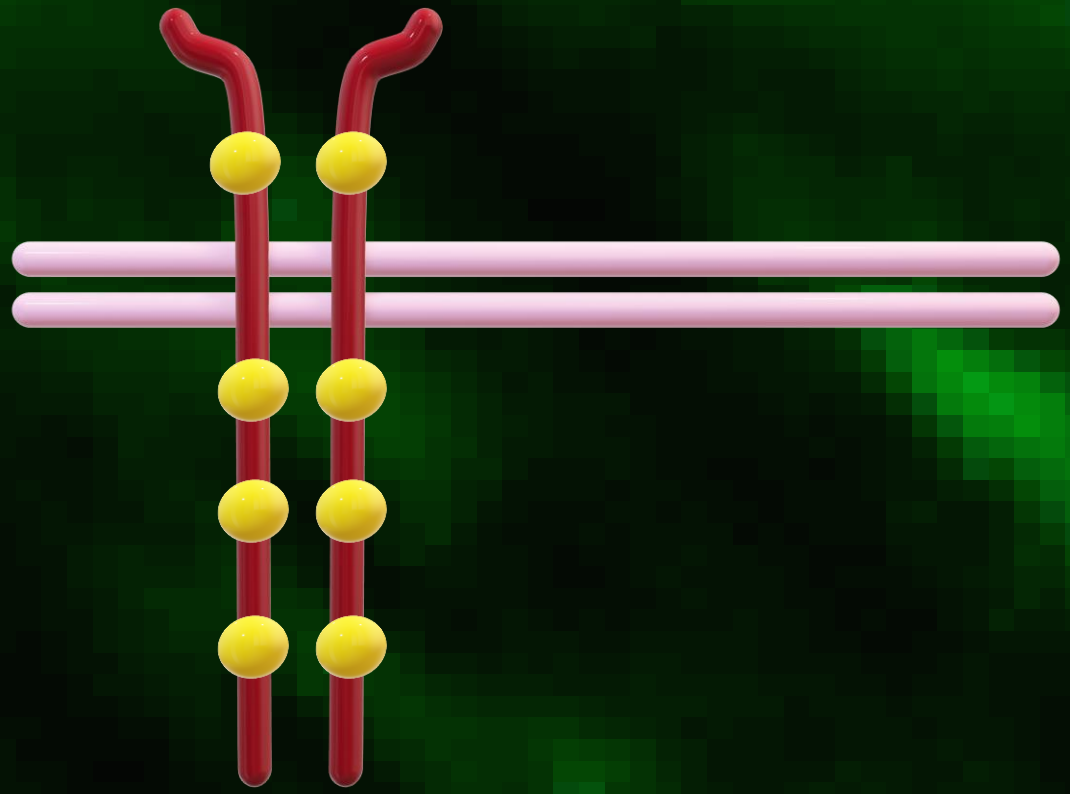
1998

Molecular Biology

- Mutations in the following exons of the c-kit gene are known to occur in GIST.

- Exon 11 is the most commonly mutated exon in GIST. In phase II trials, exon 11 mutations were found in 67% of cases. *Mutations in exon 11 generally respond to treatment with Gleevec better than mutations in other exons.*

- Found in GIST of the Stomach
- Deletions involving codons 557 and/or 558 – highly aggressive disease.

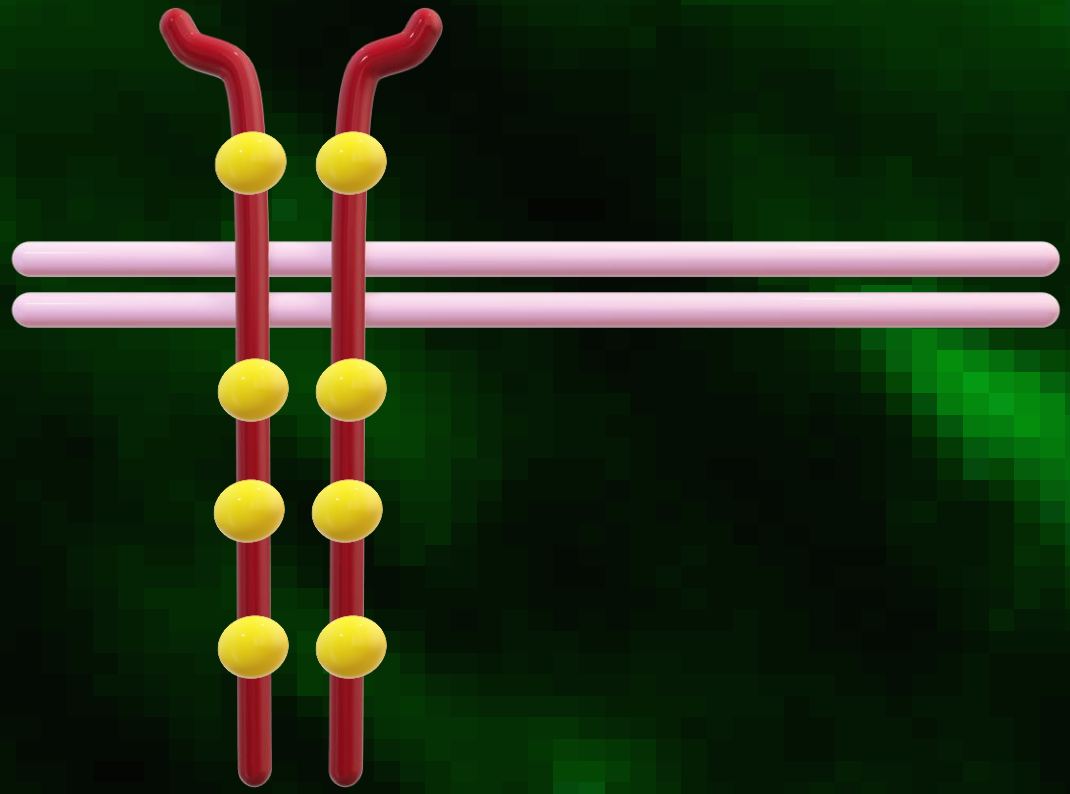


Molecular Biology

- Mutations in the following exons of the c-kit gene are known to occur in GIST.

- Exon 9 mutations are the second most common mutation. In phase II trials, exon 9 mutations were found in 17% of cases. They are only known to occur when the primary tumor originates in the small bowel and colon.

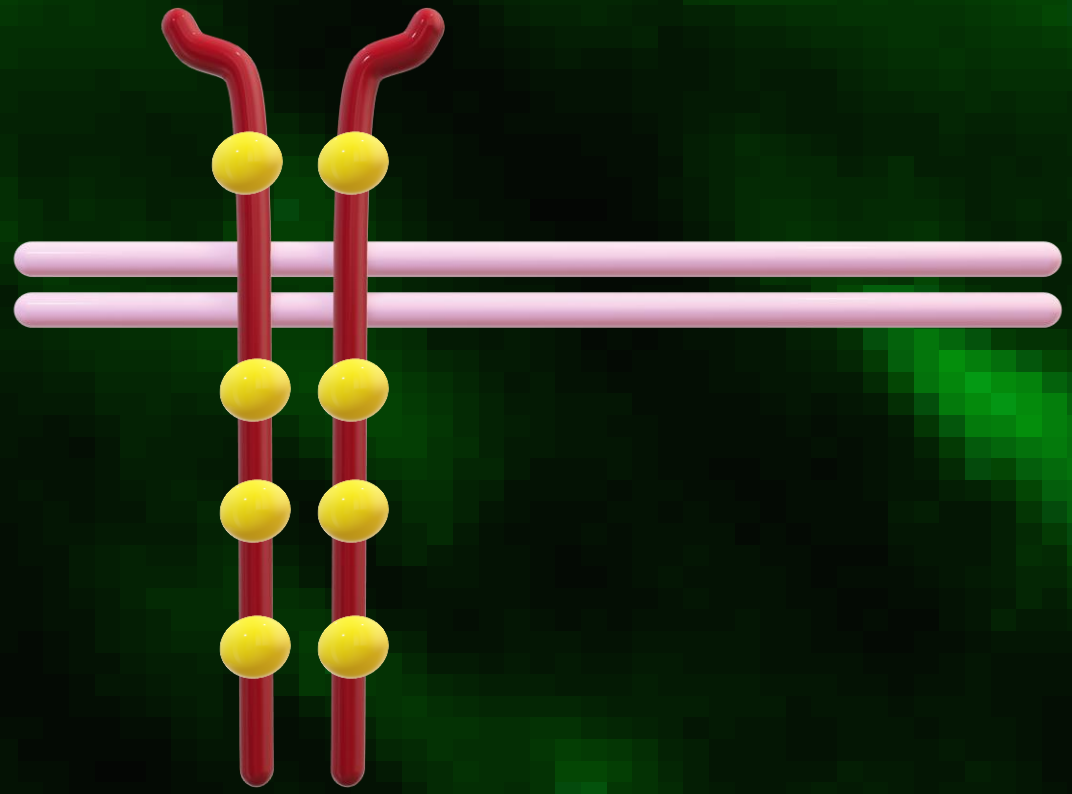
- GISTs with exon 9 mutations have a lower response rate to Gleevec therapy when compared to exon 11 mutations, but a better response rate to Gleevec than c-kit "wild-type" GIST.
- Often needs a double dose of Imatinib.



Molecular Biology

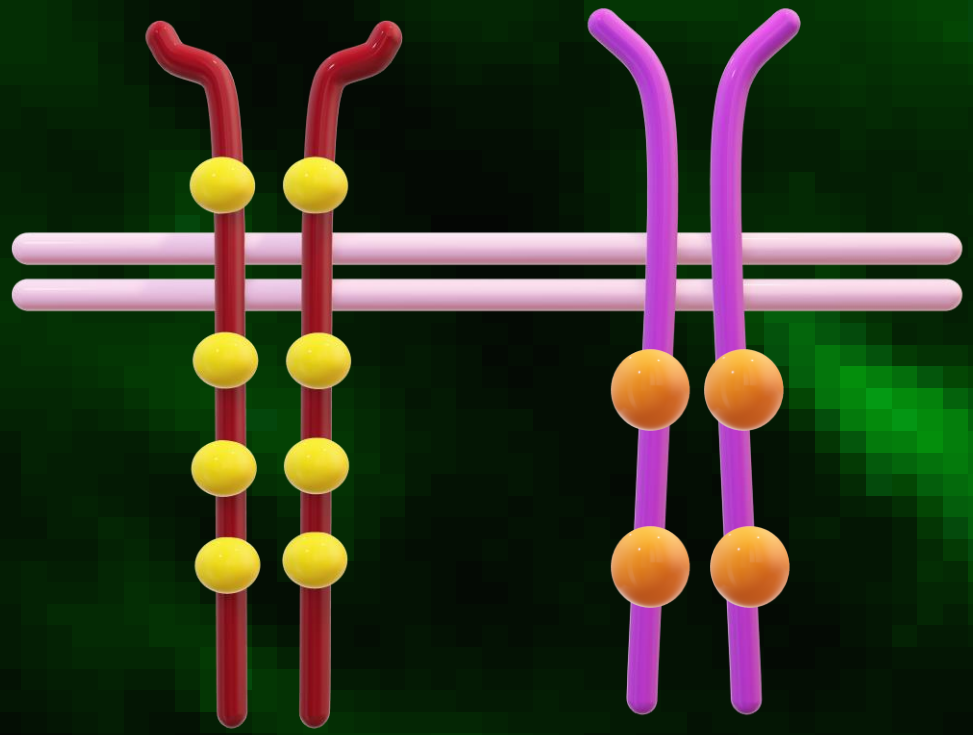
- Mutations in the following exons of the c-kit gene are known to occur in GIST.

