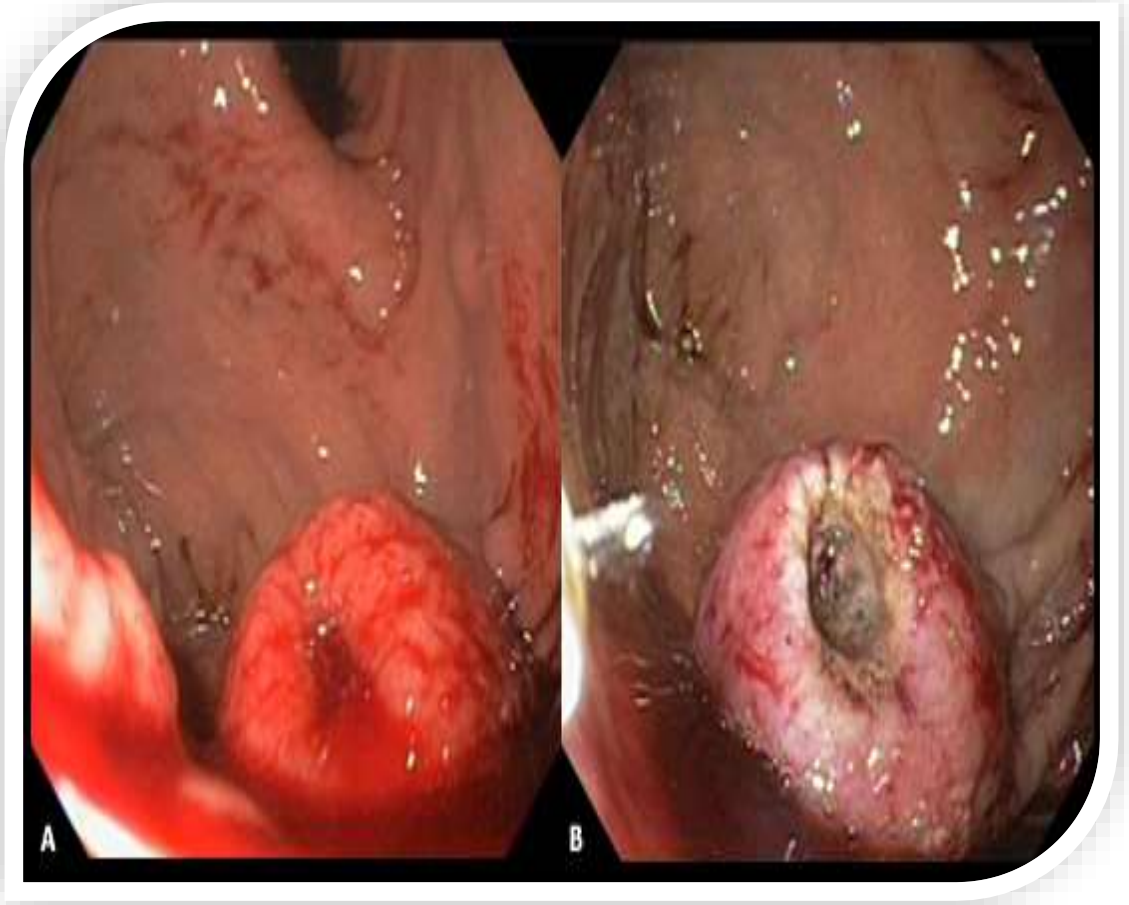
GIST
Gastro Intestinal Stromal Tumors

Dr Pardeep Garg
Associate Professor & Head
Department of Radiation Oncology
GGSMCH, Faridkot

GIST: History and Origin

- GIST are mesenchymal neoplasms of GIT.
- Term GIST was first used by Mazur & Clark in 1983.
- In 1998, Japanese research workers (Hirota et al) discovered KIT mutations in GIST that possibly distinguish GIST from other tumors.
- CELLS OF ORIGIN
  - Arise from interstitial cells of Cajal (ICC)
  - These are the fibroblast like cells located around the myenteric plexus and in the muscularis propria throughout the GIT.



GIST: Epidemiology & Incidence

- Age -60-80 yrs
  - (more predominance in 7th decade)
- If familial <30 yrs.
- Male =female
  - (Succinyl dehydrogenase SDH deficient tumors more commonly in pediatric patients and are seen twice as common in females)
- Most common benign non-epithelial tumor of GIT.
- 1% of primary GI Cancer and 2.2% of primary gastric cancer.
- **SITE**-:
  - Stomach 50-70% > Small intestine 25-40%(ileum>jejunum>duodenum) > Colorectal-10% > Esophagus-5% > Extra-gastrointestinal-6.7%

GIST: Clinical Presentation

- FOR GIST INVOLVING UPPER GIT
  - GI Bleeding occult/overt, dysphagia, obstructive jaundice.

