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Nashville

SDH 101

Dr. Andrew Blakely

SDH Deficiency and Gastrointestinal Stromal Tumors

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Outline

- A little bit about me
- Broadly discuss GIST and its subtypes
- Deeper dive into SDH-deficient GIST
- Overview of SDH deficiency
- Discuss the role of surgery in GIST

My Background

- General Surgery Residency: Rhode Island
- Complex General Surgical Oncology Fellowship: Southern California
- Attending Surgical Oncologist: NIH, started September 2019
- Developed a GIST-specific natural history surgical study in 2020

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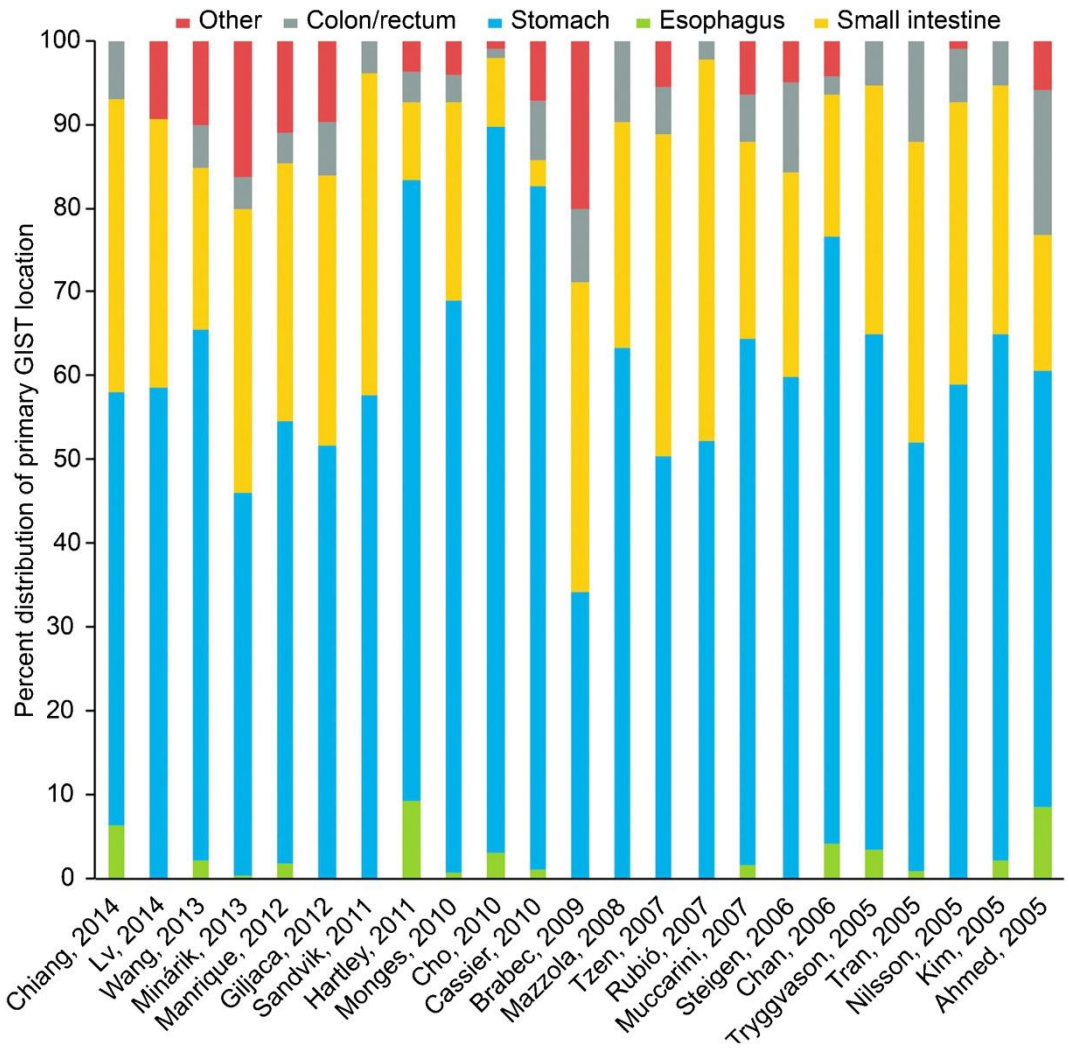
The Life Raft GROUP

Epidemiology

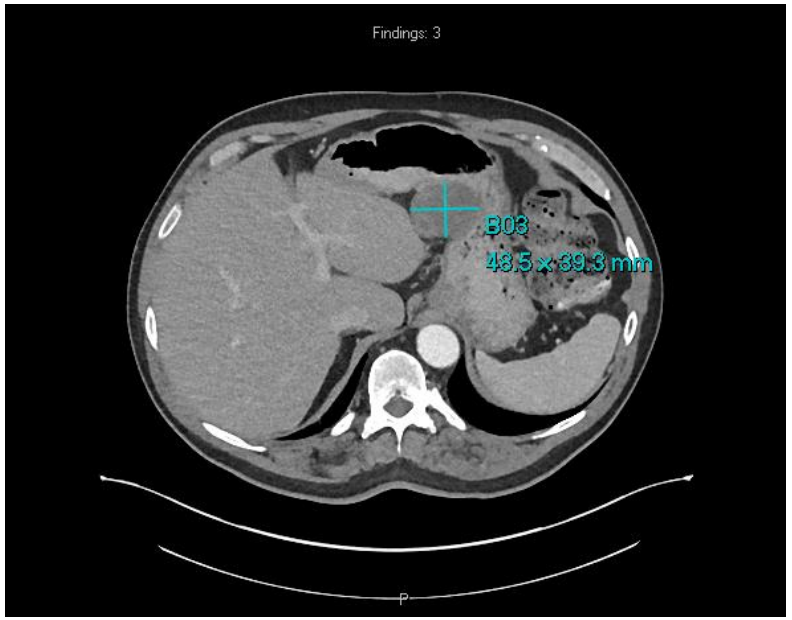
- Most common GI soft tissue sarcoma
  - 10-15 cases per million annually
  - Arise from interstitial cells of Cajal
- Median age of diagnosis: 65 years

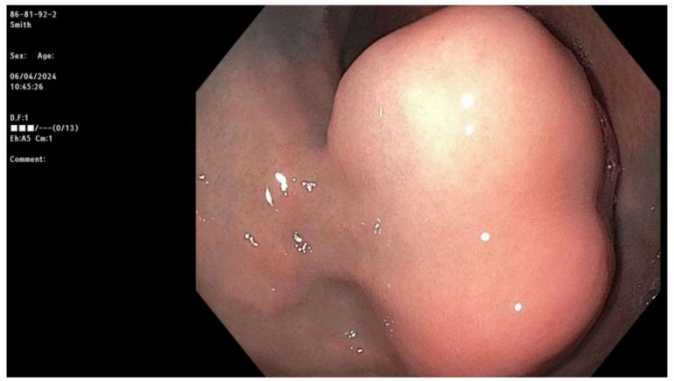


Sereide, et al. *Cancer Epidemiol* 2016.

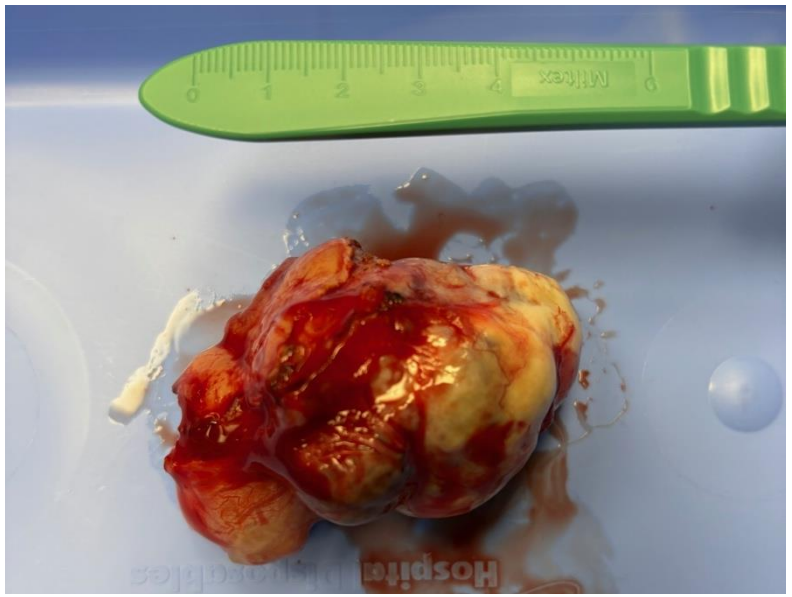
Diagnosis

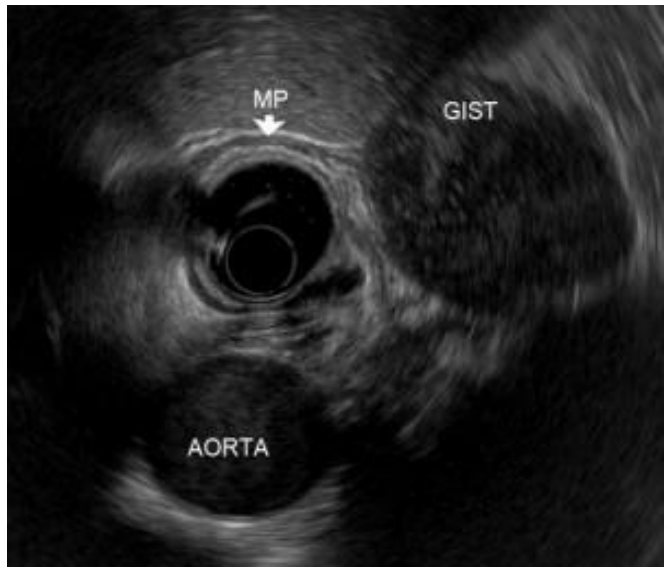
- Imaging
  - For signs/symptoms
  - Incidentaloma
- Endoscopy
- Endoscopic ultrasound
  - Arising from Level 4
- After surgery