- Exon 13 and exon 17 mutations are rare in GIST. Because they are so rare, not much is known about the response rate to Gleevec



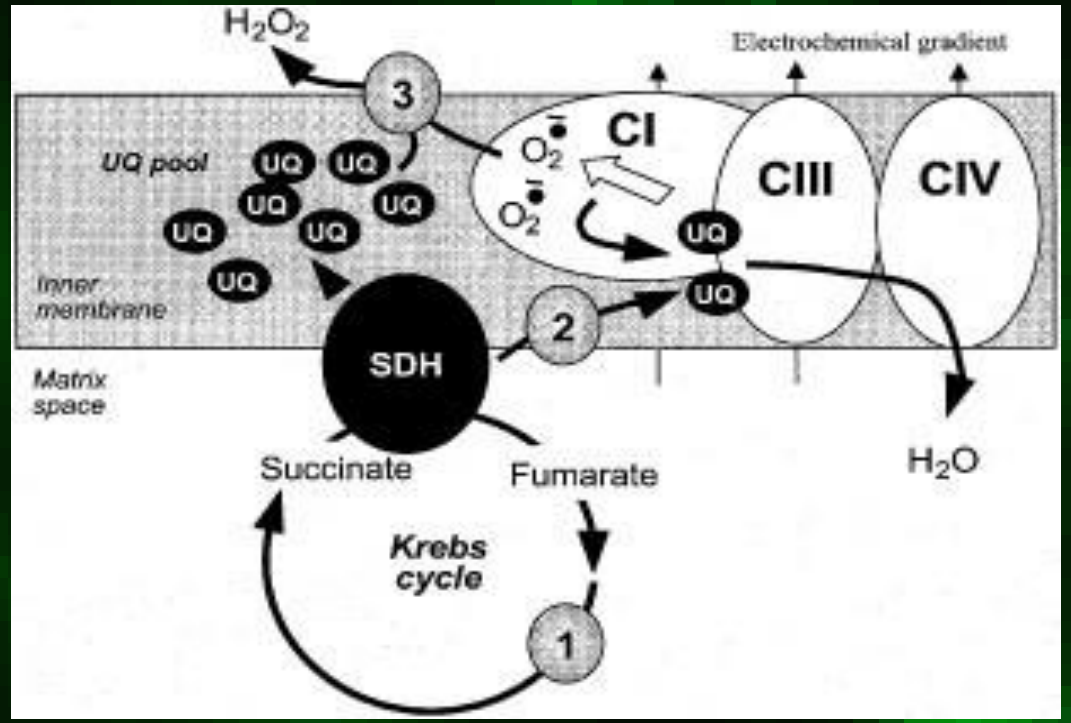
Molecular Biology

- Platelet Derived Growth Factor Receptor Alpha (PGDFRA)
- The Exon mainly involved is 18(80-90%).
- There are two variants:-
  - D842V exon 18 mutations –confers resistance to Imatinib.
  - Non D842V exon 18 mutations – which are responsive to Imatinib.
- The other Exon site involved is 12.



Molecular Biology

- KIT/PDGFRA wild type GISTs
- No detectable mutations in KIT/PDGFRA in 10 to 15%.
- Many deficient in Succinate Dehydrogenase (SDH).
- Mostly paediatric and younger female patients with GIST often located in the stomach, often multifocal and can have either an indolent or progressive course.
- Often have lymphovascular and lymph nodal involvement.
- Not responsive to imatinib, surgery the only treatment.



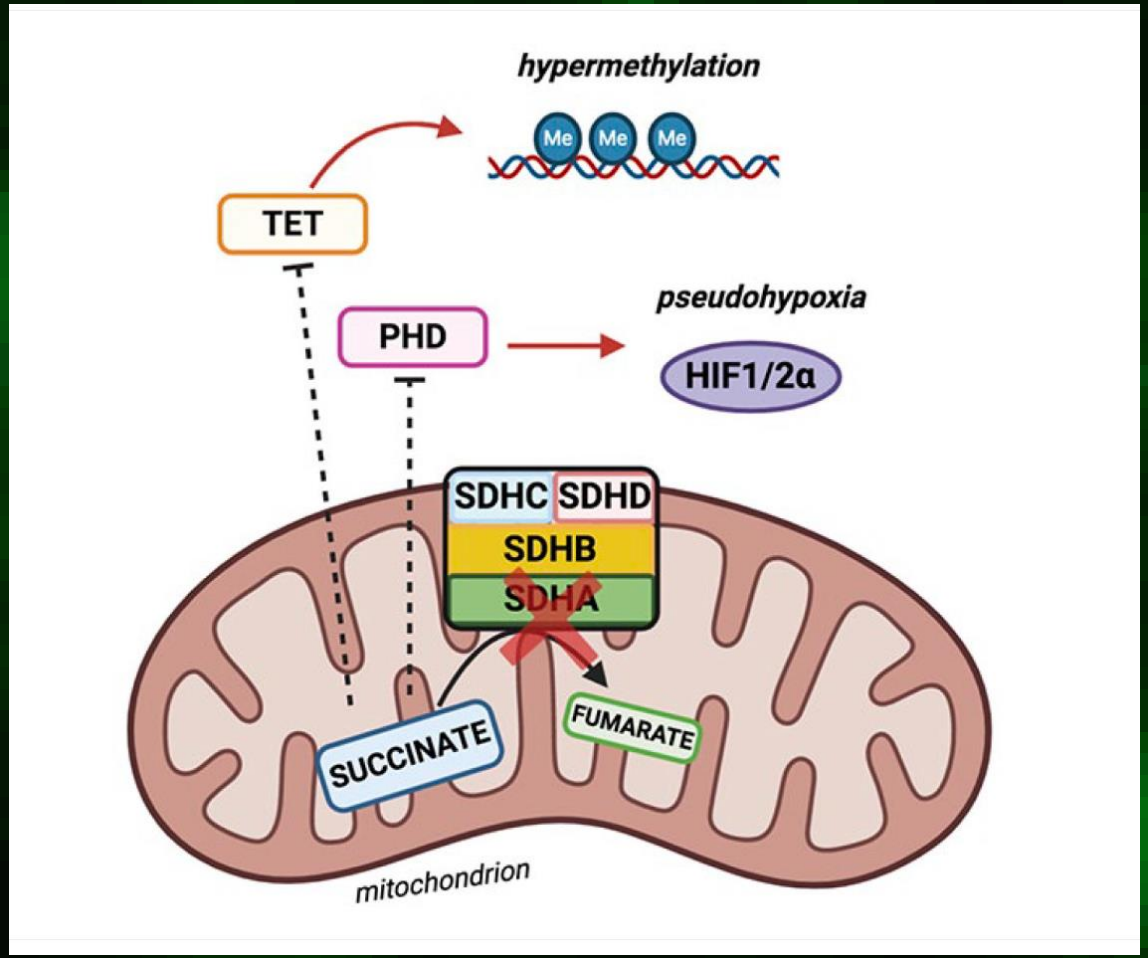
UQ: ubiquinone; CI, CIII, CIV: the various complexes of the respiratory chain.

Rustin, P., Munnich, A. & Rötig, A. Succinate dehydrogenase and human diseases: new insights into a well-known enzyme. Eur J Hum Genet 10, 289–291 (2002).

Ibrahim A, Chopra S. Succinate Dehydrogenase-Deficient Gastrointestinal Stromal Tumors. Arch Pathol Lab Med. 2020 May;144(5):655-660.

Molecular Biology

- They are at risk for other type of cancers, pulmonary chondromas and paraganglionomas.
- Can be part of the Carney Stratakis Syndrome an autosomal dominant disease with incomplete penetrance and can be passed down generations and the Carney Triad Syndrome.
- Germline mutations in
  - SDHA occur in approximately 30% of the SDH-deficient GIST,
  - whereas those in SDHB, SDHC, and SDHD occur in only 20–30% of cases.



HIF, hypoxia-inducible factor; Me, methyl group; PHD, prolyl-hydroxylase domain proteins; SDH, succinate dehydrogenase; TET, ten–eleven translocation.

Nannini M, Rizzo A, Indio V, Schipani A, Astolfi A, Pantaleo MA. Targeted therapy in SDH-deficient GIST. Therapeutic Advances in Medical Oncology. 2021;13. doi:10.1177/17588359211023278

EPIDEMIOLOGY

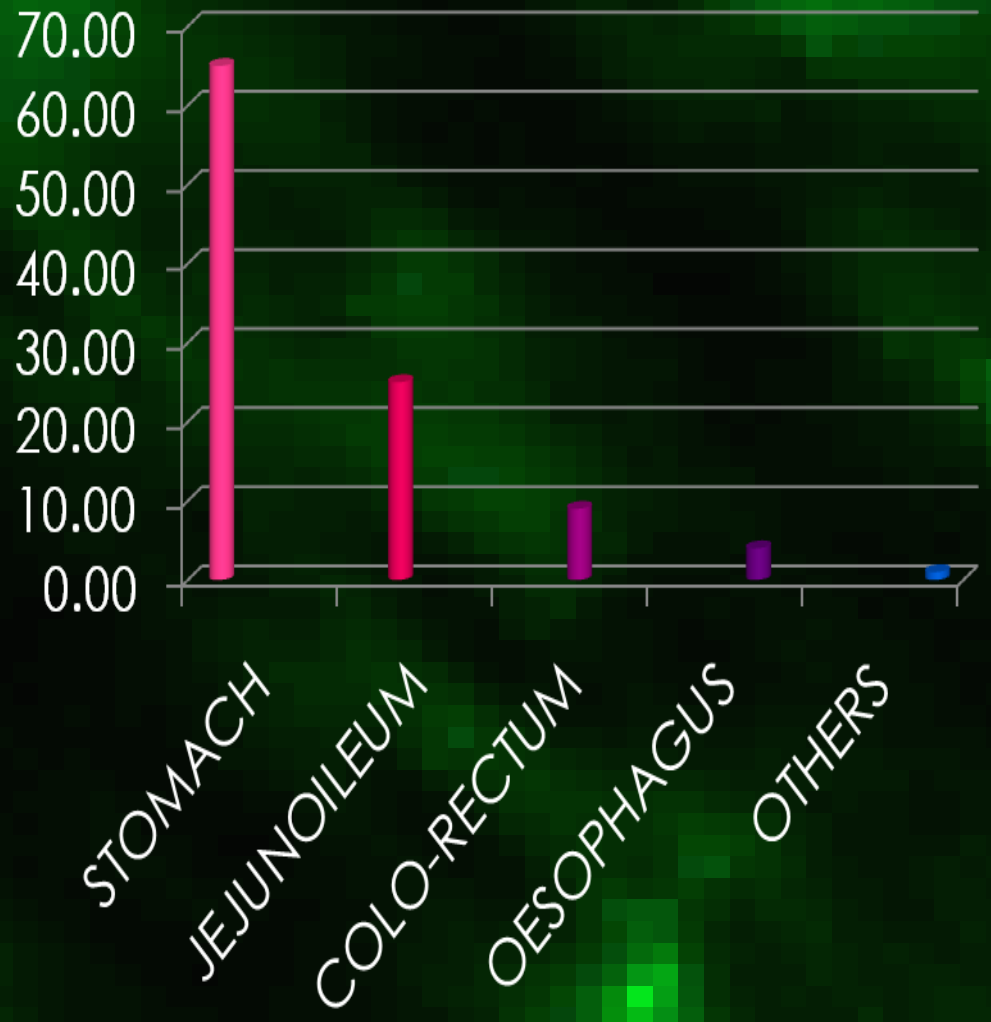
- Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract.
- GISTs can also originate in the mesentery and omentum.
- Overall, GISTs are rare and rank a distant third in prevalence behind adenocarcinomas and lymphomas among the histologic types of gastrointestinal tract tumors.

Macroscopic Pathology

- GISTs can occur anywhere in the gastrointestinal tract.
- They are submucosal lesions, which most frequently grow Endophytically in parallel with the lumen of the affected structure.
- GISTs may also manifest as exophytic extraluminal excrescences. These tumors have been reported ranging in size from smaller than 1 cm to as large as 40 cm in diameter.