- FOR GIST INVOLVING COLON, RECTUM
  - Constipation, bowel obstruction, urinary hesitancy in men due to rectal tumor abutting prostate.

- PEDIATRIC PATIENTS PRESENT WITH –GI
  - Bleed, fatigue , anaemia

- METASTATIC DISEASE
  - Most common site for metastasis are liver, omentum, peritoneum and present as abdominal pain and bowel obstruction.

- Pulmonary metastases are uncommon unlike STS

GIST: Paraneoplastic syndromes

- CONSUMPTIVE HYPOTHYROIDISM
  - It occurs due to excessive degradation of thyroid hormones caused due to over-expression of thyroid hormone inactivating enzyme type 3 iodothyronine deiodinase (D3).

- Such patients require high levels of thyroid hormone supplementation

DIAGNOSTIC EVALUATION

- CT
  - For initial evaluation of primary
- MRI
  - For patients who can't receive contrast or have rectal primary.
- Upper GI Endoscopy with USG
  - For GIST involving Stomach SI, Esophagus
- Typically appear hypoechoic homogenous lesions with well defined margins although rarely can have irregular margins and ulcerations
- COLONOSCOPY-
  - for GIST that present in colon, rectum, anus.
- EUS Guided FNA (EUS-FNA guided biopsy)

INDICATIONS FOR SURGICAL RESECTION

- For the disease that cannot be safely biopsied
  - When initial biopsy attempts have been unsuccessful or non-diagnostic
- In case of unresectable and metastatic tumor if-
  - It requires immediate surgical intervention(due to haemorrhage, tumor rupture, bowel obstruction , GI Perforation

BIOPSY and PATHOLOGICAL ASSESSMENT

- GISTs are soft and fragile tumors. The decision is based on the suspected tmor type and the extent of disease.

- EUS guided FNA BIOPSY of primary site is preferred over Percutaneous biopsy due to the risk of tumor hemorrhage and intra abdominal tumor dissemination.

- Mitotic rate is measured in the most proliferative area of tumor and is reported as the number of mitoses in 50 HPFs (equivalent to 5mm2 of tissue).

- Most GISTs express KIT (CD117) receptor tyrosine kinase 80%, PDFGRA receptor tyrosine kinase 5-10%, CD34 (70%), smooth muscle actin (25%), and desmin (less than 5%).

- SDH deficient GIST: loss of function mutation in the SDH gene subunits or loss of SDHB protein expression; wild type GISTs lacking KIT and PDGFRA mutation.

HISTOPATHOLOGY

- Histologically, appearance of these tumors falls into 3 categories
  - Spindle cell type(70%)
  - Epitheliod type(20%)
  - Mixed type(10%)

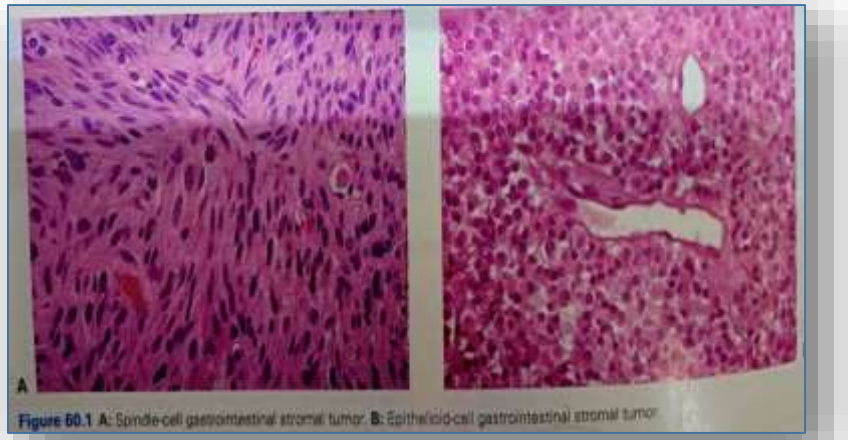


Figure 60.1 A: Spindle-cell gastrointestinal stromal tumor. B: Epithelioid-cell gastrointestinal stromal tumor.

IMMUNOHISTOCHEMISTRY

1. KIT(CD117)
   1. Approximately 90% of the patients are KIT +
   2. Primary KIT mutations occur in Exon 9 and 11

Its presence indicates good response to Imatinib (Gleevac).