9 Gastric Antrum : Mass





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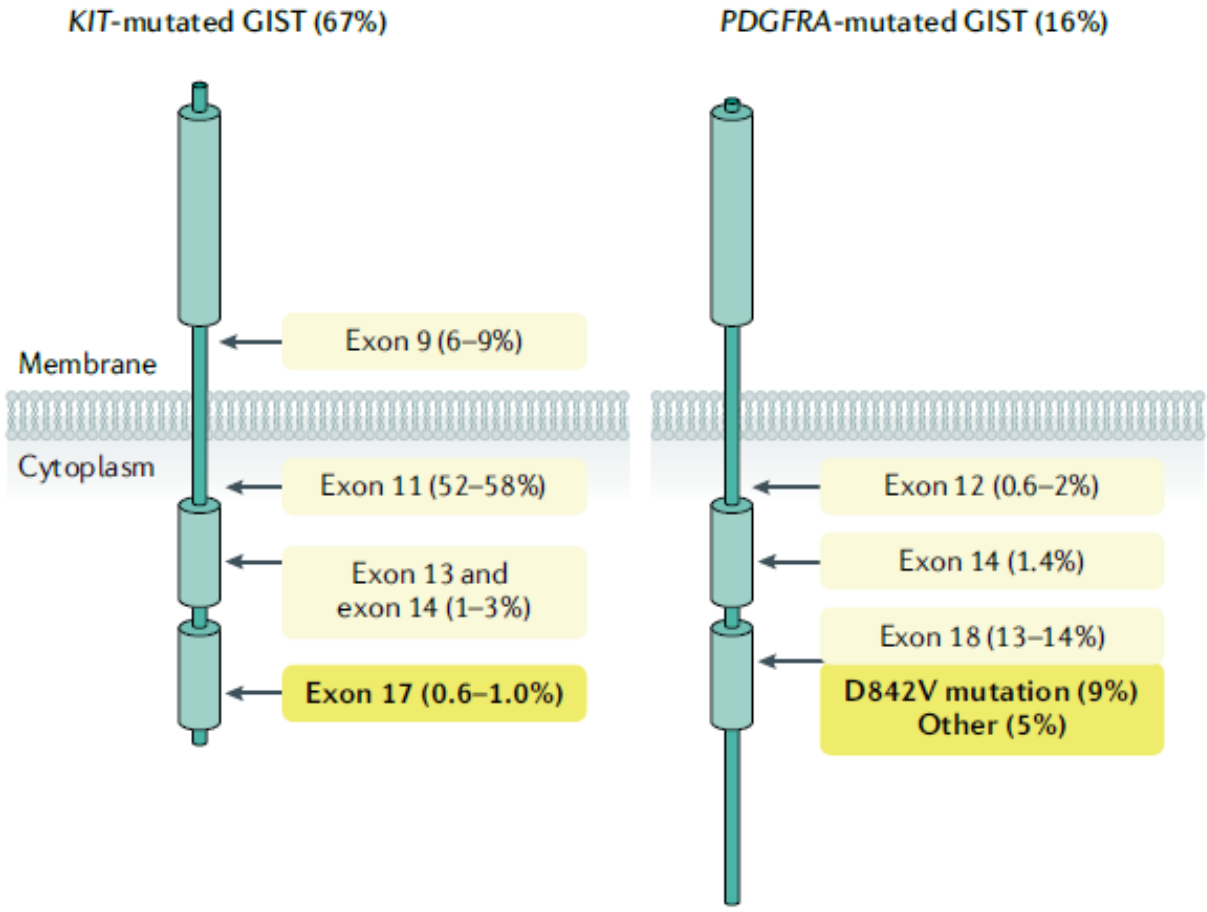
Pathogenesis

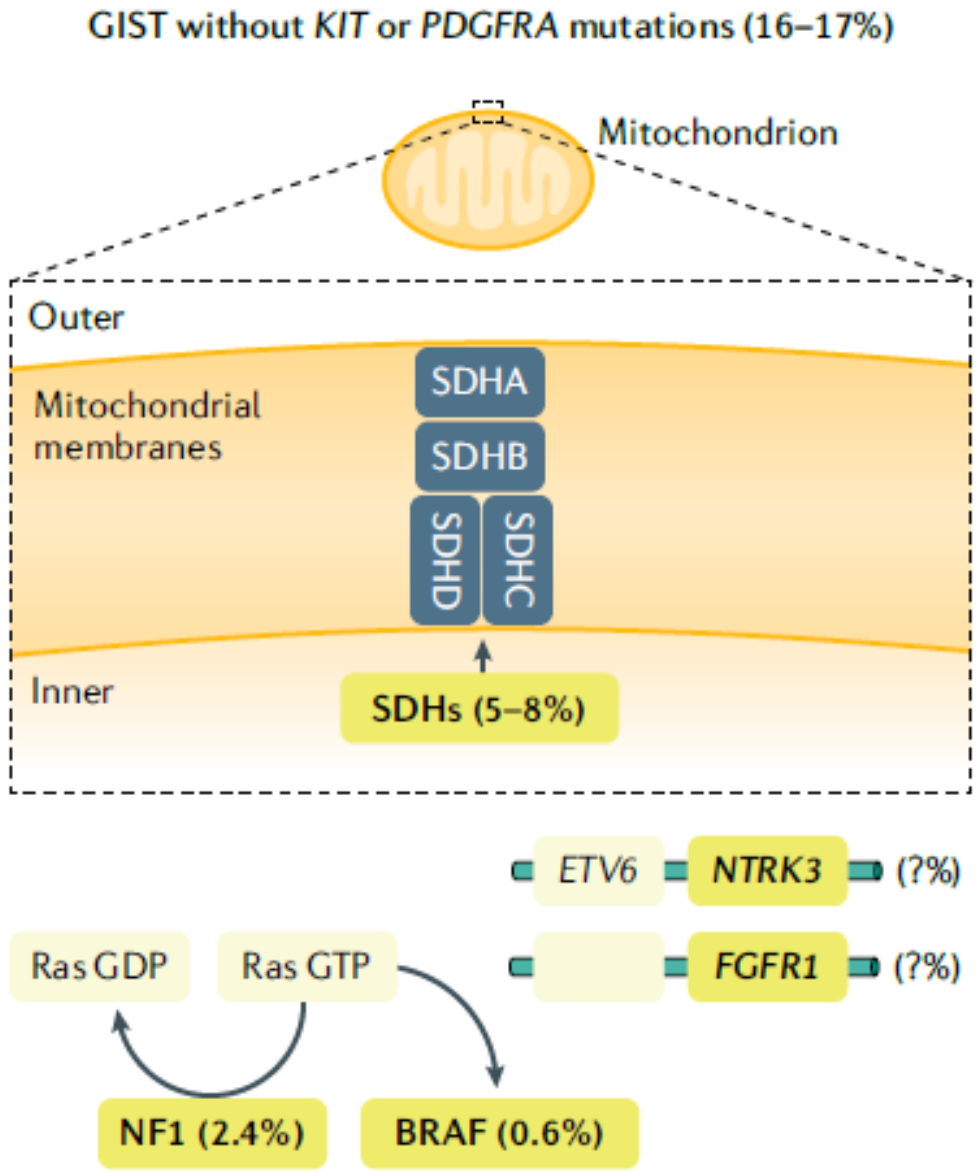
- ~85% of GISTs are characterized by *KIT* or *PDGFRA* mutations
  - Usually mutually exclusive
  - Mutations are rarely germline
  - ‘Non-wild-type’



Blay. *Nat Rev* 2021.

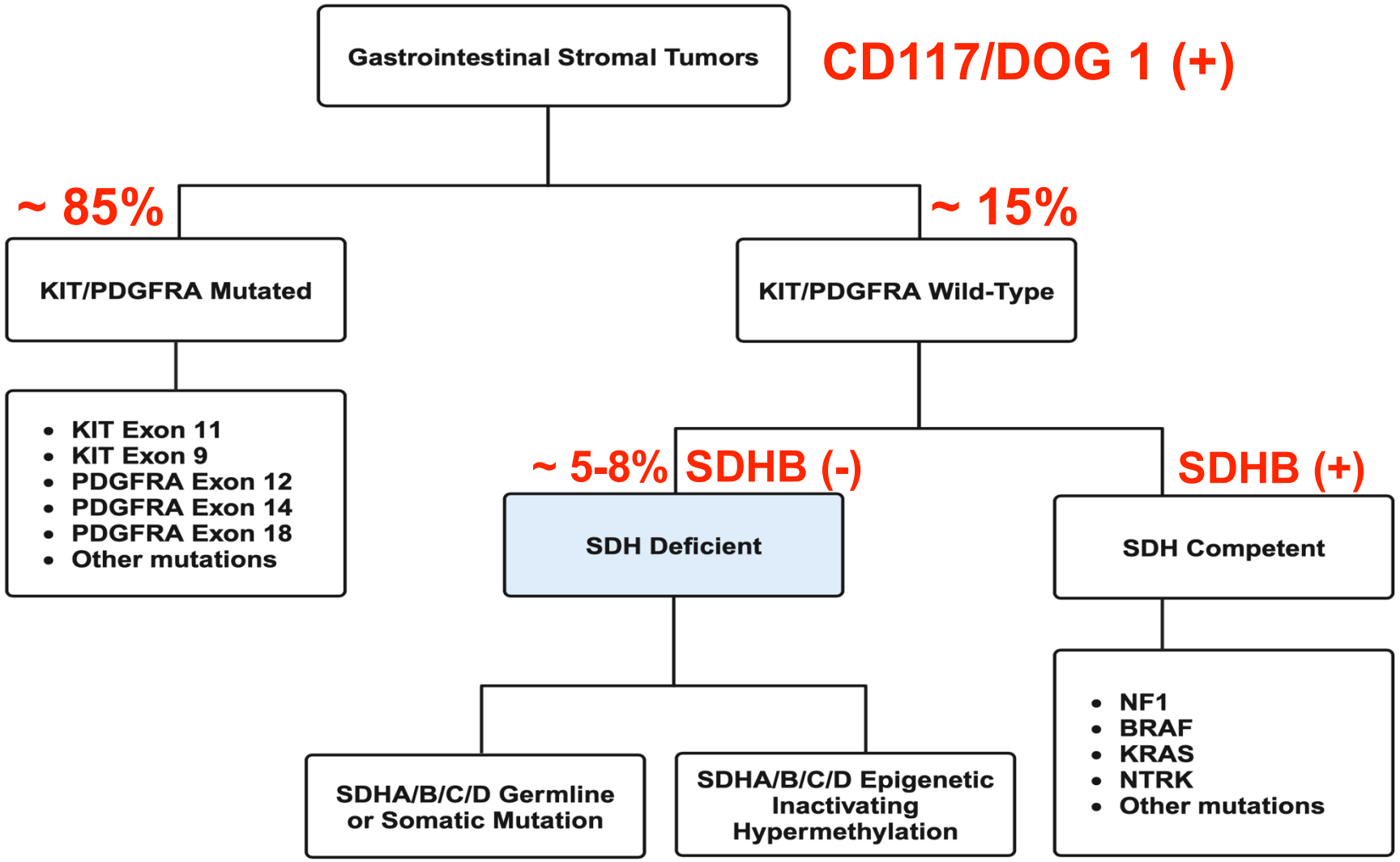
Pathogenesis

- ~15% of GISTs are characterized by non-mutated *KIT* and *PDGFRA*
  - Various other drivers
  - Mutations are often germline
  - ‘Wild-type’