Pathophysiology

- Approximately 50-70% of GISTs originate in the stomach.
- The small intestine is the second most common location, with 20-30% of GISTs arising from the jejuno-ileum.
- Less frequent sites of occurrence include the colon and rectum (5-15%) and
- Oesophagus (<5%).
- Primary omental or mesenteric GISTs have been reported but are very rare.



INITIAL ATTEMPTS OF STRATIFICATION OF RISK

The 2002 Fletcher et al stratification of the risk of aggressive or malignant behavior in GISTs, based on size and mitotic rate, is as follows:[16]

- Very low risk - Smaller than 2 cm and less than 5/50 HPFs
- Low risk - From 2-5 cm and less than 5/50 HPFs
- Intermediate risk –

  (1) smaller than 5 cm and 6-10/50 HPFs or

  (2) 5-10 cm and less than 5/50 HPFs
- High risk - Includes

  (1) larger than 5 cm and more than 5/50 HPFs,

  (2) larger than 10 cm and any mitotic rate, or

  (3) any size and more than 10/50 HPFs

2002

INITIAL ATTEMPTS
UICC TNM CLASSIFICATION for GIST

Comparison of the different risk stratification systems and the proposed UICC TNM classification for GIST

Tumor Size (cm)	Mitoses /50HPFs	Risk/Progression % AFIP, 2006 Stomach	Risk/ Progression % AFIP, 2006 Jejunum/ Ileum	Risk/ Progression % AFIP, 2006 Duodenum	Risk/ Progression % AFIP, 2006 Rectum	Risk NIH Fletcher et al, 2002 All sites	Revised NIH Risk Joensuu, 2008 Gastric tumors	Revised NIH Risk Joensuu, 2008 Non-gastric
≤2 cm	≤5	None (0%); benign UICC IA	None (0%); benign UICC I	None (0%); benign UICC I	None (0%); benign UICC I	Very low	Very low	Very low
>2–≤5 cm	≤5	Very low (1.9%) UICC IA	Low (4.3%) UICC I	Low (5.3%) UICC I	Low (6.5%) UICC I	Low	Low	Low
>5–≤10 cm	≤5	Low (3.6%) UICC IB	Intermediate (24%) UICC II	High (34%) UICC II	High (57%) UICC II	Intermediate	Intermediate	High
> 10 cm	≤5	Intermediate (12%) UICC II	High (52%) UICC IIIA	High (34%)* UICC IIIA	High (57%) UICC IIIA	High	High	High
≤2 cm	>5	0* UICC II	High (50%)* UICC IIIA	No cases UICC IIIA	High (54%) UICC IIIA	Intermediate or high†	Intermediate or high†	Intermediate or high†
>2–≤5 cm	>5	Intermediate (16%) UICC II	High (73%) UICC IIIB	High (52%) UICC IIIB	High (52%) UICC IIIB	Intermediate or high†	Intermediate or high†	High
>5–≤10 cm	>5	High (55%) UICC IIIA	High (85%) UICC IIIB	High (86%)* UICC IIIB	High (71%)* UICC IIIB	High	High	High
> 10 cm	>5	High (85%) UICC IIIB	High (90%) UICC IIIB	High (86%)* UICC IIIB	High (71%)* UICC IIIB	High	High	High

* Two groups were analyzed together because of low case numbers.
* Low case number.
† depends on whether 6-10 or >10 mitoses per 50 HPFs are detectable.

2010

INITIAL ATTEMPTS
TNM CLASSIFICATION FOR GIST

The new TNM classification for GIST[a]

Tumor size (cm)	Mitoses/ 50HPFs	T-stage gastric	T-stage non-gastric	UICC gastric	UICC non-gastric
≤2 cm	≤5	T1	T1	IA	1
>2-5 cm	≤5	T2	T2	IA	1
>5-10 cm	≤5	T3	T3	IB	II
> 10 cm	≤5	T4	T4	II	IMA
≤2cm	>5	T1	T1	II	IMA
>2-5 cm	>5	T2	T2	II	NIB
>5-10 cm	>5	T3	T3	IMA	NIB
> 10 cm	>5	T4	T4	NIB	NIB

[a]The above UICC stages are valid for NO MO tumors. All tumors with lymph node or other metastasis are considered UICC stage IV.

International union against cancer (UICC)Sobin LH, Wittekind Ch, editors. 7th ed. New York: Wiley; 2010. TNM classification of malignant tumours.

2010

NEW TNM CLASSIFICATION FOR GIST

PRIMARY TUMOUR (T)	
T CATEGORY	T CRITERIA
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour 2cm or less
T2	Tumour 2 to 5 cm
T3	Tumour 5 to 10 cm
T4	Tumour > 10cm in greatest dimension
REGIONAL LYMPH NODES (N)	
N CATEGORY	N CRITERIA
N0	No lymph node metastasis or status cannot be assessed
N1	Regional lymph node metastasi(e)s

NEW TNM CLASSIFICATION FOR GIST

DISTANT METASTASIS (M)	
M CATEGORY	**M CRITERIA**
M0	No distant metastasis
M1	Distant metastasis
MITOTIC RATE	
RATE	**DEFINITION**
LOW	Five or fewer mitotic count per $5mm^2$
HIGH	Over 5 mitotic count per $5mm^2$

GIST TNM staging AJCC UICC 8th edition.

NEW TNM CLASSIFICATION FOR GIST

STOMACH GIST				
T	**N**	**M**	**MITOTIC R**	**STAGING**
T1 orT2	N0	M0	Low	IA
T3	N0	M0	Low	IB
T4	N0	M0	Low	II
T1	N0	M0	High	II
T2	N0	M0	High	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

GIST TNM staging AJCC UICC 8th edition.

NEW TNM CLASSIFICATION FOR GIST

SMALL INTESTINE, OESOPHAGUS, COLORECTAL, MESENTERIC PERITONEAL				
T	**N**	**M**	**MITOTIC R**	**STAGING**
T1 orT2	N0	M0	Low	I
T3	N0	M0	Low	II
T4	N0	M0	Low	IIIA
T1	N0	M0	High	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

GIST TNM staging AJCC UICC 8th edition.

STRATIFICATION OF RISK

Tumour related factors in Risk Stratification

1. Anatomical site.
2. Histological type.
3. Size of tumour.
4. Depth of invasion.
5. Grade (well to poorly differentiated).
6. M staging.
7. Mitotic index.

STRATIFICATION OF RISK

Tumor size (cm)	Risk of disease progression during long-term follow-up by primary site			
	Gastric	Jejunum/ileum*	Duodenum	Rectum
Mitotic rate¶ (HPF): ≤5/50				
≤2	No risk	No risk	No risk	No risk
2 to 5	Very low	Low	Low	Low
5 to 10	Low	Intermediate	Limited data	Limited data
>10	Intermediate	High	High	High
Mitotic rate¶ (HPF): >5/50				
≤2	No risk[Δ]	High[Δ]	Limited data	High
2 to 5	Intermediate	High	High	High
>5	High	High	High[◇]	High[◇]

ARMED FORCE INSITUTE OF PATHOLOGY (AFIP) prognostic model

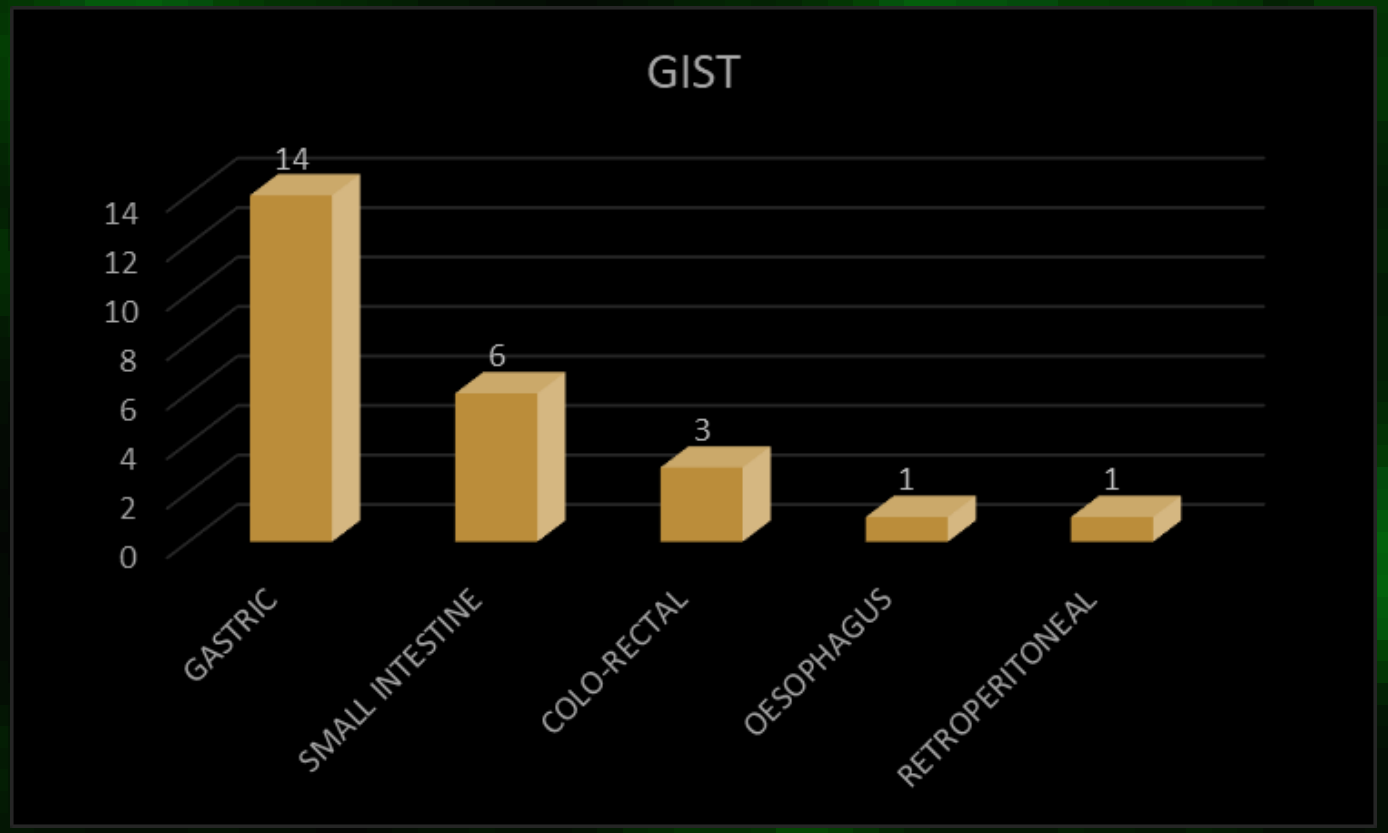
STRATIFICATION OF RISK

Additional factors in Risk Stratification

- Related to Tumour
  1. Presence of KIT mutation
  2. Mutational site in KIT or PGDFRA gene.
  3. R status and Rupture during Surgery.
  4. Primary or Recurrence.
- Related to Host
  1. Neurofibromatosis Type 1
  2. Age of presentation.