2. Over-expression of KIT and presumably aberrant KIT signaling may be present in the absence of KIT mutations, especially in pediatric GIST. These tumors typically stain for KIT but are KIT Wild type.(i.e have no detectable mutations in the KIT gene.

So they have poor response to Imatinib (Gleevac)

HISTOPATHOLOGY

- PDGFRA- Various molecular alterations associated with PDGFRA pathways-
  - Exon 18-80-90% of PDGFRA mutations.
  - D842V exon 18 mutations confers significant resistance to Imatinib and requires alternative TKI e.g. Avapritinib, Ripretinib.
  - NON D842V EXON 18 mutations confers sensitivity to Imatinib.

- DOG -1 (97%)And PKC theta(72%)
  - These are present in GIST irrespective of KIT or PDGFRA mutational status.
- SDH DEFICIENT TUMORS
  - Lack mutations in kit/PDGFRA . They have loss of function of SDH.
  - Patients with such tumors should be referred for evaluation of Carney Stratakis Syndrome and Paraganglionomas

- SMA
  - Positive in 30-40% of cases
- S-100
  - positive in 5 % of cases
- Desmin
  - very rarely

PROGNOSTIC MARKER

- Tumor size and the mitotic rate are the most widely used features for the risk stratification of GIST.
- Tumor Site also play a greater role.
- Female sex is an independent prognostic factor for hih PFS and OS in patients treated with standard dose Imatinib.
- GISTs with SDH mutations are less sensitive to TKIs, and they typically arise in stomach and are observed in younger individuals, frequently metastasise, may feature lymph nodal involvement and tend to grow slowly.
- Tumor genotype has been shown to be independent prognostic marker.
  - Poorer DFS has been associated with KIT exon 9 duplication, KIT exon 11 deletions, nongastric sites, larger tumor size, and high mitotic index.
  - PDGFRA exon 18 mutations are associated with better prognosis.

	ESOPHAGUS	STOMACH	DUODENUM	JEJUNUM AND ILEUM
INCIDENCE	5%	50-70%	10-20%	27%-37% & 27-53%
GENDER	MALE	MALE, YOUNG FEMALES	M=F	M=F
SITE	LOWER 1/3 JUNCTION	ANTRUM FOLLOWED BY PYLORUS	2ND PART OF DUODENUM	-
GROSS (SIZE OF TUMOR)	VARIABLE	USUSALLY >5CM	VARIABLE	>4.5 CM
MORPHOLOGY	SPINDLE/ EPITHELOID	M/C SPINDLE	CELLULAR, >2 /50 HPF MITOSIS	VARIABLE
BEHAVIOUR AND PROGNOSIS	AGGRESSIVE	GOOD SURVIVAL WITH COMPLETE RESECTION	30-50% ARE MALIGNANT	WORSE OUTCOME THAN GASTRIC GIST

	COLON	APPENDIX	ANORECTUM	EXTRAGASTROINTESTINAL GIST
INCIDENCE	5%	VERY RARE	5%	4.5%
GENDER	M=F	-	-	-
SITE	ASCENDING AND DESCENDING COLON	-	-	OMENTU, MESENTRY, RETROPERITONEUM
GROSS	VARIABLE	VARIABLE	>5 CM	OMENTAL GIST CAN BE LARGE
MORPHOLOGY	HETEROGENOUS BUT M/C IS SPINDLE	SPINDLE MORPHLOGY WITH LOW MITOSIS	VARIABLE >5 MITOSIS/50HPF	VARIABLE
BEHAVIOUR	VARIABLE	GOOD PROGNOSIS, METS TO LIVER AND LUNG AFTER 10-15 YEARS	32-54% MALIGNANT	OMENTAL GIST RESEMBLE STOMACH GIST AND MESENTERIC GIST RESEMBLE SI GIST

GIST: Associated Syndromes

	FAMILIAL	CARNEYS TRAID	CARNEYS-STSTRATAKIS SYNDROME	NF-1
CLINICAL FEATURE	MUCOCUTANEOUS HYPERPIGMENTATION MAST CELL LESIONS MELANOMA ESOPHAGEAL DYSMOTILITY	PARAGANGLIOMA PULMONARY CHONRDOMA ALSO, ADRENAL ADENOMA , ESOPHAGEAL LEIOMYOMA	PARAGANGLIOMA	NEUROFIBROMATOSSI CAFÉ AU LAIT SPOTS LISH NODULES OPTIC GLIOMA NEUROBLASTOMA RHABDOMYOSARCOMA PHEOCHROMOCYTOMA
INHERITANCE	AD	NONE	AD	AD
GENDER	EQUAL	85% FEMALE	EQUAL	EQUAL
GIST LOCATION	SMALL BOWEL	STOMACH	STOMACH	SMALL BOWEL