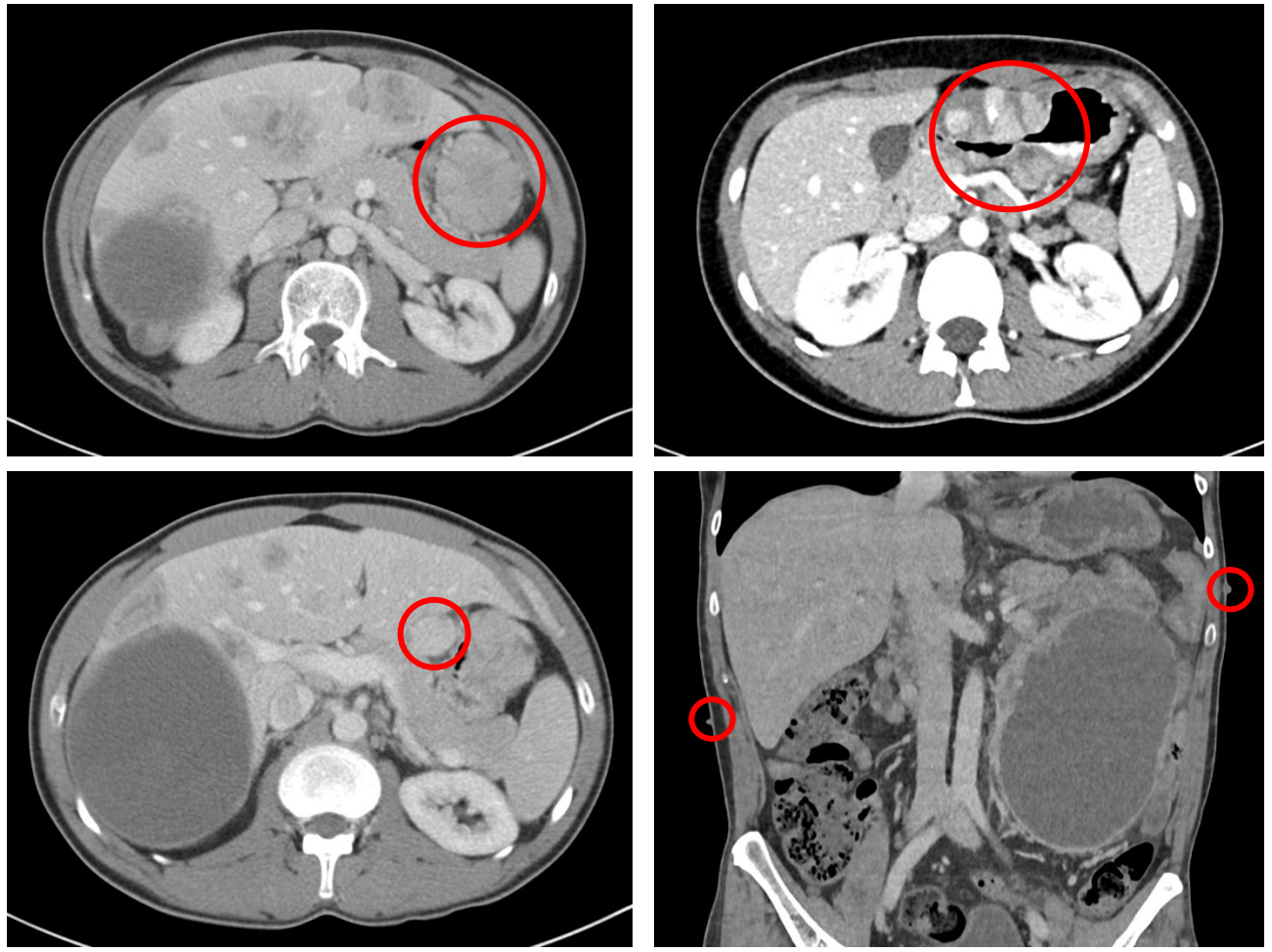
Blay. *Nat Rev* 2021.

Classification



When to Think about Wild-Type GIST

- Young patient age
- Regional lymph node involvement
- Primary tumor multifocality
- Tumor predisposition manifestations
  - Signs/symptoms
  - Other primary tumors



Succinate Dehydrogenase Deficiency

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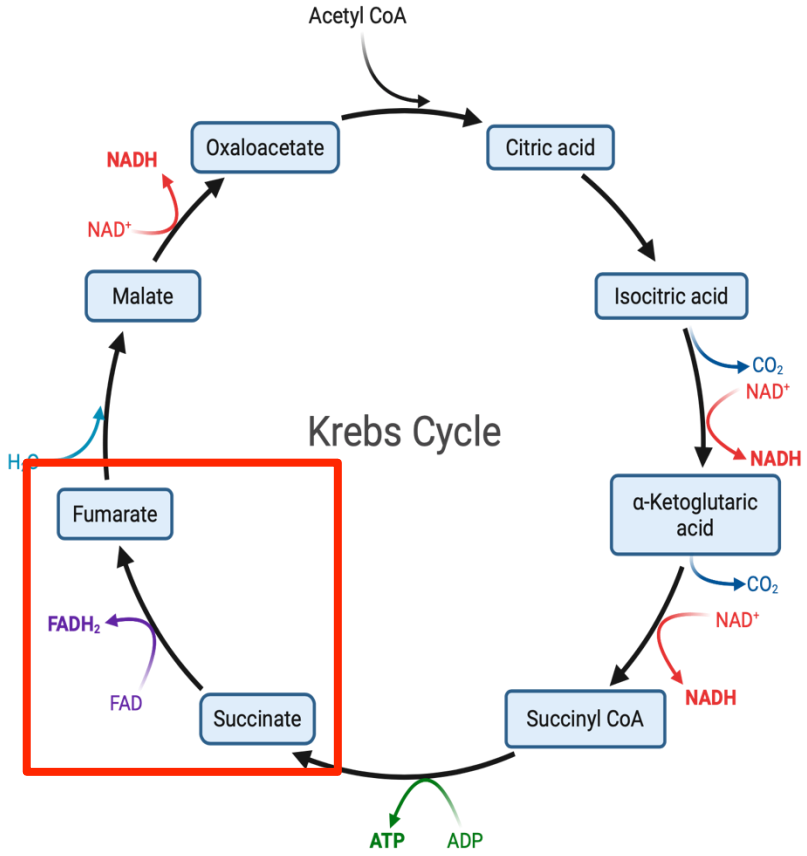
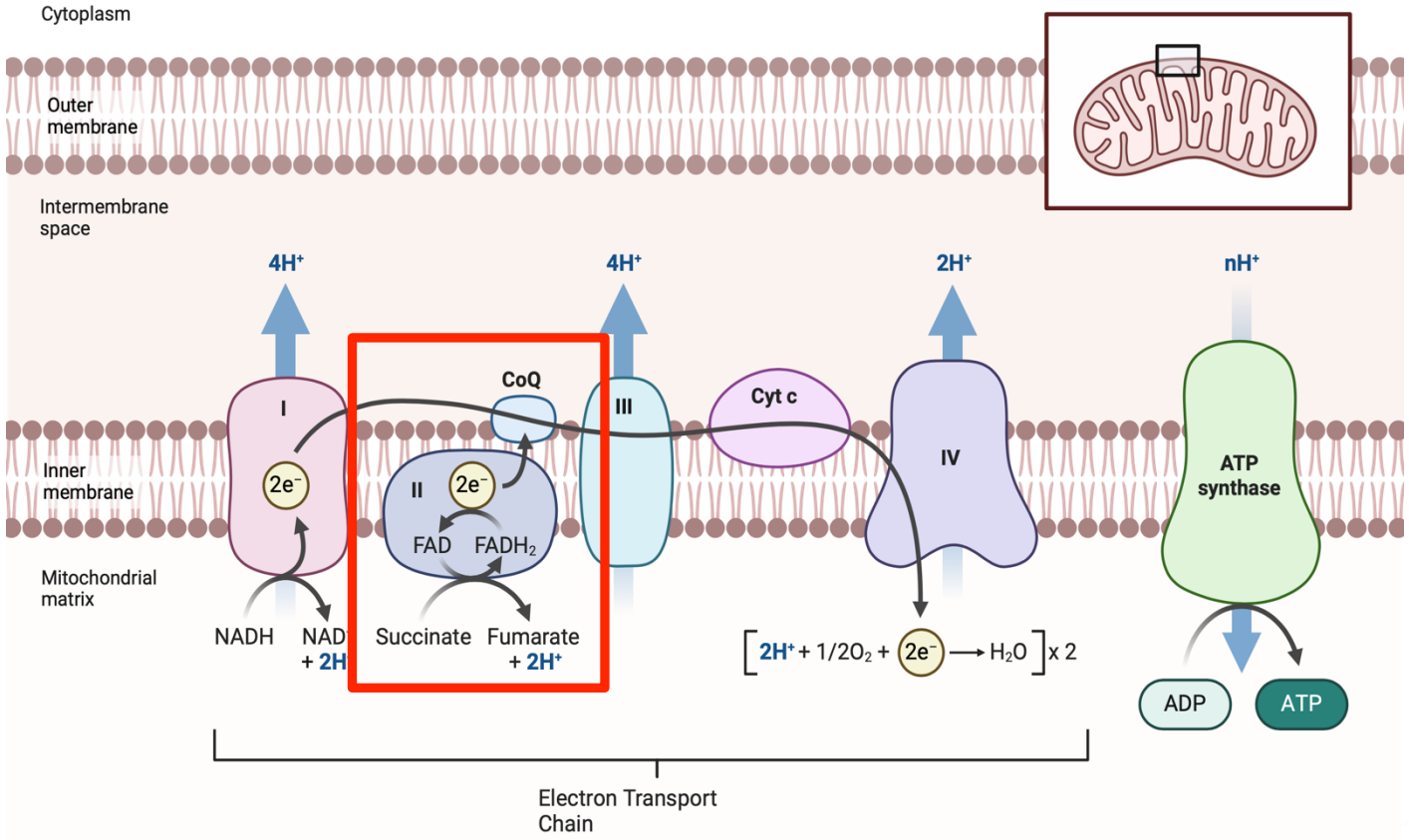
Function of Succinate Dehydrogenase