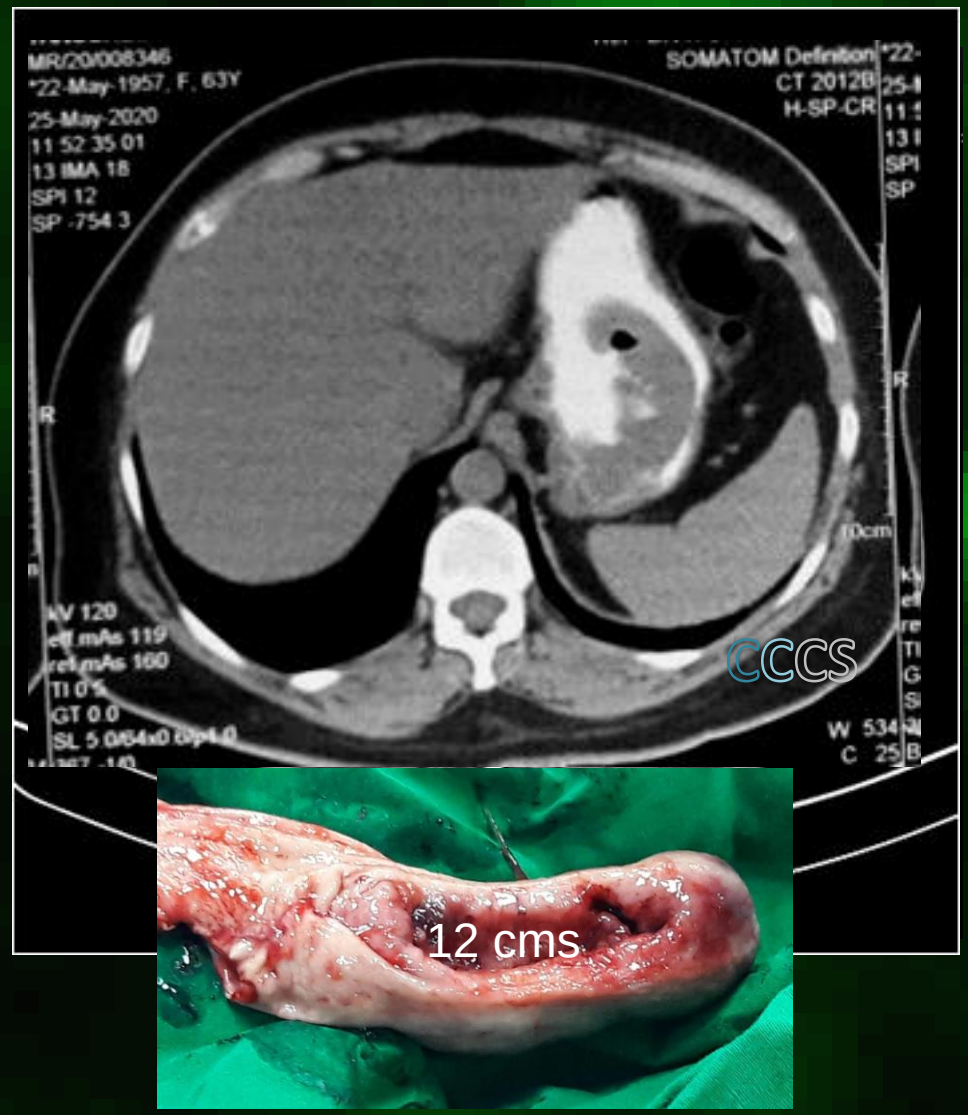
Patient with GIST personal series

- RECORDS OVER LAST 2 DECADES +
- SITES
- GASTRIC 14
- SMALL INTESTINE 6
- COLO-RECTAL 3
- OESOPHAGUS 1
- RETROPERITONEAL 1



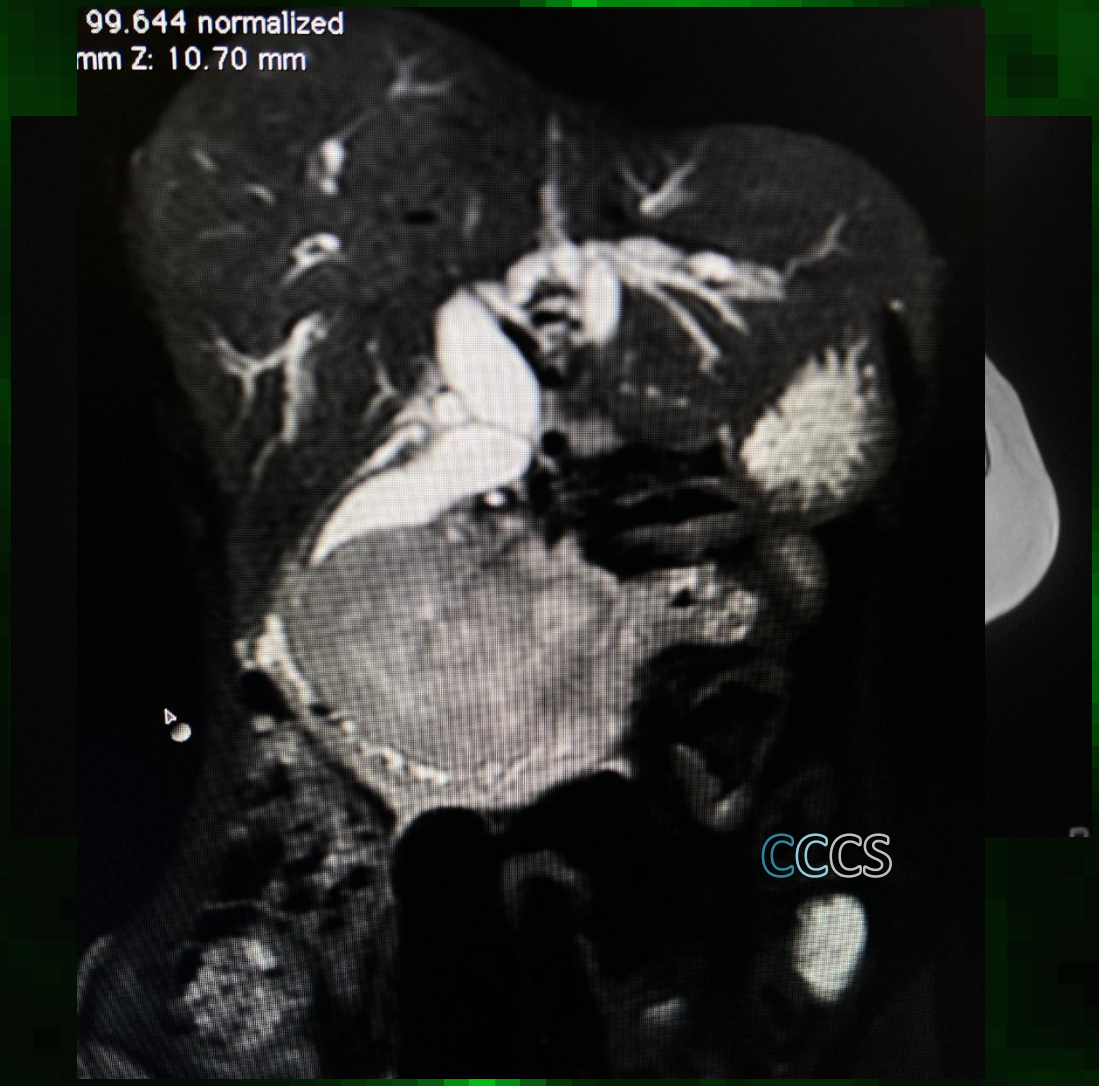
IMAGING IN GIST
AN ATTEMPT TO SCORE

- Correlates for chances of recurrence and metastasis
  1. tumours that are larger than 5 cm, are
  2. an exophytic growth pattern
  3. lobulated,
  4. enhance heterogeneously,
  5. mesenteric fat infiltration,
  6. ulceration,
  7. non-gastric or
  8. regional lymphadenopathy
- on CT/MRI are more likely to metastasize and/or recur.



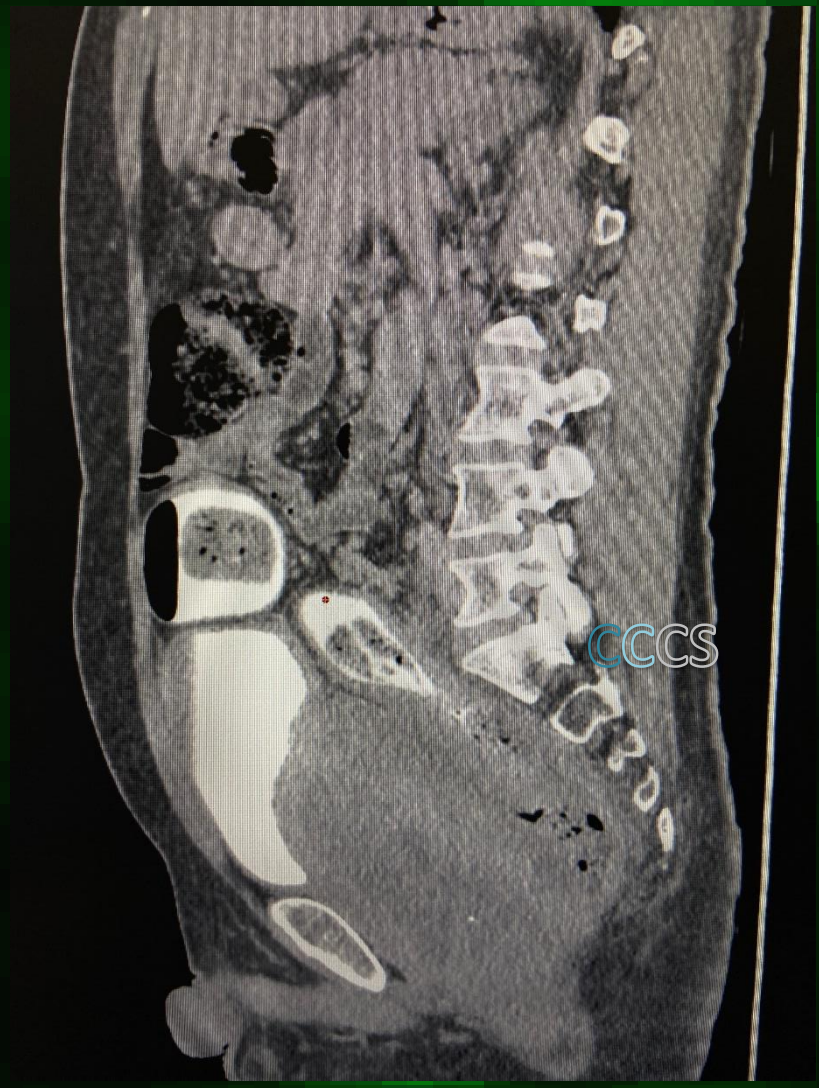
IMAGING IN GIST
AN ATTEMPT TO SCORE

- Correlates for chances of recurrence and metastasis
  1. tumours that are larger than 5 cm, are
  2. an exophytic growth pattern
  3. lobulated,
  4. enhance heterogeneously,
  5. mesenteric fat infiltration,
  6. ulceration,
  7. non-gastric or
  8. regional lymphadenopathy
- on CT/MRI are more likely to metastasize and/or recur.