GIST STAGING: AJCC 8TH EDITION 2017

T	PRIMARY TUMOR
Tx	Primary tumor can not be assessed
T0	No evidence of primary tumor
T1	Tumor less than 2 cm
T2	>2 cm, but not more than 5cm
T3	>5cm, but not more than 10 cm
T4	>10 cm in greatest dimension

N	REGIONAL LYMPH NODES
N0	No regional lymph nodes or u/k LN status
N1	Regional lymph node status

M	DISTANT METASTASIS
M0	No Distant metastasis
M1	Distant metastasis

Grading for GISTs is dependent on mitotic rate	
LOW	5 or fewer mitoses per 5 mm2, or per 50 HPF
HIGH	Over 5 mitoses per 5 mm2 or per 50 HPF

GISTs staging: staging/ Prognostic groups

	T	N	M	MITOTIC RATE
Stage 1A	T1/T2	N0	M0	Low
Stage 1B	T3	N0	M0	Low
Stage 2	T1	No	M0	High
	T2	N0	M0	High
	T4	N0	M0	Low
Stage 3A	T3	N0	M0	High
Stage 3B	T4	N0	M0	High
Stage 4	Any T	N1	M0	Any Rate
	Any T	Any N	M1	Any Rate

GASTRIC GISTs
Also to be used for omentum

	T	N	M	MITOTIC RATE
Stage 1	T1/T2	N0	M0	
Stage 2	T3	N0	M0	
Stage 3A	T1	N0	M0	
	T4	N0	M0	
Stage 3B	T2	N0	M0	
	T3	N0	M0	
	T4	N0	M0	
Stage 4	Any T	N1	M0	
	Any T	Any N	M1	

SMALL INTESTINAL GISTs
Also to be used for esophagus, Colorectal, mesenteric and peritoneal

PREDICTORS OF GIST BIOLOGIC RISK

TUMOR SIZE	MITOTIC RATE	RISK	RISK PER CAP
</= 2 CM	</= 5 MITOSIS PER 50 HPF	METASTASIS RATE : 0%	NONE
	>5 MITOSIS PER 50 HPF	METASTASIS RATE : 0%	NONE
>2 CM AND </=5CM	</= 5 MITOSIS PER 50 HPF	METASTASIS RATE : 1.9%	VERY LOW (1.9%)
	>5 MITOSIS PER 50 HPF	METASTASIS RATE : 16%	MODERATE (16%)
>5CM AND </=10CM	</= 5 MITOSIS PER 50 HPF	METASTASIS RATE : 3.6%	LOW (3.6%)
	>5 MITOSIS PER 50 HPF	METASTASIS RATE : 55%	HIGH (55%)
>10CM	</= 5 MITOSIS PER 50 HPF	METASTASIS RATE : 12%	MODERATE (12%)
	>5 MITOSIS PER 50 HPF	METASTASIS RATE : 86%	HIGH (86%)

GASTRIC GIST

PREDICTORS OF GIST BIOLOGIC RISK

TUMOR SIZE	MITOTIC RATE	RISK	RISK PER CAP
</= 2 CM	</= 5 MITOSIS PER 50 HPF	METASTASIS RATE : 0%	NONE
	>5 MITOSIS PER 50 HPF	METASTASIS RATE : 50-54%	INSUFFICIENT DATA- HIGH (54%)
>2 CM AND </=5CM	</= 5 MITOSIS PER 50 HPF	METASTASIS RATE : 1.9-8.5%	LOW (4.3-8.5%)
	>5 MITOSIS PER 50 HPF	METASTASIS RATE : 50-73%	HIGH (50-73%)
>5CM AND </=10CM	</= 5 MITOSIS PER 50 HPF	METASTASIS RATE : 24%	INSUFFICIENT DATA- MODERATE (24%)
	>5 MITOSIS PER 50 HPF	METASTASIS RATE : 85%	INSUFFICIENT DATA-HIGH (85%)
>10CM	</= 5 MITOSIS PER 50 HPF	METASTASIS RATE : 34-57%	HIGH (34-57%)
	>5 MITOSIS PER 50 HPF	METASTASIS RATE : 71-90%	HIGH (71-90%)