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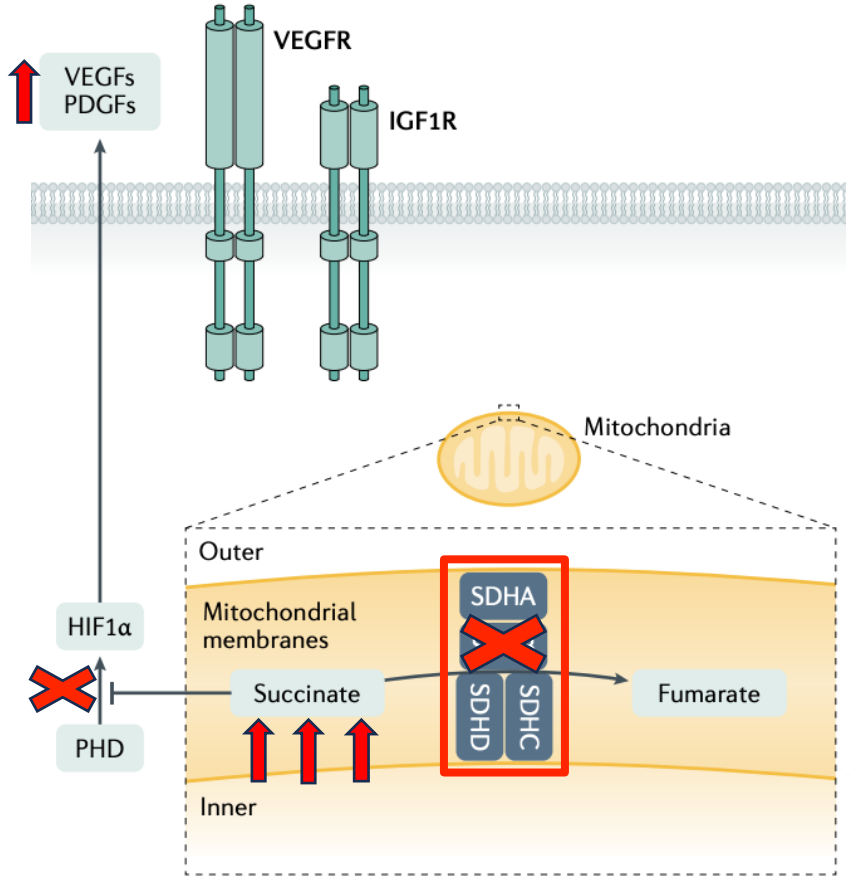
Loss of Succinate Dehydrogenase

- Inactivation of any SDH subunit → lack of functional SDH complex
  - Loss of SDHB on pathology staining
  - Succinate, an oncometabolite, accumulates
  - HIF1α is stabilized → pseudohypoxic state
  - Angiogenesis pathways stimulated
  - Inhibits α-ketoglutarate dioxygenases
    - May promote diffuse hypermethylation



Blay. *Nat Rev* 2021.

Subclassifying SDH-Deficient GIST

Tumour	SDHA mutation	SDHB mutation	SDHC mutation	SDHD mutation	SDHAF2 mutation	SDHC promoter hypermethylation (Carney triad)
Pheo/PGL	+	+++	++	+++	+	++
GIST	+++	+	+	+	–	+++
Renal carcinoma	+	+++	+	+/–	–	–
Pituitary adenoma	++	+	+	+	–	–
Pulmonary chondroma	–	–	–	–	–	+++

SDH, Succinate dehydrogenase; Pheo/PGL, Pheochromocytoma and paraganglioma

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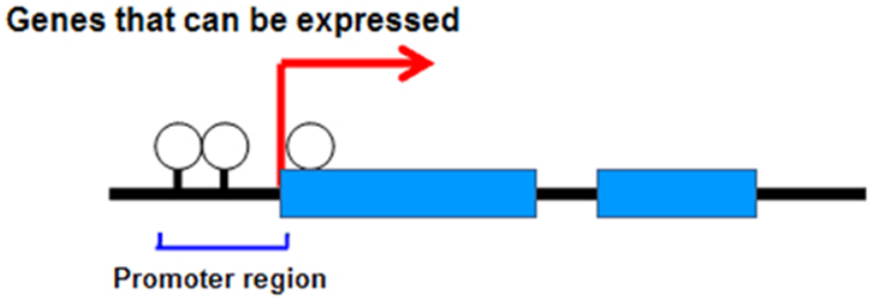
Gill. *Histopathol* 2018.

Epigenetic Silencing of *SDHC*

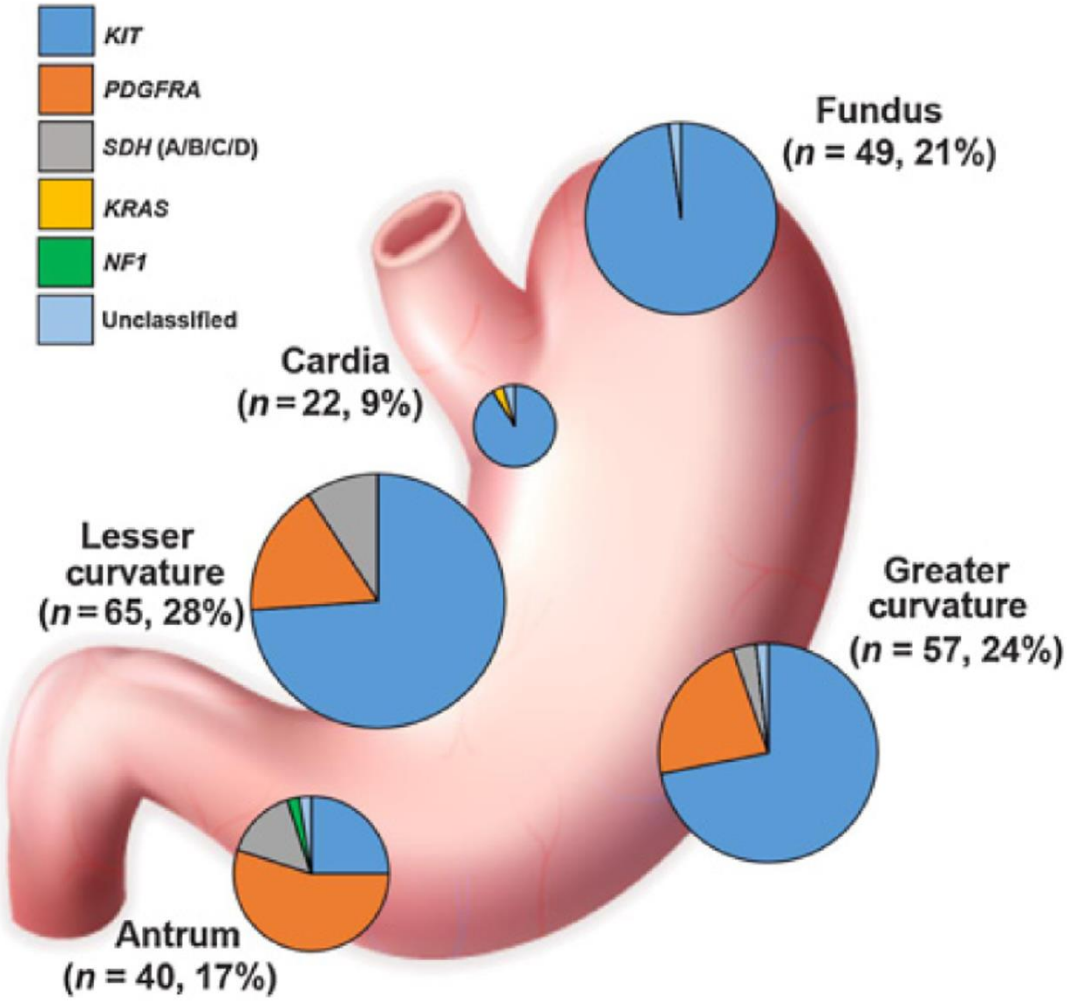
- Promoters turn genes ‘on’
- Methylation is a normal process that can turn the promoter ‘off’
  - No expression of *SDHC*
  - No production of SDHC subunit
- Not heritable
  - No mutations on germline or somatic tests



Credit: Samantha Greenberg.

SDH-Deficient GIST Location

- Mostly arises from the body and distal stomach
- Open question of benefit of distal gastrectomy compared to wedge gastrectomy
- *SDHC* epimutant GIST more likely multifocal, proximal



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Sharma. *Clin Cancer Res* 2021.