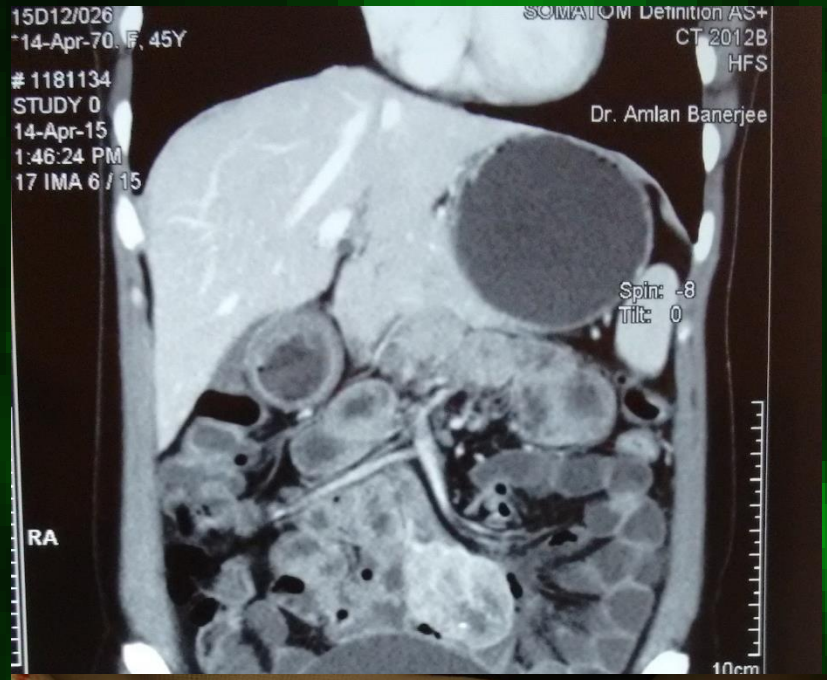
IMAGING IN GIST
AN ATTEMPT TO SCORE

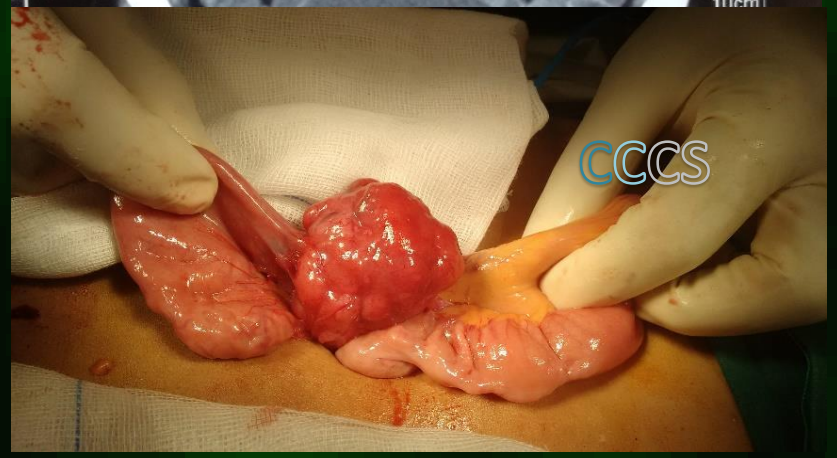
- Correlates for chances of recurrence and metastasis
  1. tumours that are larger than 5 cm, are
  2. an exophytic growth pattern
  3. lobulated,
  4. enhance heterogeneously,
  5. mesenteric fat infiltration,
  6. ulceration,
  7. non-gastric or
  8. regional lymphadenopathy
- on CT/MRI are more likely to metastasize and/or recur.



IMAGING IN GIST
AN ATTEMPT TO SCORE

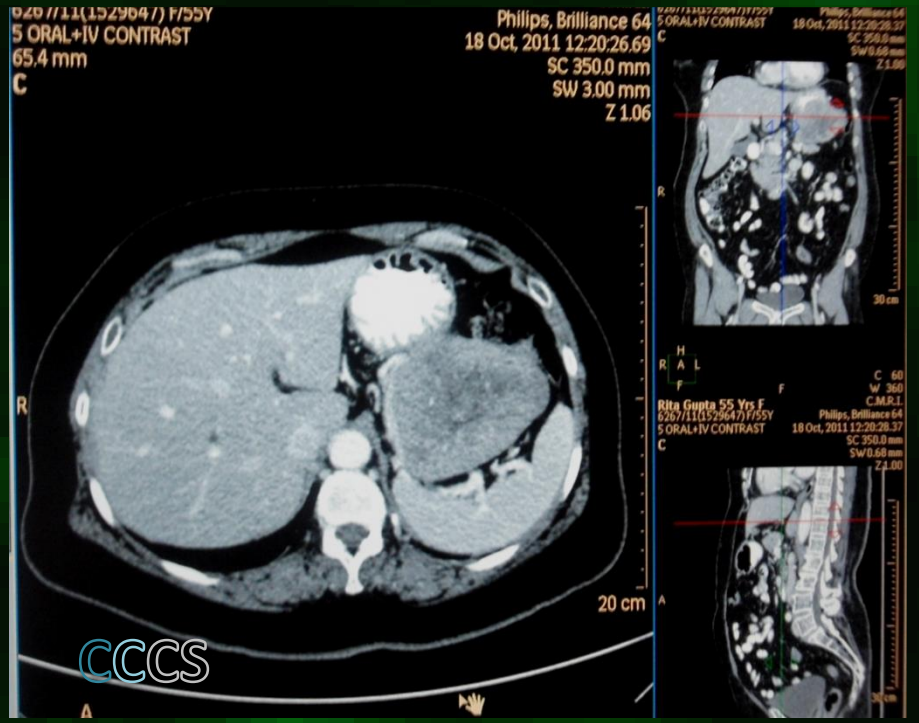
- Correlates for chances of recurrence and metastasis
  1. tumours that are larger than 5 cm, are
  2. an exophytic growth pattern
  3. lobulated,
  4. enhance heterogeneously,
  5. mesenteric fat infiltration,
  6. ulceration,
  7. non-gastric or
  8. regional lymphadenopathy
- on CT/MRI are more likely to metastasize and/or recur.

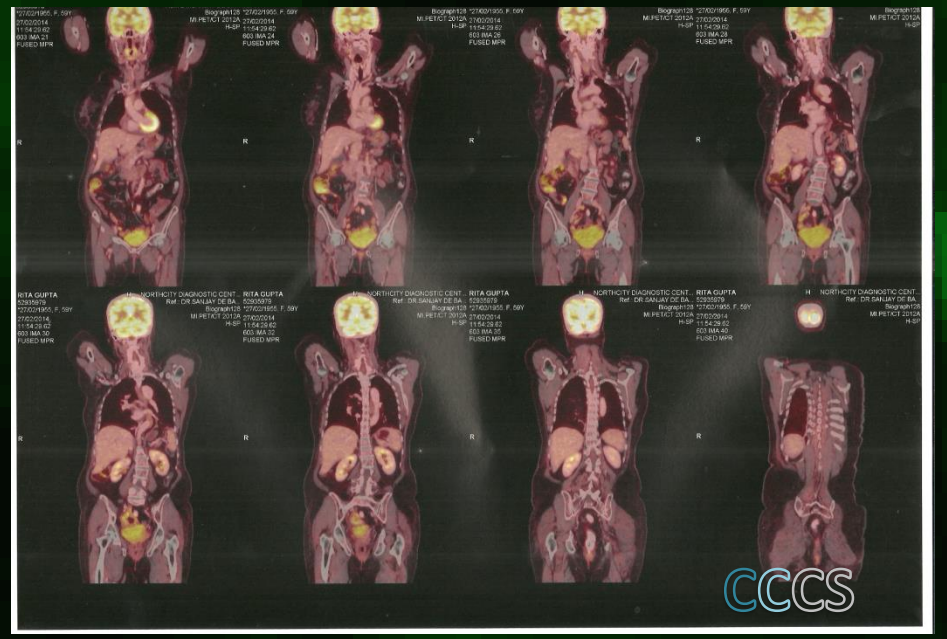




IMAGING IN GIST
AN ATTEMPT TO SCORE

- Role of PET-CT SCAN





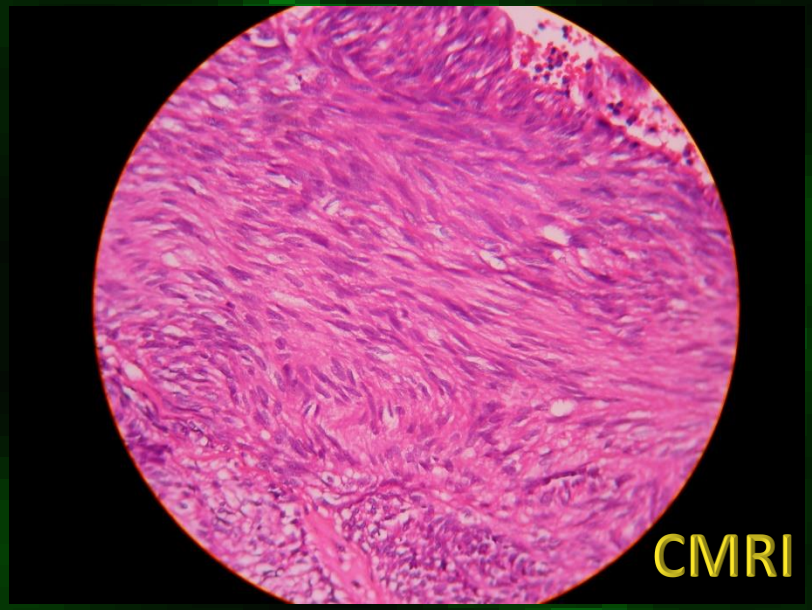
T3 N0 M0 MR<5/hpf; Spindle cell

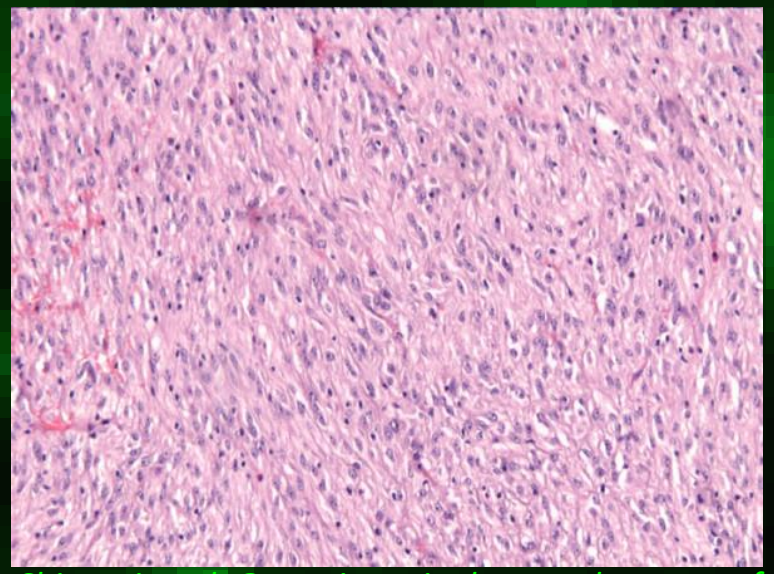
STAGE IB

PATHOLOGY

HISTOLOGY

- Spindle cell – 70%.
- Epitheloid cells - 20% often KIT negative and harbour PDGFRA mutations and frequently present in the stomach.
- Mixed – 10%.