NON GASTRIC GIST include small bowel and colorectal GIST

TREATMENT GUIDELINES: GIST

- GIST <2 CM3
  - No high risk feature: periodic endoscopic or radiological surveillance.
  - High risk features: complete surgical resection

- CLINICALLY SUSPICIOUS GIST:
  - If resectable: gp or complete surgical resection
  - If resectble with significant morbidity: Biopsy with molecular testing: neo-adjuvant therapy
    - Response and resectable: surgery
    - Unresectable: continue therapy
  - If unresectable or metastatic disease : NA therapy

- R1 or R2 resection: adjuvant therapy after molecular testing
- TUMOUR RUPTURE: considered as metastatic: adjuvant therapy

TREATMENT GUIDELINES: GIST

INTERVENTIONAL RADIOLOGICAL TREATMENT OPTIONS

1. CATHETER DIRECTED:
    - Transarterial embolisation (TAE)
    - Transarterial chemoembolisation (TACE)
    - Transarterial radioembolisation (TARE)
2. ABLATION
    - Thermal therapies (cryotherapies, RFA, MWA, Laser ablation, HIFU)
    - non-thermal therapies (Irreversible electroporation(IRE))

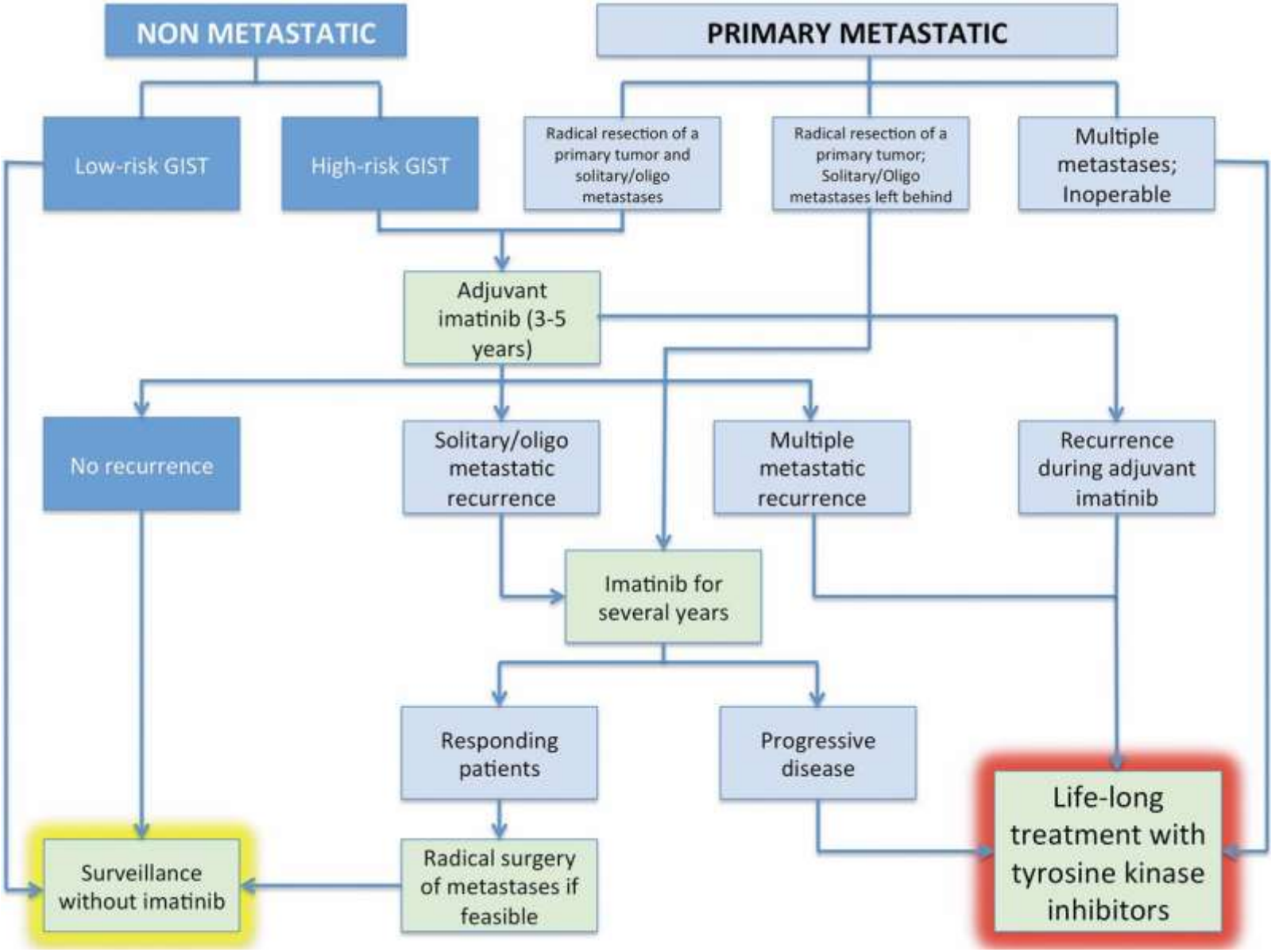
TREATMENT GUIDELINES: GIST

- NEO-ADJUVANT THERAPY FOR RESECTABLE DISEASE WITH SIGNIFICANT MORBIDITY
  - Preferred regimen: Imatinib for KIT/ PDGFRA exon 18 mutations
  - Avapritinib for GIST with PDGFRA exon 18 mutations that are insensitive to Imatinib (PDGFRA D842V)

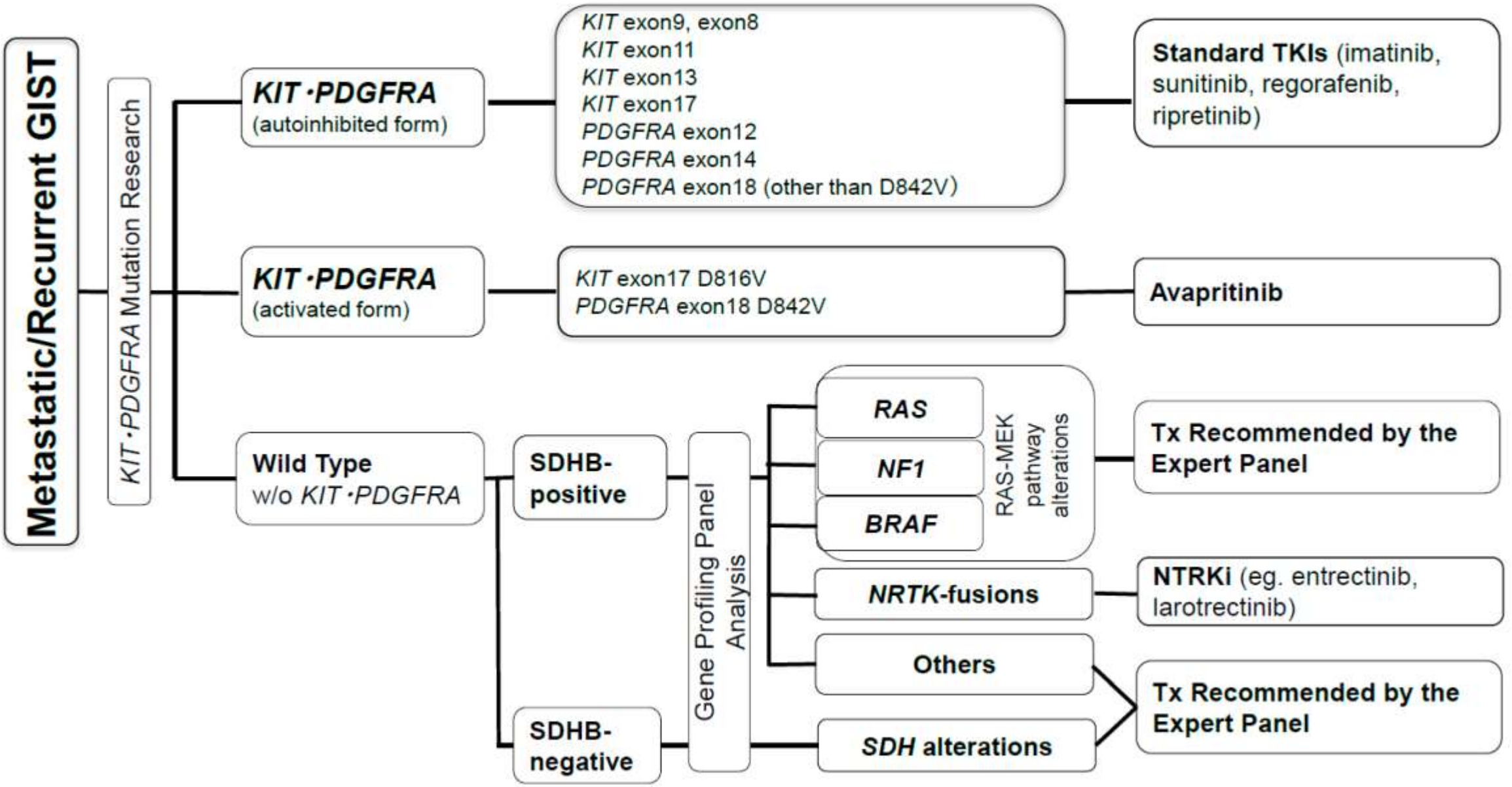
- USEFUL in certain circumstances:
  - Larotrectinib or entrectinib (for NTRK gene fusion positive GIST)
  - Sunitinib (for SDH deficient GIST)
  - Dabrafenib / Trametinib (for BRAF V600E mutated GIST)