Tumors Seen with SDH-Deficient GIST

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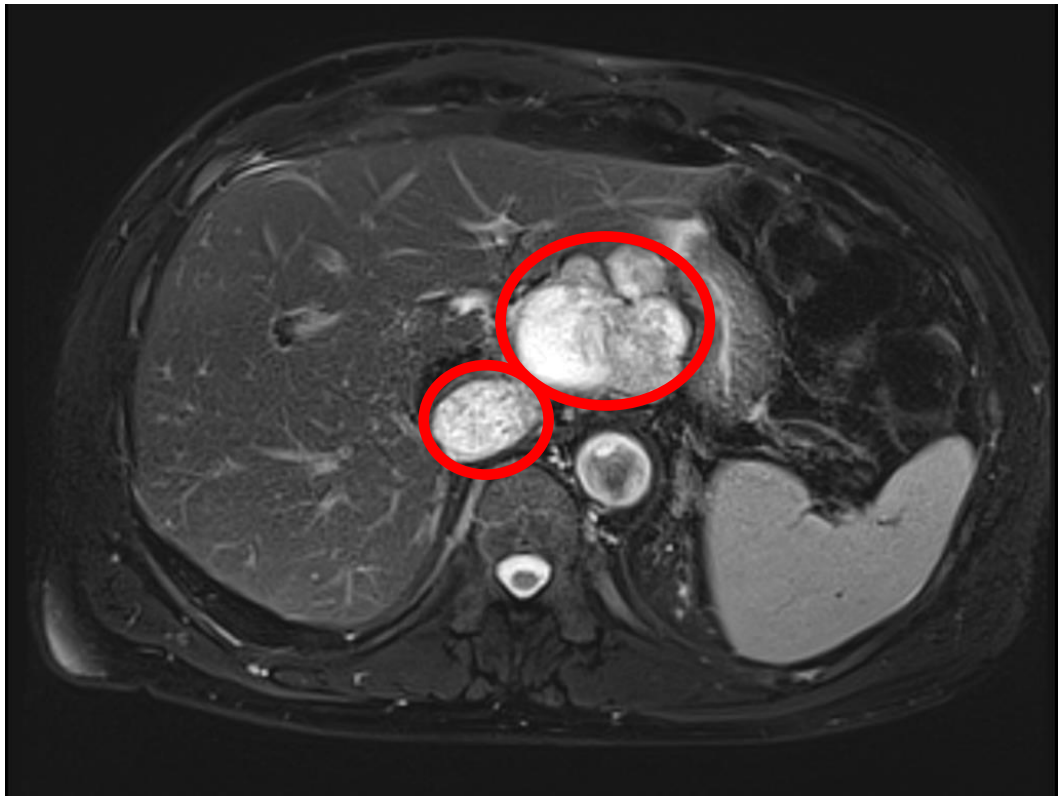
Paraganglioma and Pheochromocytoma

- Symptoms: hypertension, tachycardia, sweating, syncope
- Diagnosis: serum or 24-hour urine catecholamines, metanephrines
- Initial management: alpha blockade, high-salt diet, beta blockade
- Staging: CT or MRI
  - FDG versus Gallium PET/CT



Paraganglioma and Pheochromocytoma

Syndrome	Genetics	Frequency	Gender	Associated Tumors
PGL1	SDHD	Common	M = F	Carotid body, abdominal, GIST
PGL2	SDHAF2	Very rare	M = F	Head and neck
PGL3	SDHC	Rare	M = F	Carotid body, GIST, renal carcinoma
PGL4	SDHB	Common	M = F	Abdominal, head and neck, renal carcinoma, GIST
PGL5	SDHA	Rare	M = F	Abdominal, GIST
Carney Triad	SCHC HM	Very rare	M <<< F	Abdominal, GIST, pulmonary chondroma

Also seen in ~4% of patients with NF1

For this reason, it is important to check serum metanephrines and catecholamines before GIST-directed surgery in SDH deficiency or NF1

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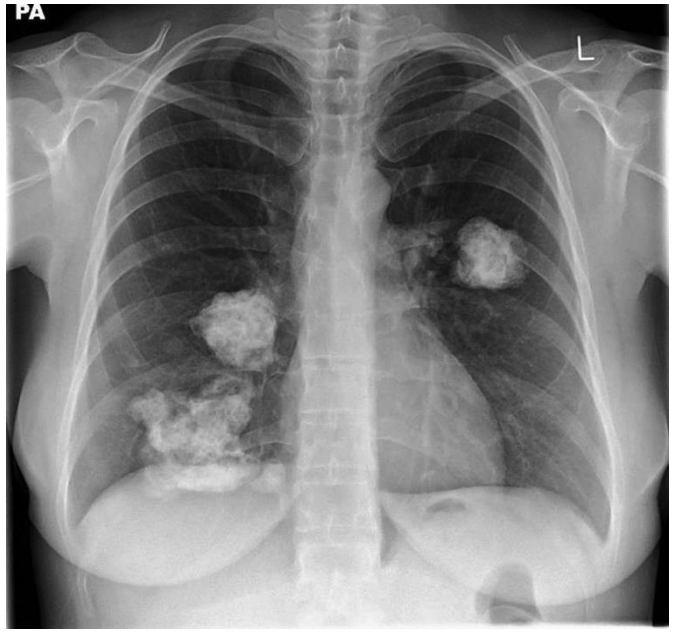
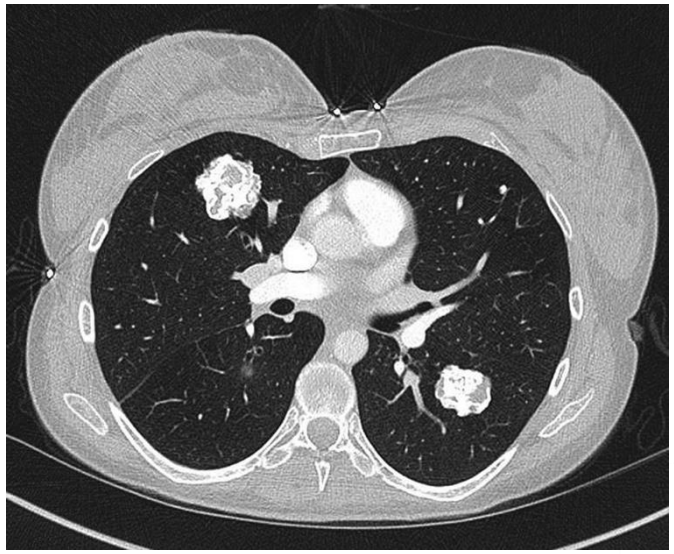
Pitsava, et al. *Frontier Endocrinol* 2021.

Pulmonary Chondroma

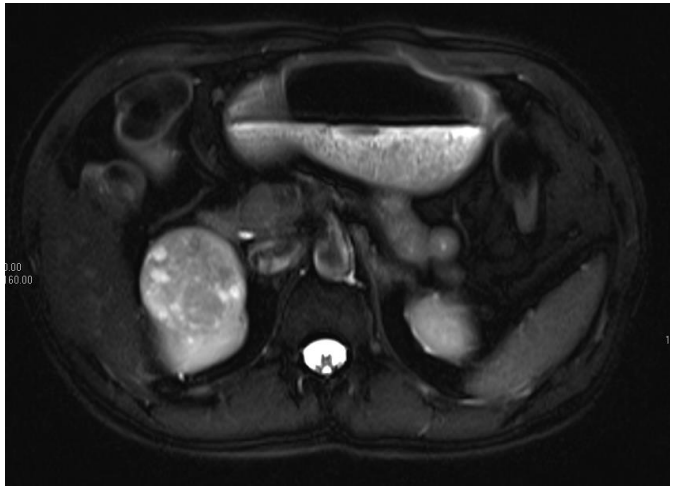
- Benign lung neoplasm
- Associated with *SDHC* hypermethylation
  - Can develop as part of Carney Triad along with GIST and paraganglioma/pheochromocytoma
- Specific features on radiograph or tomography
  - Benign mass: round or oval, smooth edges
  - Usually contains calcium deposits

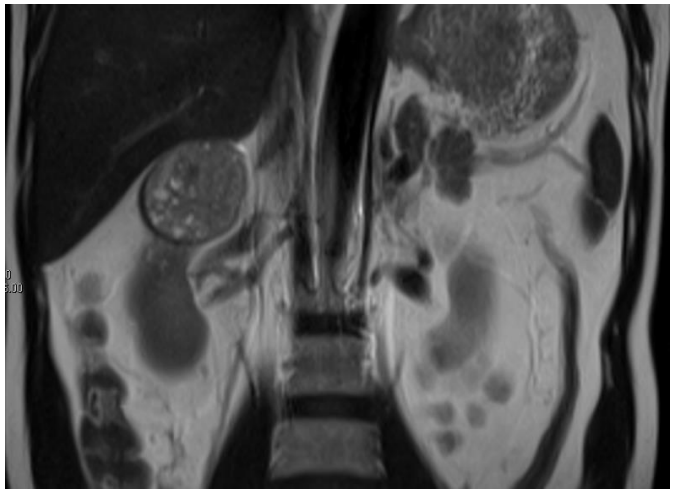




Pitsava, et al. *Frontier Endocrinol* 2021.

Kidney and Pituitary





- Renal Cell Carcinoma
  - <0.5% of renal carcinoma is SDH-deficient
  - Associated with *SDHB* (83%) or *SDHA/SDHC/SDHD*
  - Partial nephrectomy/nephrectomies to remove

- Pituitary Adenoma
  - <1% of pituitary adenomas are SDH-deficient
  - Can present with paraganglioma/pheochromocytoma: 3PAs
  - Macroadenoma, some are functional: prolactin, somatotropin

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Pitsava, et al. *Frontier Endocrinol* 2021.

Screening in SDH Deficiency

- Whole body non-contrast MRI every 2-3 years
- Dedicated MRI neck with contrast
- Serum catecholamines, metanephrines, chromogranin A annually
- Surveillance imaging based on areas of known disease

Credit: Samantha Greenberg.

Surgical Considerations

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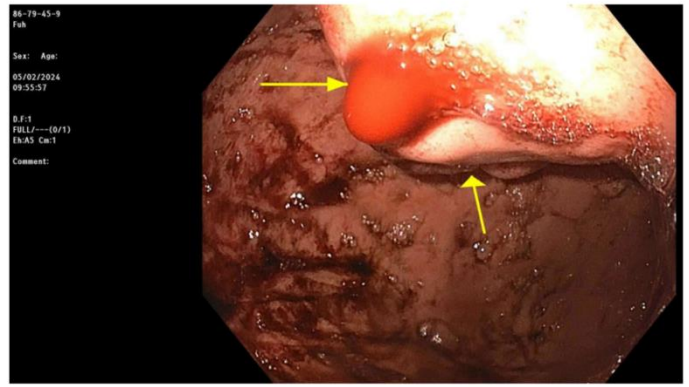
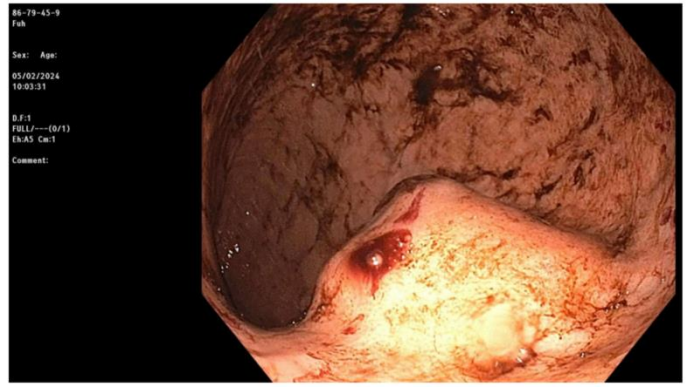
Goals of Surgery