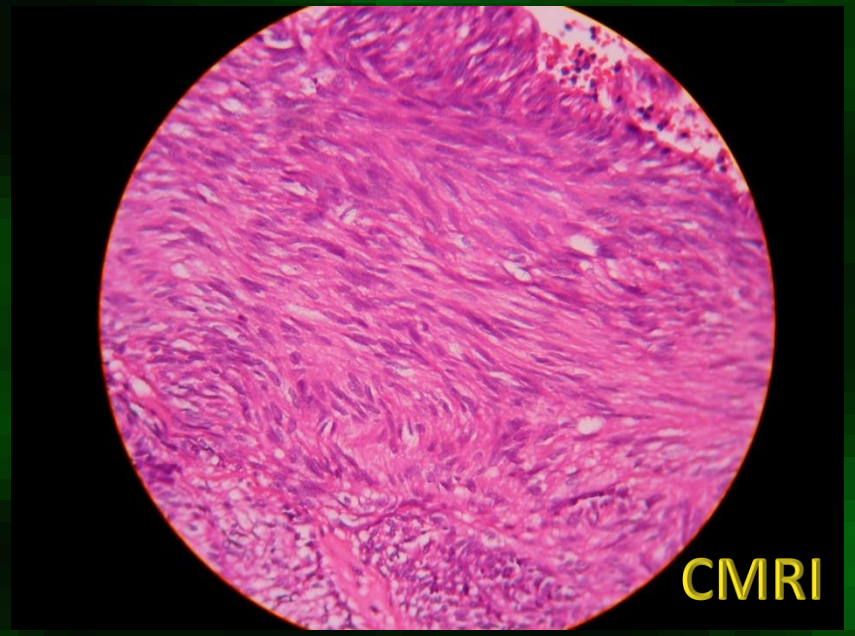


Chiarugi et al; Gastrointestinal stromal tumour of the duodenum in childhood: a rare case report

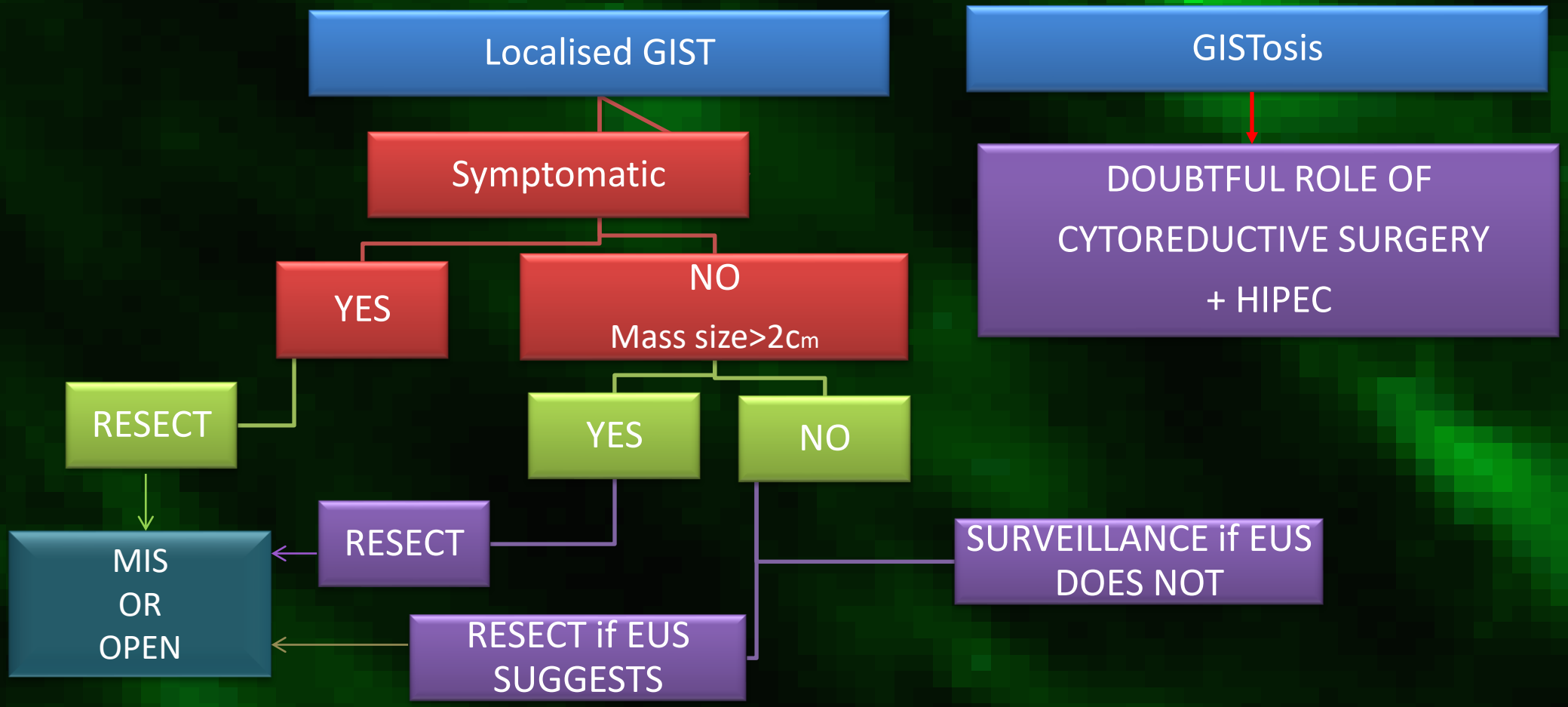
IHC

PATHOLOGY

- *KIT* mutation in 90%
- *PGDFRA* gene mutation in rest.
  - D842V exon 18 mutations
- CD-34 often found to be positive.
- DOG-1 (found in GIST-1)
- PKC theta is an IHC markers that is present irrespective of *KIT/PDGFRA* mutation status.
- Succinate Dehydrogenase (SDH) estimation in “Wild-type” GIST. Deficiency of SDHB.
- Other mutations
- BRAF – 13%
- NF-1 – mitogen–activated protein kinase (MAPK)



SURGICAL TREATMENT



Adapted from Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. Nat Rev Gastroenterol Hepatol 2009; 6:363.

EUS FINDING OF SMALL SUBEPITHELIAL LESIONS (SELs)

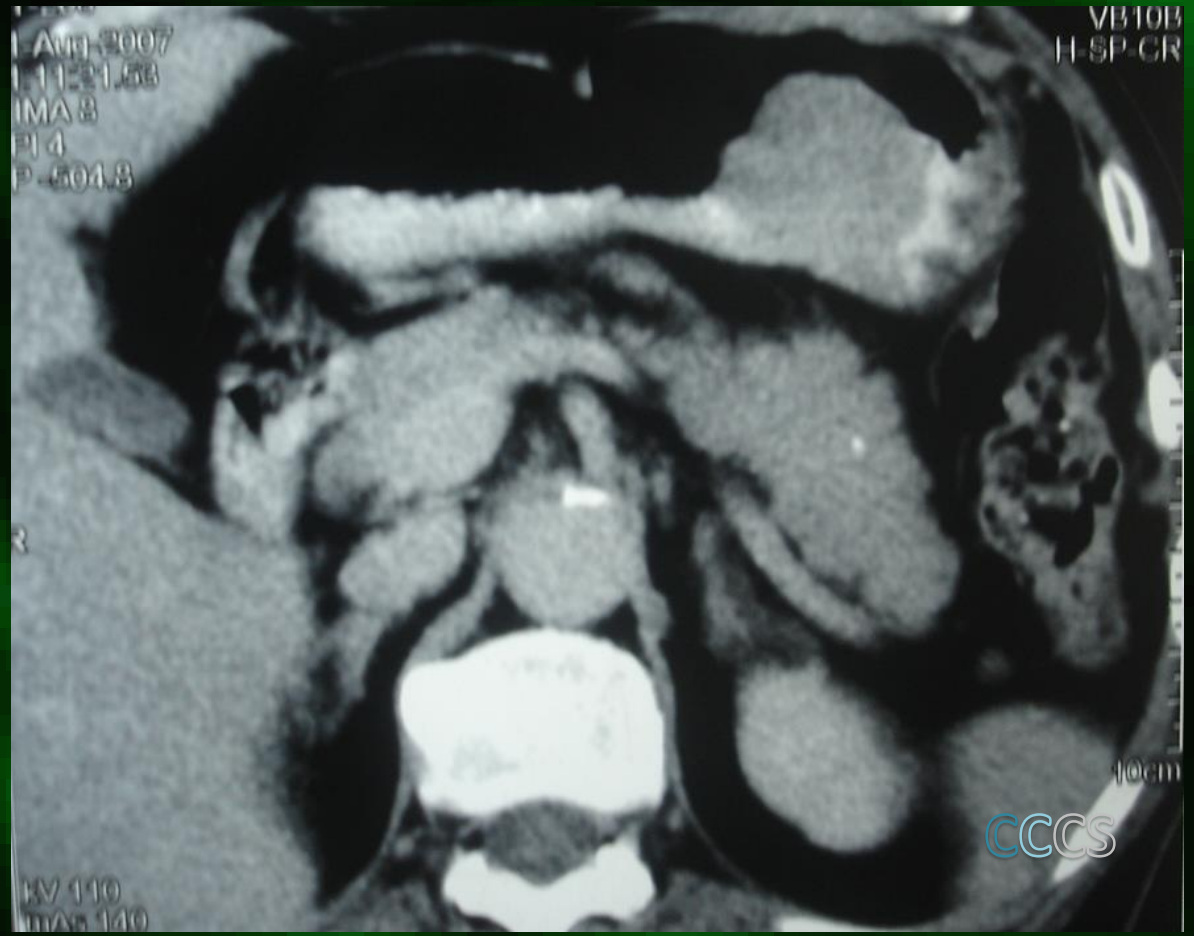
- Accuracy only 45.55 to 48% (so EUS-FNA/BIOPSY suggested)

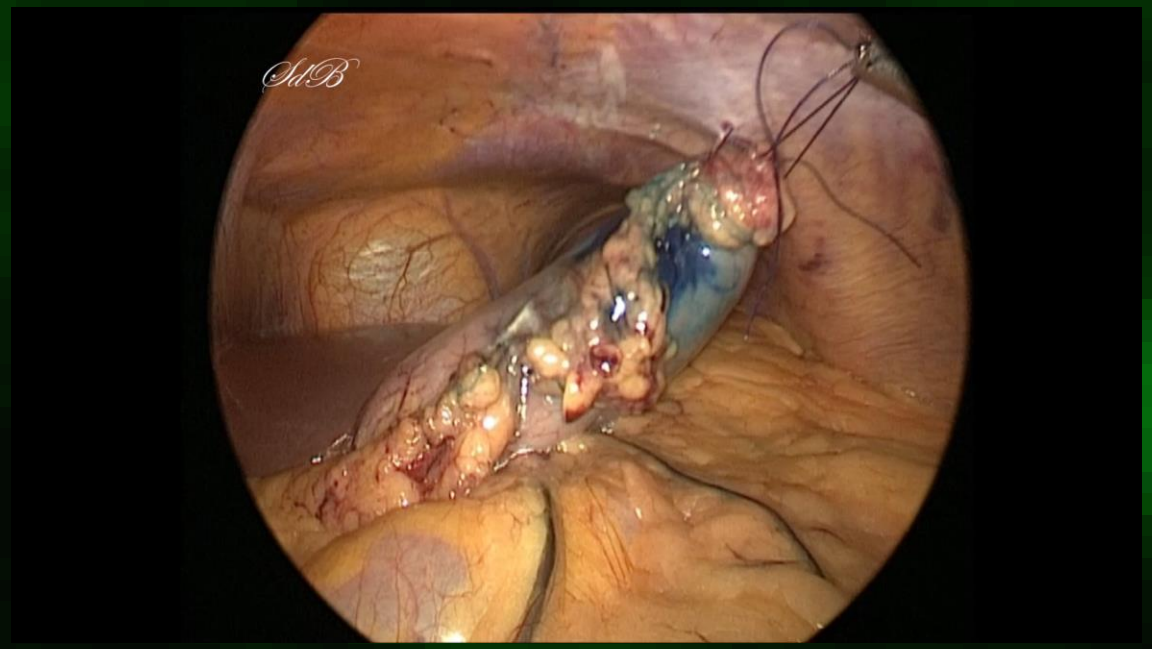
- LIPOMA - highly echoic
- CYSTS – anechoic masses
- GIST – hypoechoic solid mass