- ADJUVANT THERAPY FOR RESECTABLE DISEASE
  - Adjuvant Imatinib

TREATMENT GUIDELINES: GIST



TREATMENT GUIDELINES



ADJUVANT AND NEOADJUVANT THERAPIES

GIST

- FIRST LINE THERAPY
  - IMATINIB

GIST

- SECOND LINE THERAPY
  - SUNITINIB

GIST

- THIRD LINE THERAPY
  - REGORAFENIB

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Radiotherapy for GIST

Radiotherapy for GIST progressing during or after tyrosine kinase inhibitor therapy: A prospective study

Heikki Joensuu [a,*], Mikael Eriksson [b], Juhani Collan [a], Marja H. Balk [c], Serge Leyvraz [d], Michael Montemurro [d]

[a] Department of Oncology, Helsinki University Hospital and University of Helsinki, Finland; [b] Department of Oncology, Lund University, Sweden; [c] Department of Radiology, HUS Medical Imaging Center, Helsinki University Hospital and University of Helsinki, Finland; [d] Department of Oncology, University Hospital Lausanne, Switzerland

Eligible patients had histologically verified inoperable GIST, either locally advanced or metastatic disease wer taken for radiotherapy

25 patients were enrolled

Two (8%) patients achieved partial remission, 20 (80%) had stable target lesion size for 3 months after radiotherapy with a median duration of stabilization of 16 months, and 3 (12%) progressed. The median time to radiotherapy target lesion progression was 4-fold longer than the median time to GIST progression at any site (16 versus 4 months).

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Teaching Case

Case Report: Stereotactic Body Radiation Therapy Produces a Durable Response in a Perirectal Gastrointestinal Stromal Tumor

Nathanial Harris, PhD, MD,[a] Olivia Fraser, FRCR,[a] Melanie Bauer, BMRSc,[a] Farshad Foroudi, MBBS (Hons), MPA, DMedSc, FRANZCR,[a] Andrew Bui, MBBS, MSc, FRACS,[b] Niall Tebbutt, PhD, MRCP, FRACP,[c] Michael Chao, MBBS, FRANZCR, DMedSc,[a] and Daryl Lim Joon, MBBS, PhD, FRANZCR[a,*]

- Stereotactic body radiation therapy (SBRT) offers the potential to deliver ablative doses
- The perirectal tumor as visualized on diagnostic CT, PET-CT, and MRI was delineated as gross tumor volume (GTV). Clinical target volume was defined as equal to the GTV. Planning target volume (PTV) was created by adding anisotropic 5-mm margin to GTV according to institutional protocol.
- SBRT was planned for a dose of 50 Gy in 5 fractions to the perirectal GIST.
- Rectal examination findings (March 2022) are also consistent with reduction in size compared with November 2020

OncoTargets and Therapy

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EXPERT OPINION

Considering the role of radiation therapy for gastrointestinal stromal tumor

- There exist several potential scenarios where RT could provide benefit in the management of GISTs.
- If given adjuvantly prior to failure, RT could potentially limit the development of resistance and serve as an important adjunct to imatinib.
- For tumors at high risk of local recurrence or R1 resection, preoperative RT could be considered, potentially with imatinib, for cytoreductive effect.
- Additionally, radiotherapy may be a local treatment option for patients with tumors that are surgically inaccessible due to location, or in whom resection would lead to severe functional impairment, such as duodenal or esophageal locations.
- Finally, RT can be used for palliation of local symptoms.
- short courses of RT have been shown to be effective for tumor control and symptom management, with low rates of toxicity.