- Primary, non-metastatic GIST
  - Curative intent
- Metastatic disease
  - Relieve active symptoms
  - Achieve ‘No Evidence of Disease’ status
    - ‘Reset the clock’ on disease burden
    - Prolong use of systemic agents
  - Preserve eligibility for clinical trials



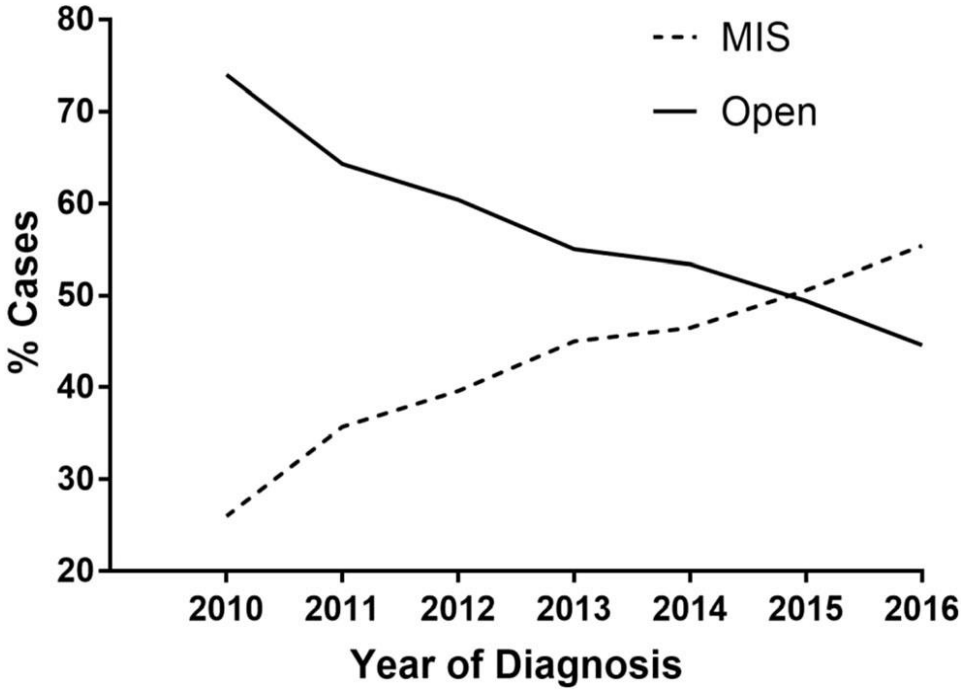
11 Gastric Body : Mass with active bleeding.



13 Gastric Body : Mass

Surgical Approach

- Laparoscopic/robotic resection increasingly utilized
  - Limited multifocality or extra-gastric spread
  - Tumors ≤ 5 cm in diameter
  - Body of stomach, along greater curve
  - Exophytic versus endophytic growth pattern



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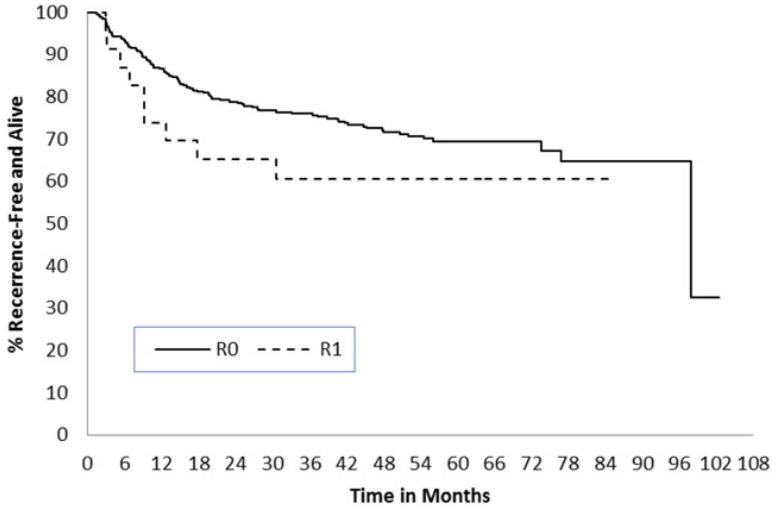
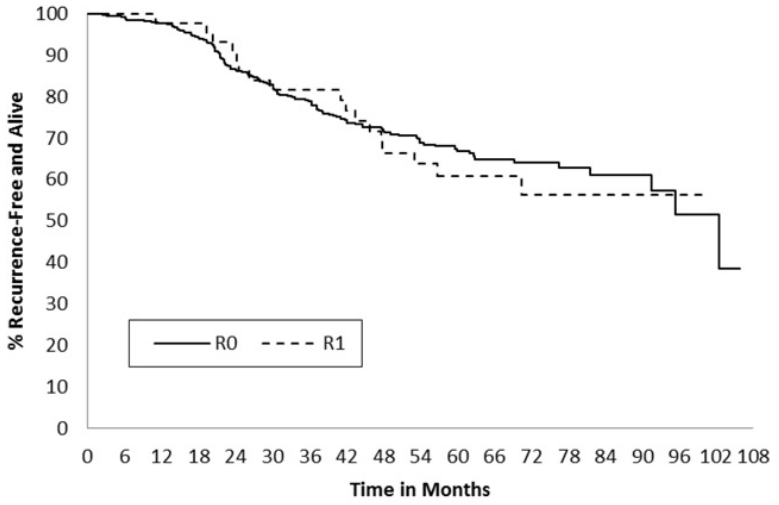
Hagerty et al. *J Gastrointest Surg* 2021.
Iordanou et al. *Oncol Lett* 2021.

Tumor Resection Margins

- Goal should be negative (R0) margin
- Microscopic positive (R1) margin
  - Decreased recurrence-free survival
  - Similar overall survival
  - No clear benefit of re-resection for R1 margin

KIT mutant GIST; placebo (top), adjuvant imatinib (bottom)





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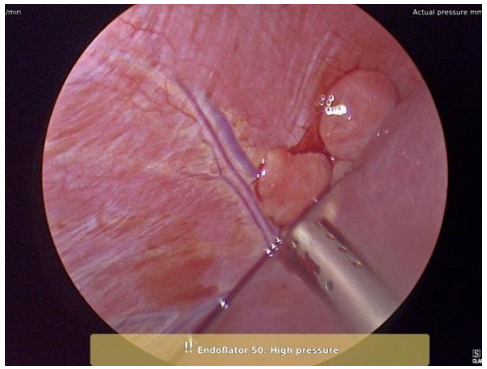
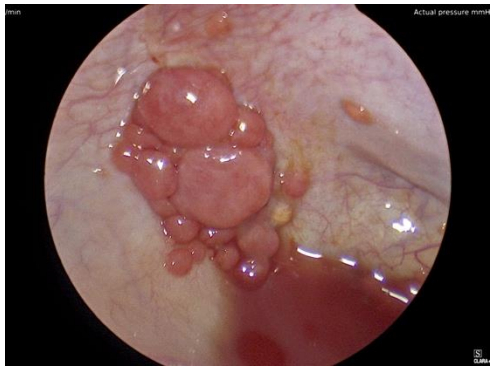
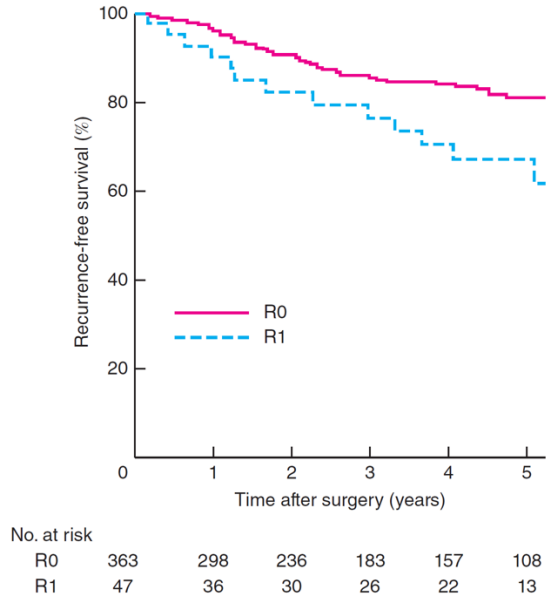
McCarter et al. *J Am Coll Surg* 2012.
Corless et al. *J Clin Oncol* 2014.

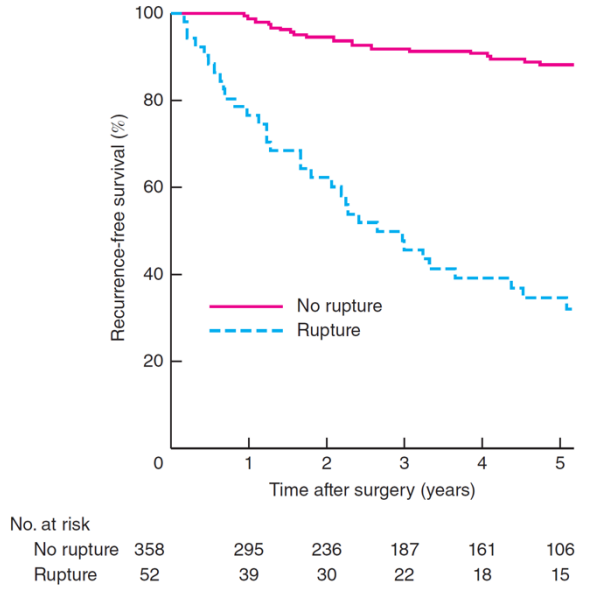
Specimen Handling

- Utmost importance to avoid rupture
  - Handle tissues adjacent to tumor
  - Preserve pseudocapsule
  - Avoid morcellating, even in retrieval bag