➢ HIGH RISK

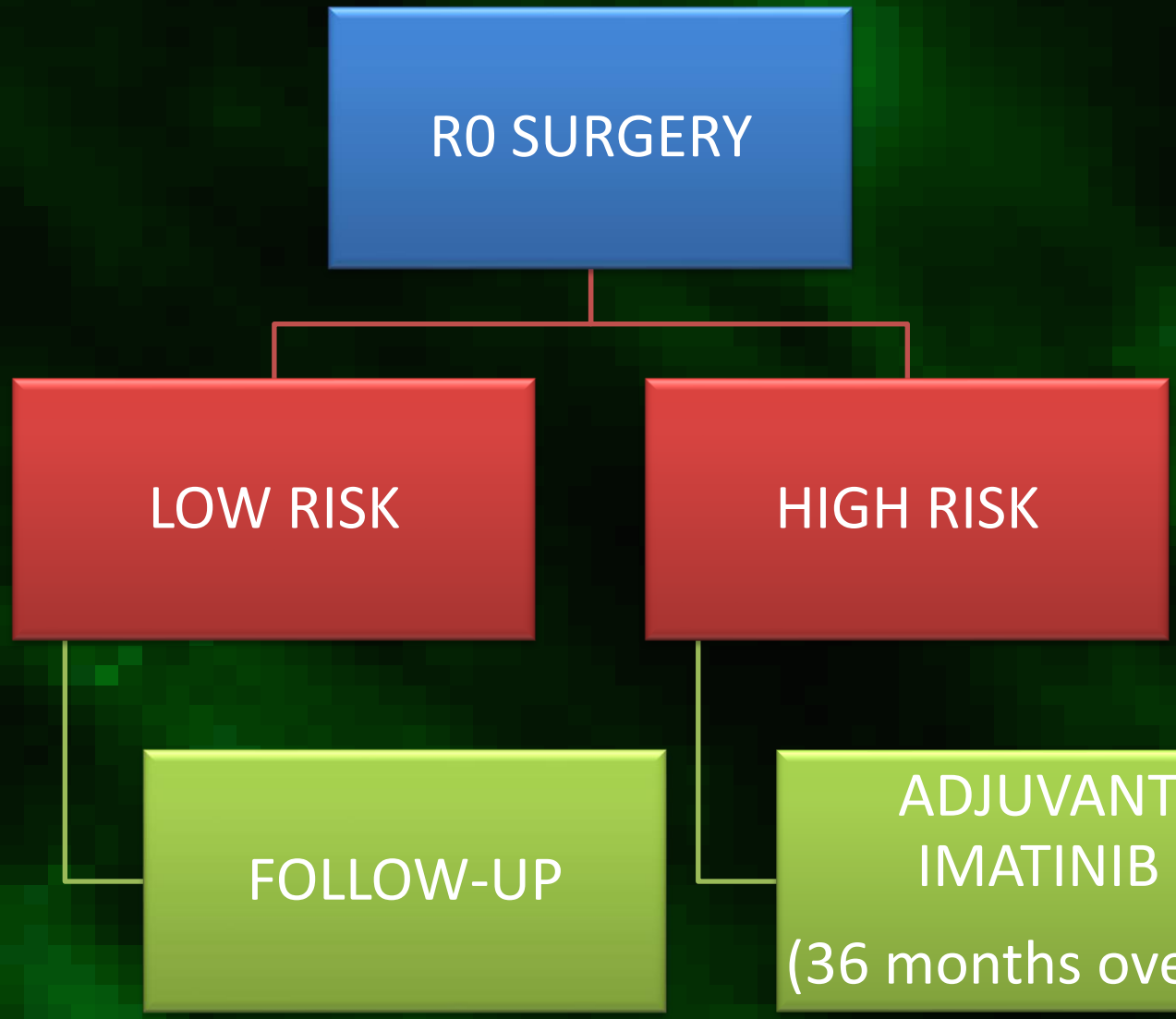
1. size > 2cm
2. irregular borders
3. heterogenous echo-pattern
4. anechoic spaces
5. echogenic foci
6. rapid growth on follow-up

MIS IN GIST





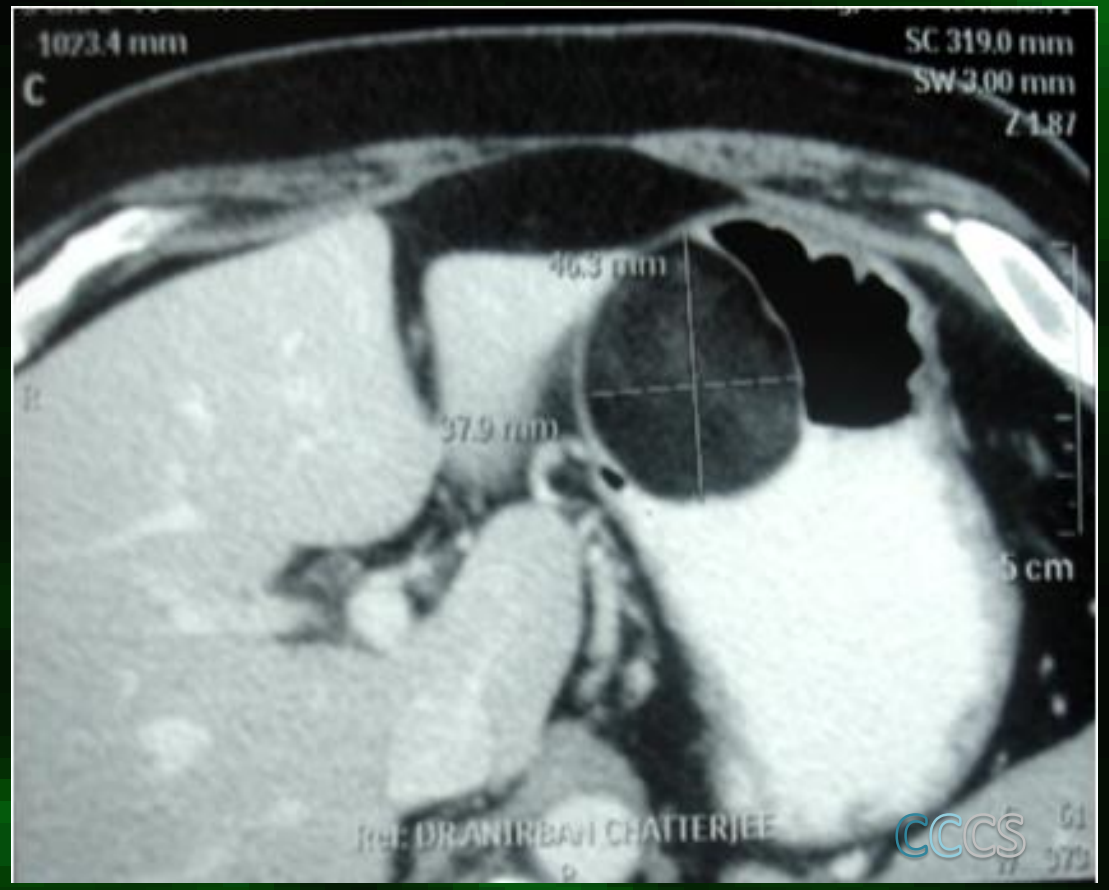
ADJUVANT THERAPY



ESMO GUIDELINES

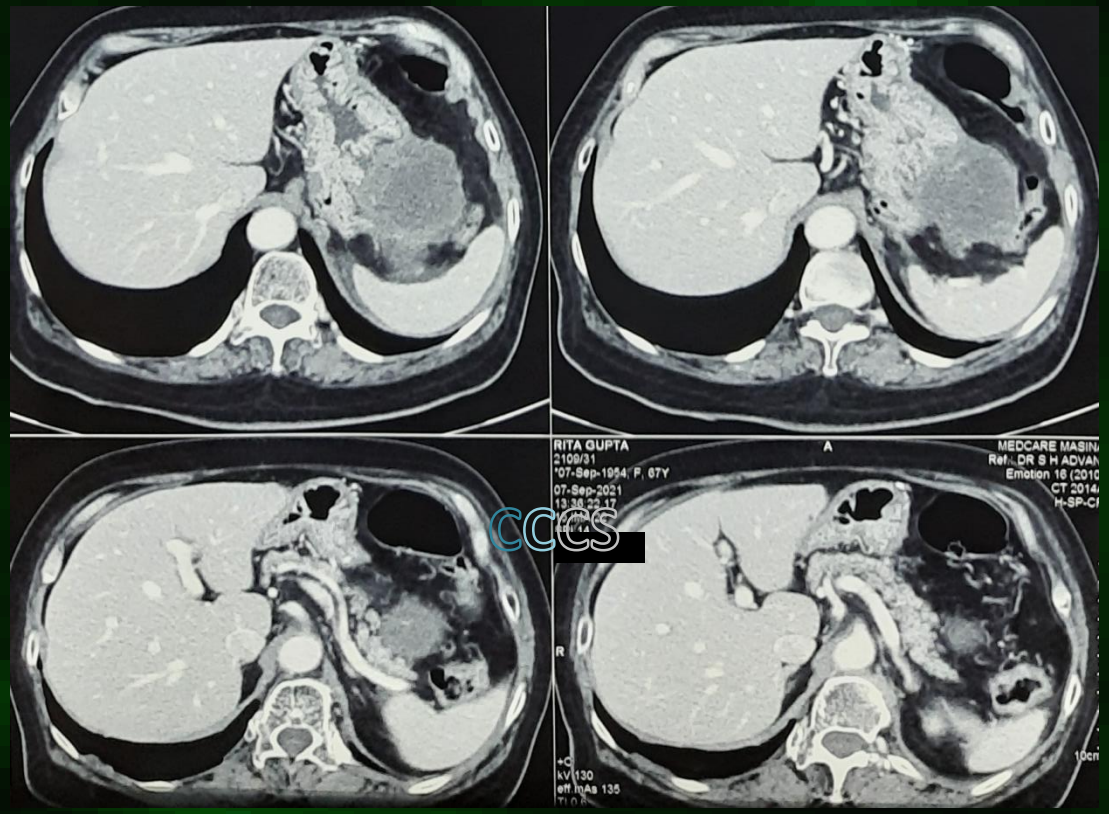
SWEDISH SARCOMA GROUP XVIII TRIAL

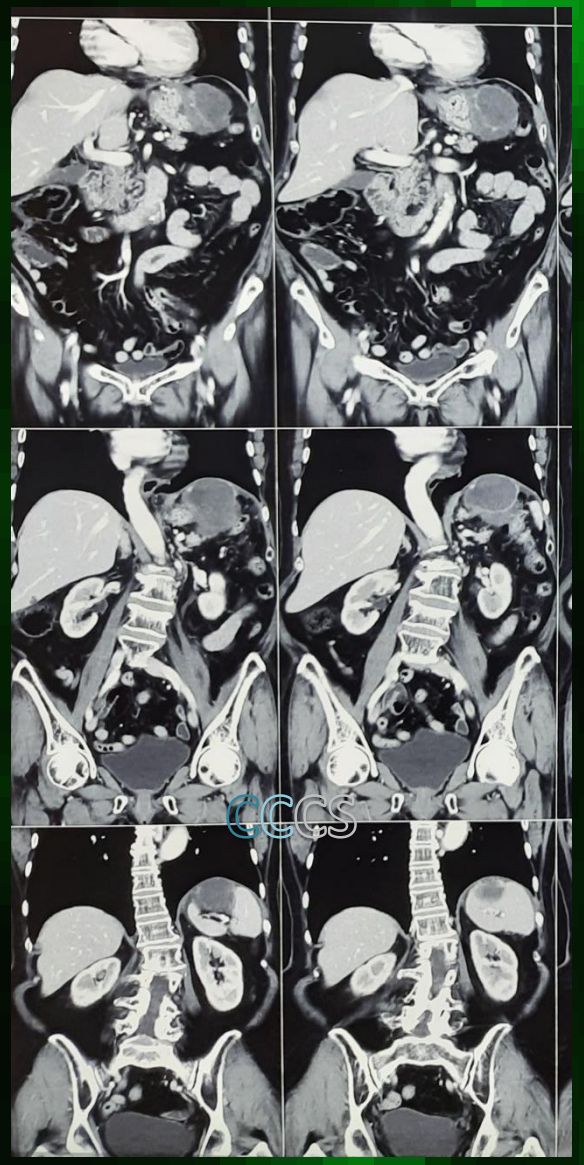
GIST STOMACH



- T2 N0 M0
- MITOTIC RATE >5/50hpf
- INTERMEDIATE
- Did well - 4 years on Imatinib!
- 5th year----------