Review Article

Radiotherapy for Gastrointestinal Stromal Tumors

Emine Elif Ozkan
Department of Radiation Oncology, Suleyman Demirel University, Isparta 32260, Turkey

Conclusions: Recently reported long-term local control rates indicate that GIST is a radiosensitive disease. This makes radiotherapy a valuable alternative in GIST management with curative intent, especially in patients who (1) cannot tolerate or are resistant to chemotherapy agents, (2) have an unresectable disease, (3) have a gross or microscopic residual disease after surgery, and (4) have a recurrent disease.

In their study, radiation therapy was delivered with 300 cGy × 10, 180 cGy × 25, and 200 cGy × 25 fractions in the patients treated conventionally.

Stereotactic body radiation therapy was used for 9 tumors (2400 cGy × 1, n = 2; 900 cGy × 3, n = 2; 800 cGy × 3, n = 1; 600 cGy × 5, n = 2; and 500 cGy × 5, n = 2).

PRINCIPLES OF IMAGING

Workup

- For very small GIST <2 cm: Perform abdominal/pelvic CT with contrast and/or abdominal/pelvic MRI with contrast.
- For all other GIST:
  - Abdominal/pelvic CT with contrast and/or abdominal/pelvic MRI with contrast
  - Chest imaging using x-ray or CT

Response Assessment

Resectable disease with significant morbidity

- Obtain baseline abdominal/pelvic CT and/or MRI.
- Consider PET/CT
  - Obtain baseline PET/CT if using PET/CT during follow-up; PET/CT, with a non-diagnostic CT, is not a substitute for a diagnostic CT.
- Imaging to assess response to preoperative TKI
  - Abdominal/pelvic CT or MRI is indicated every 8–12 weeks.
  - PET may give indication of TKI activity after 2–4 weeks of therapy when rapid readout of activity is necessary.
- Progression may be determined by abdominal/pelvic CT or MRI with clinical interpretation; PET/CT may be used to clarify if CT or MRI is ambiguous.
- For R2 resection or discovery of metastatic disease, assess response to postoperative TKI using abdominal/pelvic CT or MRI every 8–12 weeks.

Definitively unresectable, recurrent, or metastatic disease

- Obtain baseline abdominal/pelvic CT and/or MRI.
- Consider imaging of chest intermittently.
- Consider PET/CT.
  - Obtain baseline PET/CT if using PET/CT during follow-up; PET/CT, with a non-diagnostic CT, is not a substitute for a diagnostic CT.
- Imaging to assess response to TKI
- Abdominal/pelvic CT or MRI every 8–12 weeks of initiating therapy; in some patients, it may be appropriate to image before 3 months.
- Progression may be determined by abdominal/pelvic CT or MRI with clinical interpretation; PET/CT may be used to clarify if CT or MRI is ambiguous.

Follow-up

- For completely resected primary disease, perform abdominal/pelvic CT every 3–6 months for 3–5 years, then annually.
  - Less frequent imaging surveillance may be acceptable for low-risk or very small tumors (<2 cm).
  - More frequent imaging surveillance may be required for patients with high-risk disease who discontinue TKI therapy.
- For incompletely resected disease or discovery of metastatic disease during surgery, perform abdominal/pelvic CT every 3–6 months.
- Progression may be determined by CT or MRI with clinical interpretation; PET/CT may be used to clarify if CT or MRI is ambiguous.
- After treatment for progressive disease, reassess therapeutic response with abdominal/pelvic CT or MRI.
  - Consider PET/CT only if CT results are ambiguous.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PALLIATIVE CARE

- Gist not controlled by surgery , might spread to liver and montum, bones
- Liver failure, intestinal and urinary obstruction are –palliative challenges
- Extra-abdominal gist occasionally seen in bones and may require palliative radiotherapy for pain management

SUMMARY

CLINICAL PRESENTATION

- 1.2/100,000/ Year
- Stomach> small bowel> rectum> colon
- 7^{th} decade
- Pauci-symptomatic

WORK-UP

- blood investigation
- endoscopy
- Imaging
- Biopsy

SARCOMA TUMOR BOARD

DIAGNOSIS

- H&E: cell type, mitotic count
- IHC: CD117. DOG-1, SDHB

MOLECULAR

- **KIT/ PDGFRA mutant (app. 90%)**
  - KIT exons 11> 9>13=17
  - PDGFRA exons 18> 12> 14

RISK STRATIFICATION

NIH
AFIP
NIH consensus

Tumor size
Mitotic count
Location
Tumor rupture

LOCALISED DISEASE

- surgery
- Neo/ adjuvant Imatinib

METASTATIC DISEASE

- Targeted therapies
  - Imatinib
  - Sunitinib
  - Regorafenib
- Clinical trials
- Surgery

Thank you