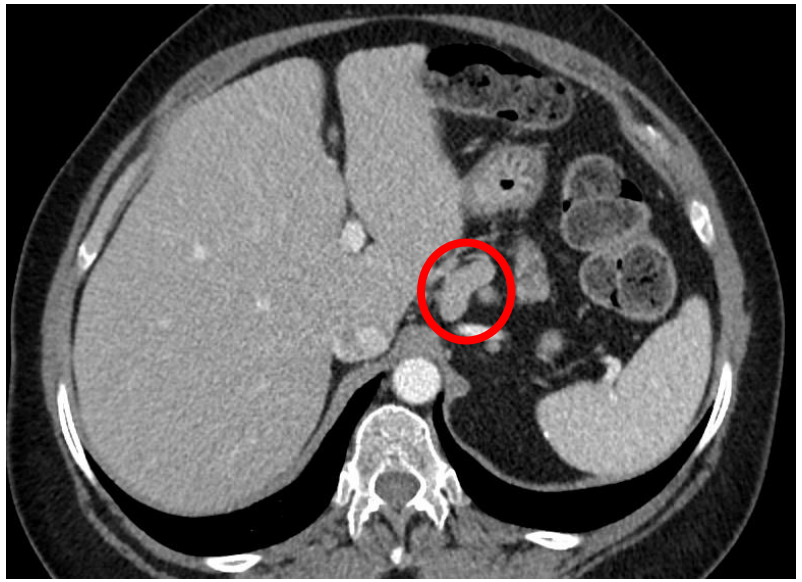


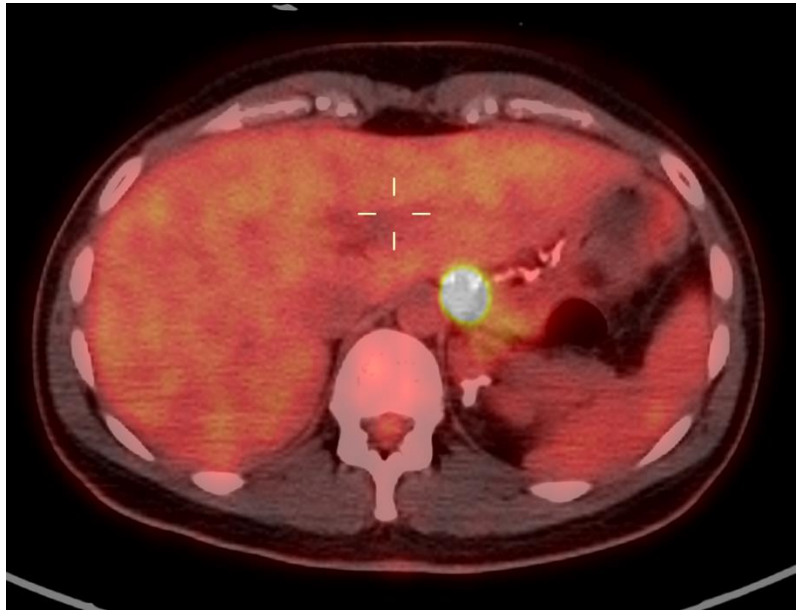


Hølmebakk et al. *Br J Surg* 2018.
Kong et al. *Eur J Sug Oncol* 2021.

Role of Lymphadenectomy

- Lymph node involvement
  - Very uncommon in non-wild-type
  - Rather common in wild-type
  - Rare outside of abdomen/pelvis
- Selective regional lymph node resection





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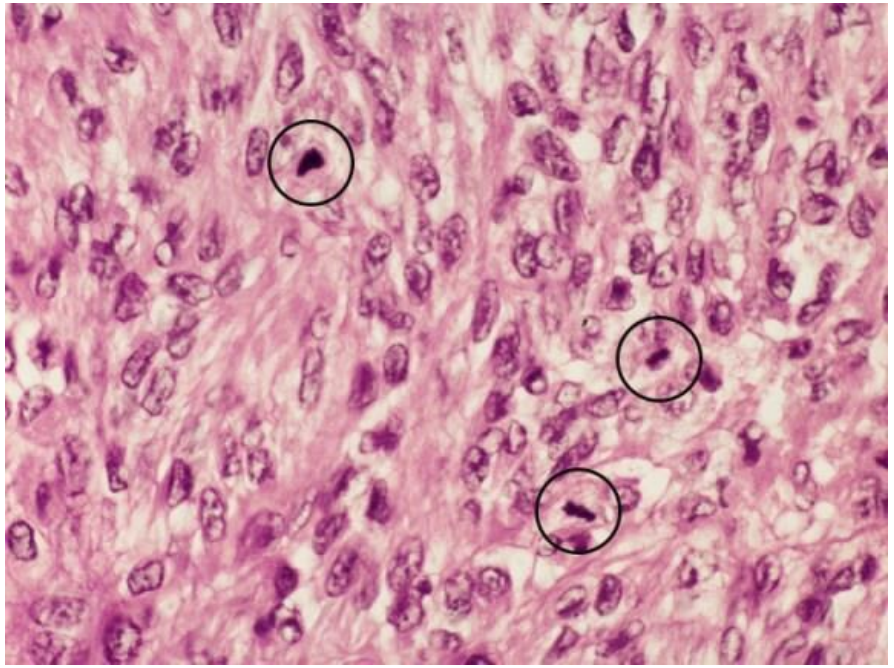
Boikos et al. *JAMA Oncol* 2016.
Vassos et al. *J Gastrointest Surg* 2011.

Synoptic Pathology Report Components

- Immunohistochemistry: CD117/KIT, DOG1, SDHB
- Histologic type: spindle cell, epithelioid, or mixed
- Tumor size: greatest dimension
- Mitotic rate: number per 50 HPF or per 5 mm^2
  - Grade: high (> 5 mitoses/5 mm^2) or low (≤ 5)
- Necrosis: presence or absence, percentage
- Margins: negative with distance in mm, positive, or unable to be assessed
- Lymph nodes: number evaluated, number positive
- Metastases: present or absent



Miettinen et al. *Gastroenterol Clin N Am* 2013.
DeMatteo et al. *Cancer* 2008.

Important Considerations

- IHC staining for CD117/KIT does not reflect KIT mutation status
- Mitotic rate:
  - Can be difficult to determine after effective neoadjuvant therapy
  - Has unclear significance in recurrence risk stratification for wild-type GIST
- Driver mutation-specific risk nomograms are not yet validated
- SDHB IHC may or may not be available; calibration can be challenging

Next-Generation Sequencing

- Include *KIT*, *PDGFRA*, *SDHA/B/C/D*, *NF1*, *BRAF*
- Various common secondary mutations may reflect tumor biology
  - *CDKN2A*, *CDKN2B*, *PTEN*, *TP53*, *ATRX*, *ARID1A*
- Evolution of variants of unknown significance (VUS) to be reclassified as pathogenic/likely pathogenic (P/LP)

Cancer-Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
BRAF	**Seq**	**RNA-Tumor**	**Pathogenic Fusion**
		DNA-Tumor	Mutation Not Detected
MSI	Seq	DNA-Tumor	Stable
NTRK1/2/3	Seq	RNA-Tumor	Fusion Not Detected
RET	Seq	RNA-Tumor	Fusion Not Detected
Tumor Mutational Burden	Seq	DNA-Tumor	Low, 2 mut/Mb
ERBB2 (Her2/Neu)	CNA-Seq	DNA-Tumor	Amplification Not Detected
NF1	Seq	DNA-Tumor	Mutation Not Detected
PD-L1 (SP142)	IHC	Protein	Negative | 1+, 3%
SDHA	Seq	DNA-Tumor	Mutation Not Detected
SDHB	Seq	DNA-Tumor	Mutation Not Detected
SDHC	Seq	DNA-Tumor	Mutation Not Detected
SDHD	Seq	DNA-Tumor	Mutation Not Detected

Important Considerations

- Large exon deletions produce false negatives
- Negative NGS prompts RNA fusion testing
- Only one tumor selected for NGS
  - Strive to pick the most clinically relevant metastasis
  - Even within the tumor, potential for sampling error
  - Potential of ctDNA to assess mutations across sites
- Cost is a consideration

Result

KIT PDGFRA

Provided diagnosis: small bowel gastrointestinal stromal tumor

No reportable alterations were identified within the analyzed regions of the tested genes listed in the method description.

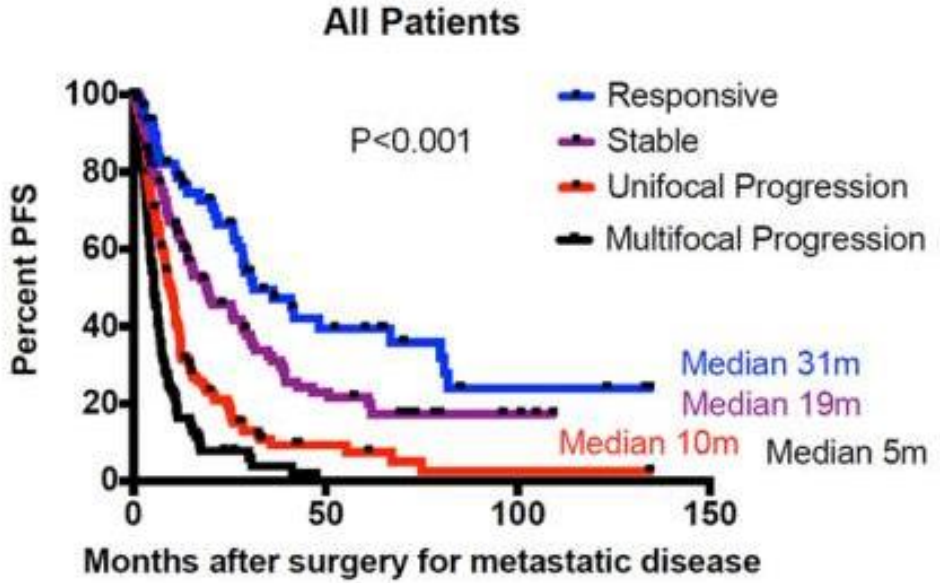
KIT	chr4:55,593,593	NM_000222.3	c. 1662_1715del	p.E554_I571del	20% (of 630 reads)

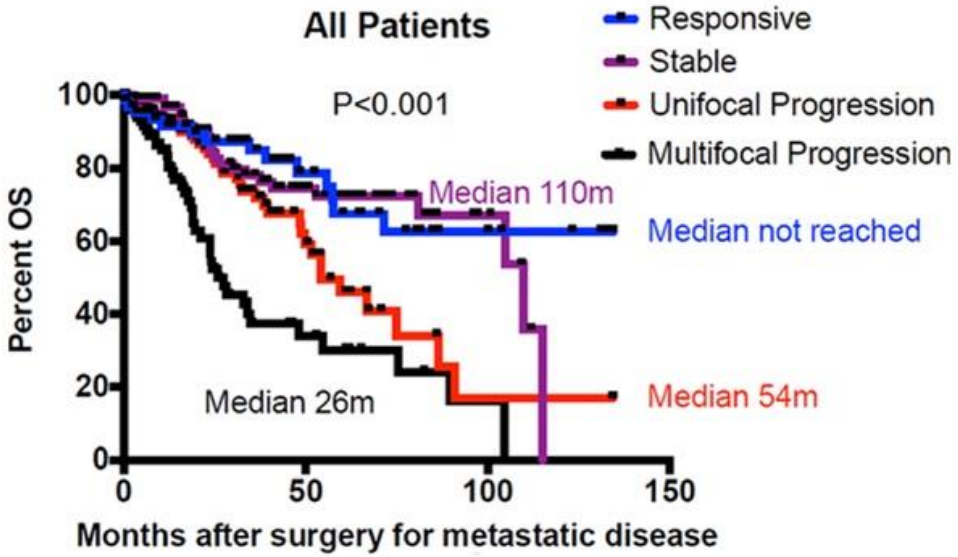
Surgery for Metastasis

Resectability is in the eye of the beholder!