RECC GIST STOMACH



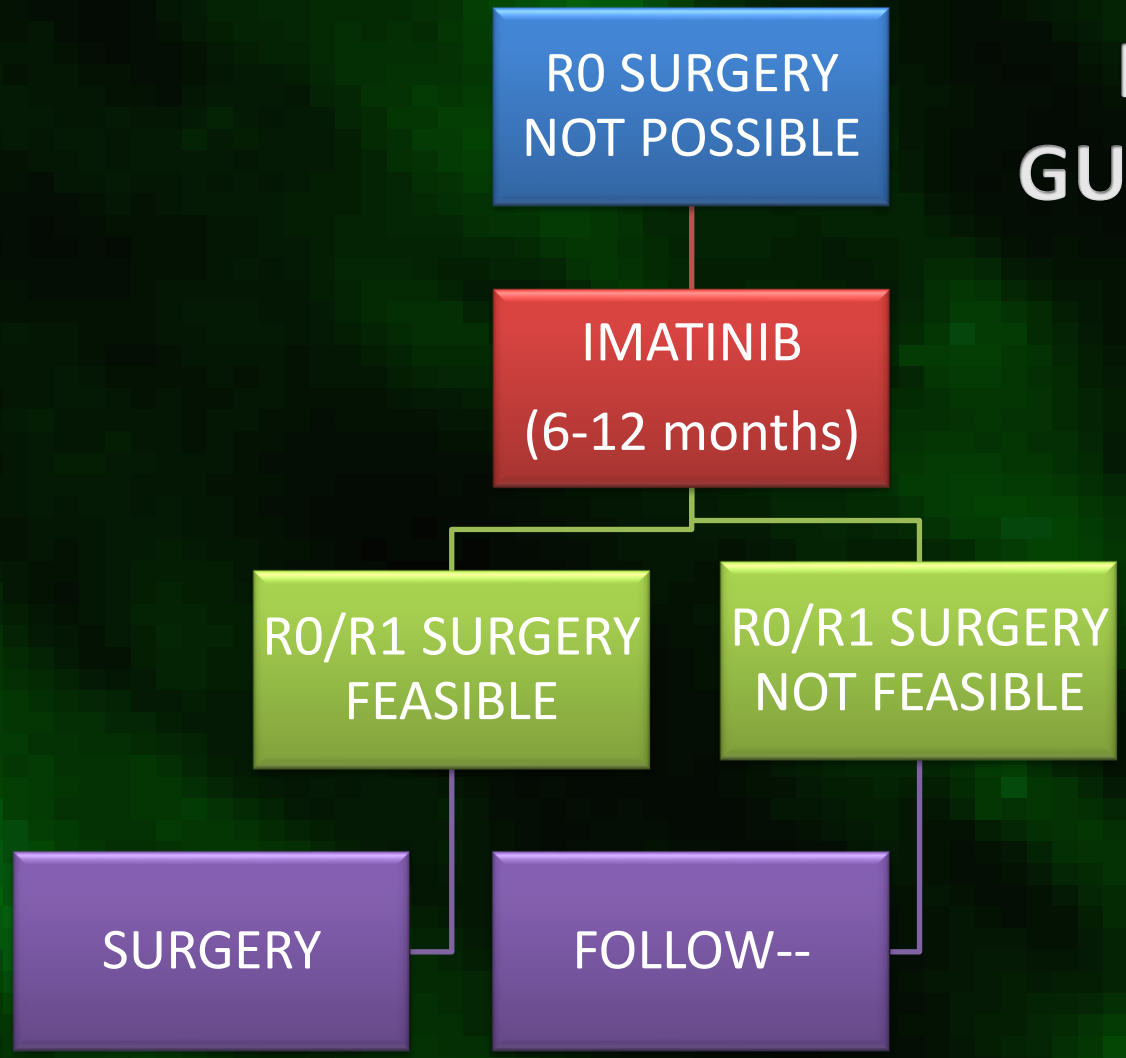


Blanke CD, DeMatteo RP. Duration of Adjuvant Therapy for Patients With Gastrointestinal Stromal Tumors: Where Is Goldilocks When We Need Her? JAMA Oncol. 2016 Jun 1;2(6):721-2. doi: 10.1001/jamaoncol.2016.0094. PMID: 27031092.

DURATION OF THERAPY – A major point of concern!!!!

- Data from preclinical studies suggest that imatinib causes cellular quiescence BUT NOT DEATH.
- The PERSIST 5 TRIAL – 5 years rather than 3!!!!
  - Criteria for intermediate and high risk being-
    - GIST of any site > 2cm,
    - with a mitotic count > 5/50HPF,
    - non-gastric primary GIST >5 cm.
- 6 of 91 patients recurred after discontinuation of Imatinib (5 years)!!!

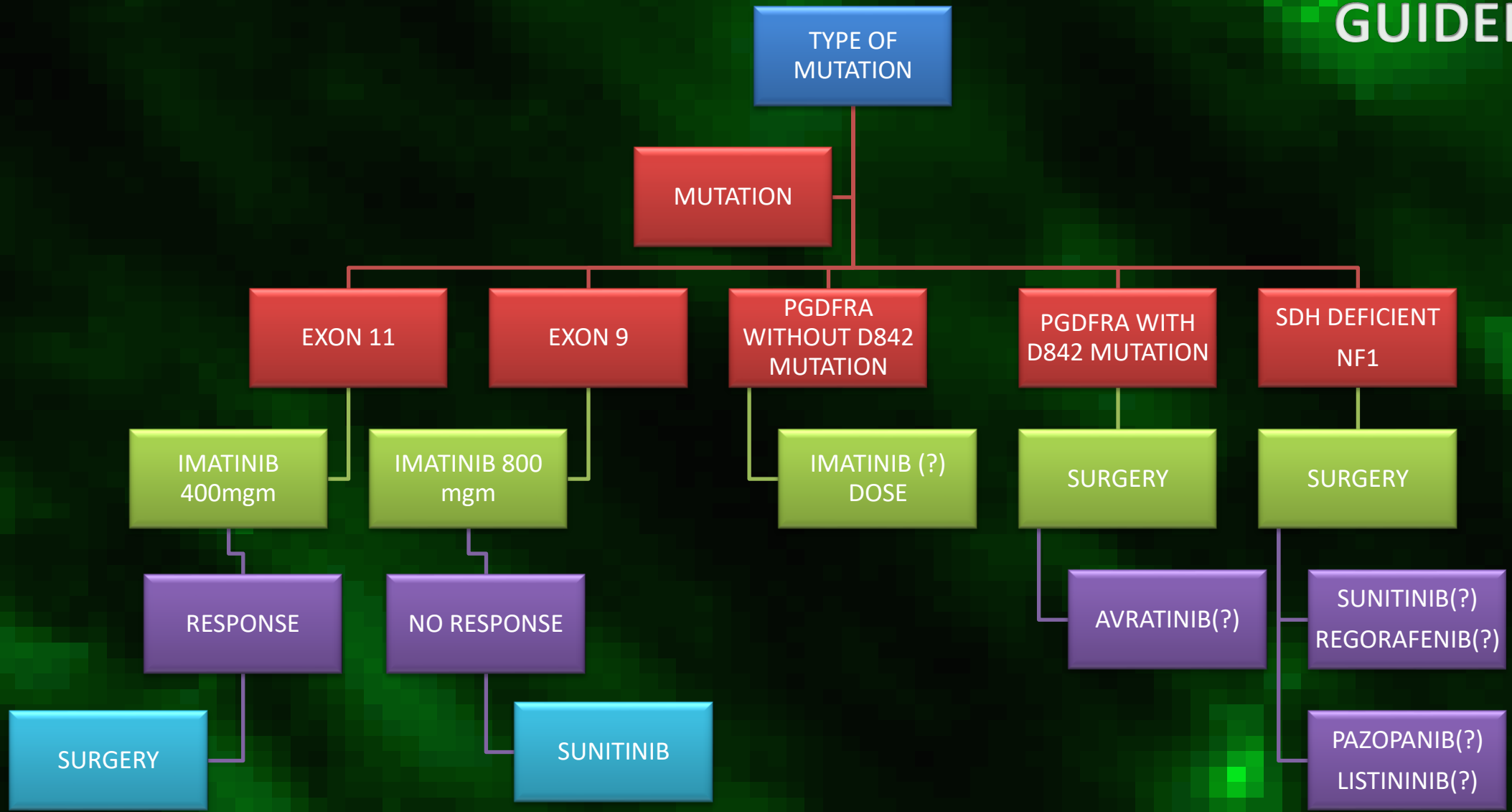
NEO-ADJUVANT THERAPY



ESMO GUIDELINES

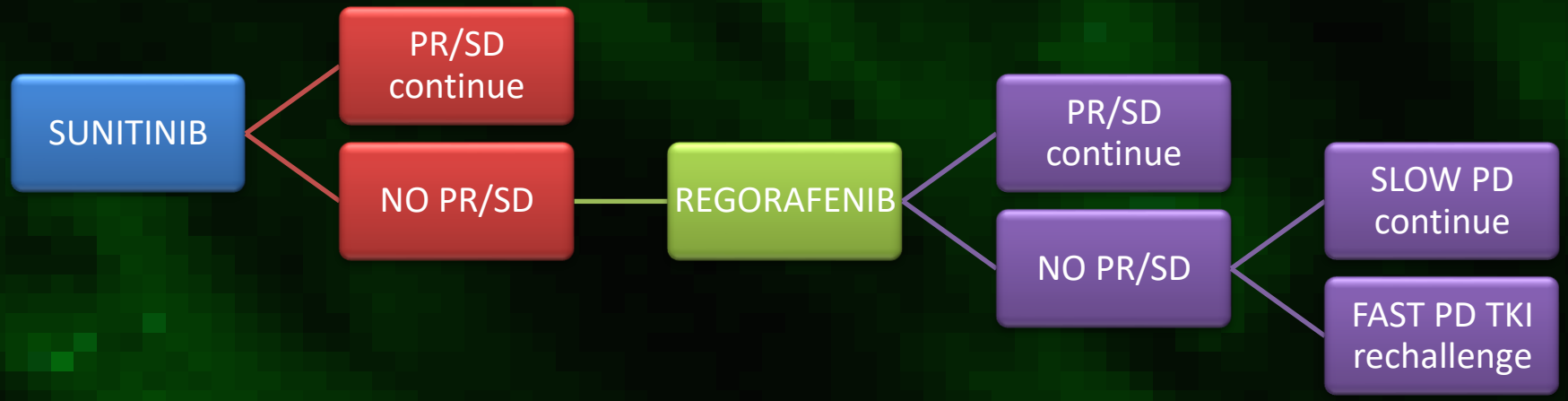
NEO-ADJUVANT THERAPY

ESMO GUIDELINES



NEO-ADJUVANT THERAPY

ESMO GUIDELINES



ASSESSMENT

RESPONSE CRITERIA

RESPONSE	RECIST 1.1	CHOI
CR	**Disappearance of all** target and nontarget lesions without any new lesions	Disappearance of all lesions without any new lesions
PR	**30% decrease** in sum of the maximum diameters of all individual measurable lesions without any new lesions or progression of any nontarget lesions	Decrease in tumor size1 10% or decrease in tumor density (HU) 15% on CT without any new lesions or obvious progression of nonmeasurable lesions
SD	**Does not meet criteria** for other responses	Does not meet criteria for other responses and does not have symptomatic deterioration attributable to tumor progression
PD	**20% increase** in sum of maximum diameters of all individual measurable lesions, unequivocal progression of any nontarget lesion or appearance of new lesion	Increase in tumor size 10% without meeting criteria for PR by tumor density on CT, or appearance of new lesions or new intratumoral nodules or increase in size of existing intratumoral nodules


Traces of Mist—
Still Remain.....
© SanjayDB


THANK YOU!
Dr Sanjay De Bakshi
MS(Cal); FRCS (Eng; Edin –ad eundem)
www.drsanjaydebakshi.org
© SanjayDB