Surgery for Metastasis

- Signs and symptoms
  - Obstruction, pain, bleeding, anxiety
- Organ system(s) involved
  - Most frequently liver and peritoneum
- Effect of systemic therapy
  - As assessed by images and symptoms





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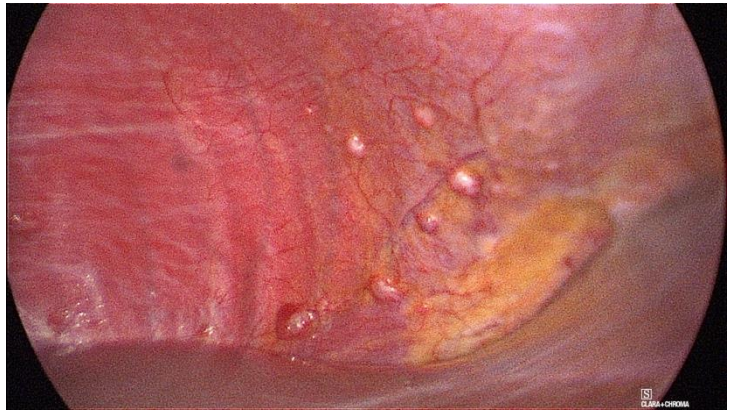
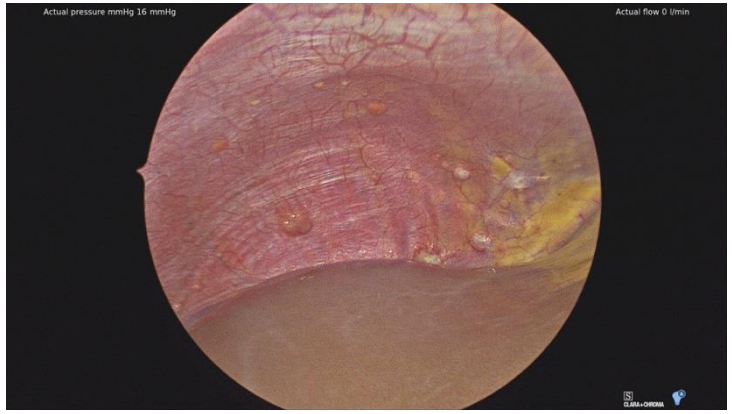
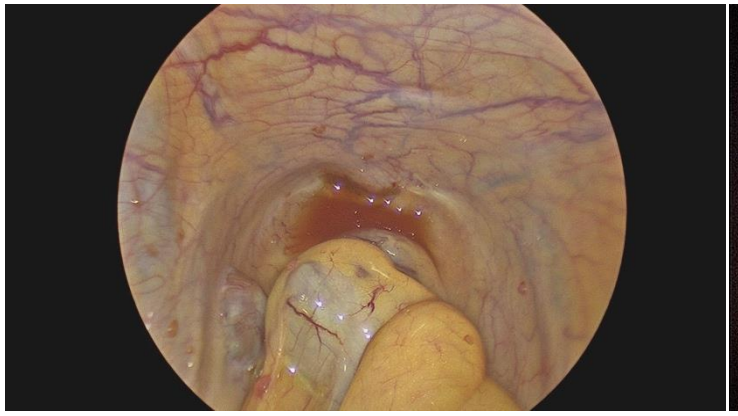
Fairweather et al. *Ann Surg* 2018.

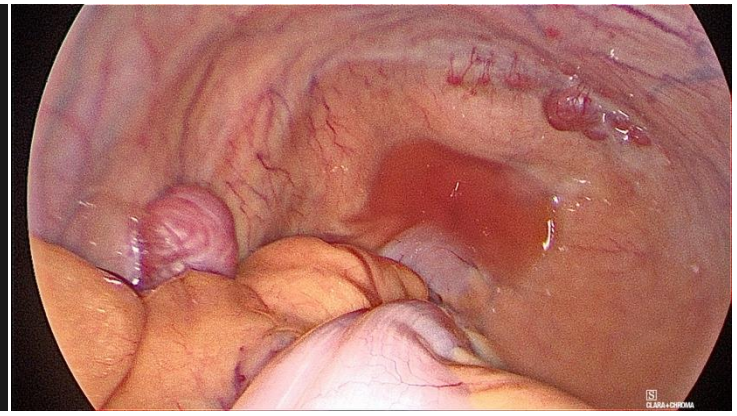
Diagnostic Laparoscopy

- Provides visual inspection of peritoneal surfaces
  - Some nodules are too small to be seen by CT or MRI
- Opportunity for tissue harvest and analysis
- Can be repeated over time
  - Assess treatment response
  - Monitor mutational profile



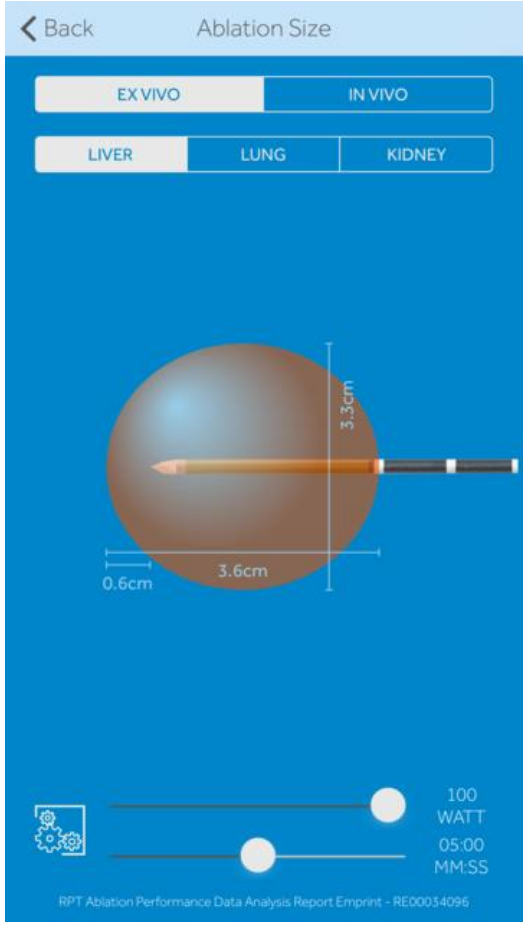






Combined Liver Resection and Ablation

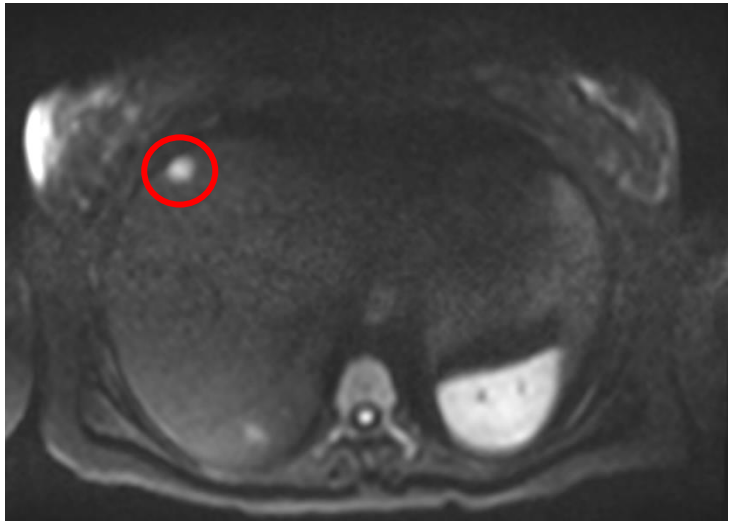
- Resect larger (>3 cm) and peripheral tumors
- Ablate deeper small tumors
  - Wide range of ablative techniques out there
- Dual goals:
  - Remove or ablate as much tumor tissue as possible
  - Preserve as much normal liver tissue as possible



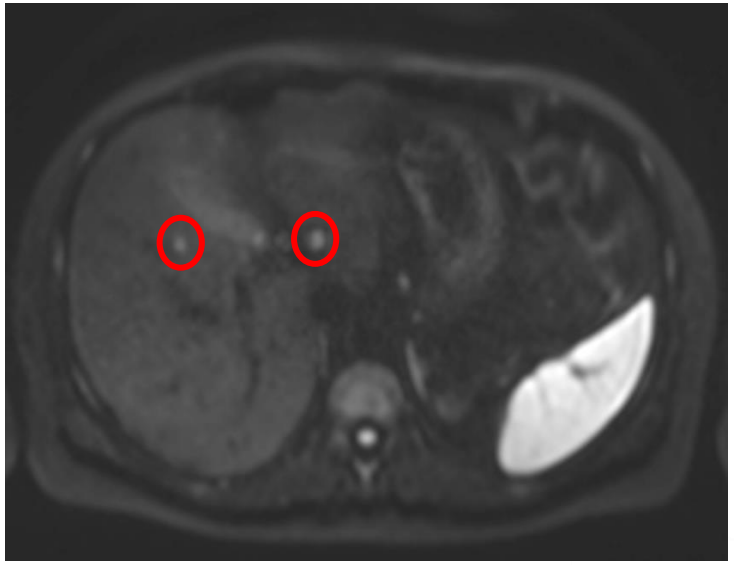
Limitations of Surgery

- We cannot remove what we cannot see
- Only so many major cytoreductions are possible
- Short-interval recurrence is known to happen
  - Particular area of interest for our research

Pre-Op MRI



Post-Op MRI



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Summary

- SDH-deficient GIST is a unique entity
  - Rare disease with ultra-rare subtypes
- Systemic/regional/local therapies and surveillance are all important
  - Tailoring treatment to the individual is key
- Everyone deserves at least a couple of opinions

Thank You

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