Management of metastatic GIST: What is the role of surgery when the tumor has spread?

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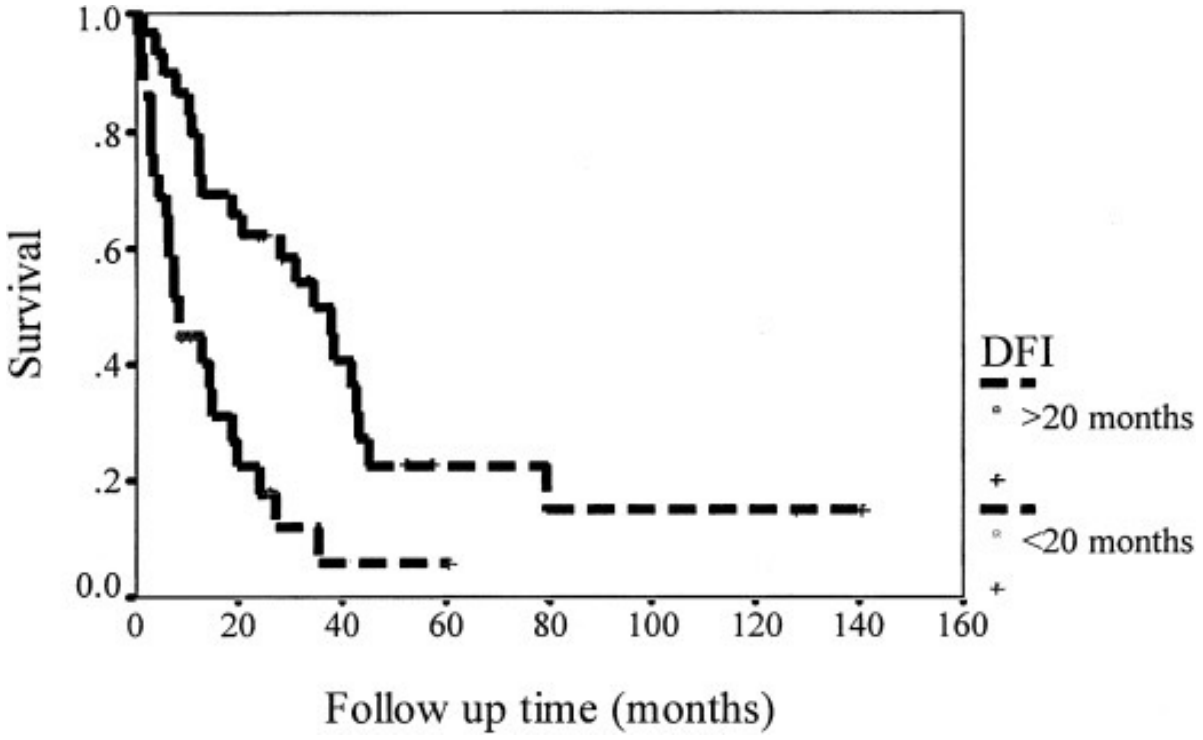
Surgery alone is of limited benefit in metastatic GIST

- 60 patients with recurrent gastrointestinal sarcoma treated at MSKCC between 1982 and 1994.
- 45% with local recurrence or sarcomatosis, 55% with liver metastases
- 30% after gastric primary, 60% with small bowel primary
- 30% of patients were able to undergo complete resection of the recurrent disease
- Even in context of complete resection, survival in metastatic disease was only about 3 months.



Mudan *et al.* (1999) *Cancer* 88(1): 66-74.

Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors

- Randomized trial of patients with unresectable or metastatic GIST to 400 vs. 600mg. imatinib

Characteristic	All patients (n=147)
Age (yr)	
Median	54
Range	18-83
Site of primary tumor	
Small intestine	72 (49.0%)
Stomach	50 (34.0%)
Liver	25 (17.0%)
Peritoneum	19 (12.9%)
Omentum	17 (11.6%)
Site of tumor recurrence	
Any recurrence	132 (89.8%)
Liver	115 (78.2%)
Peritoneum	56 (38.1%)
Retroperitoneum	21 (14.3%)
Prior treatment	
Surgery	144 (98.0%)
Chemotherapy	75 (51.0%)
Radiation	22 (15.0%)

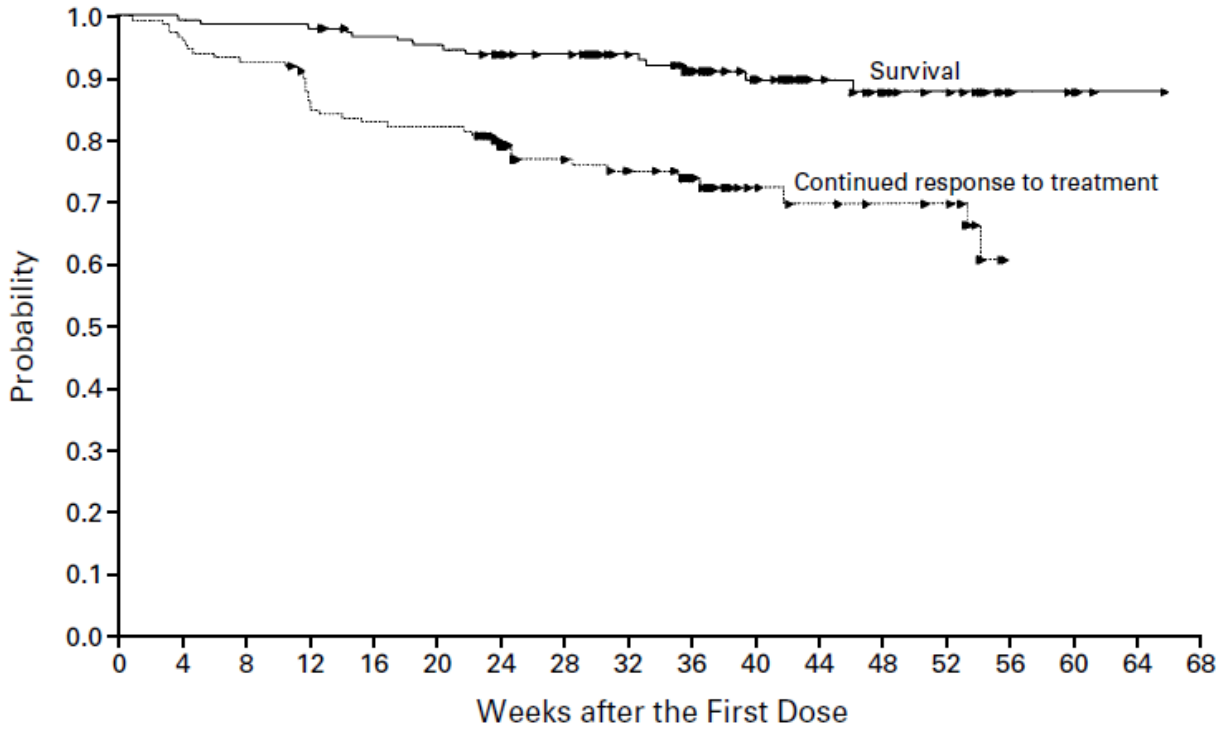
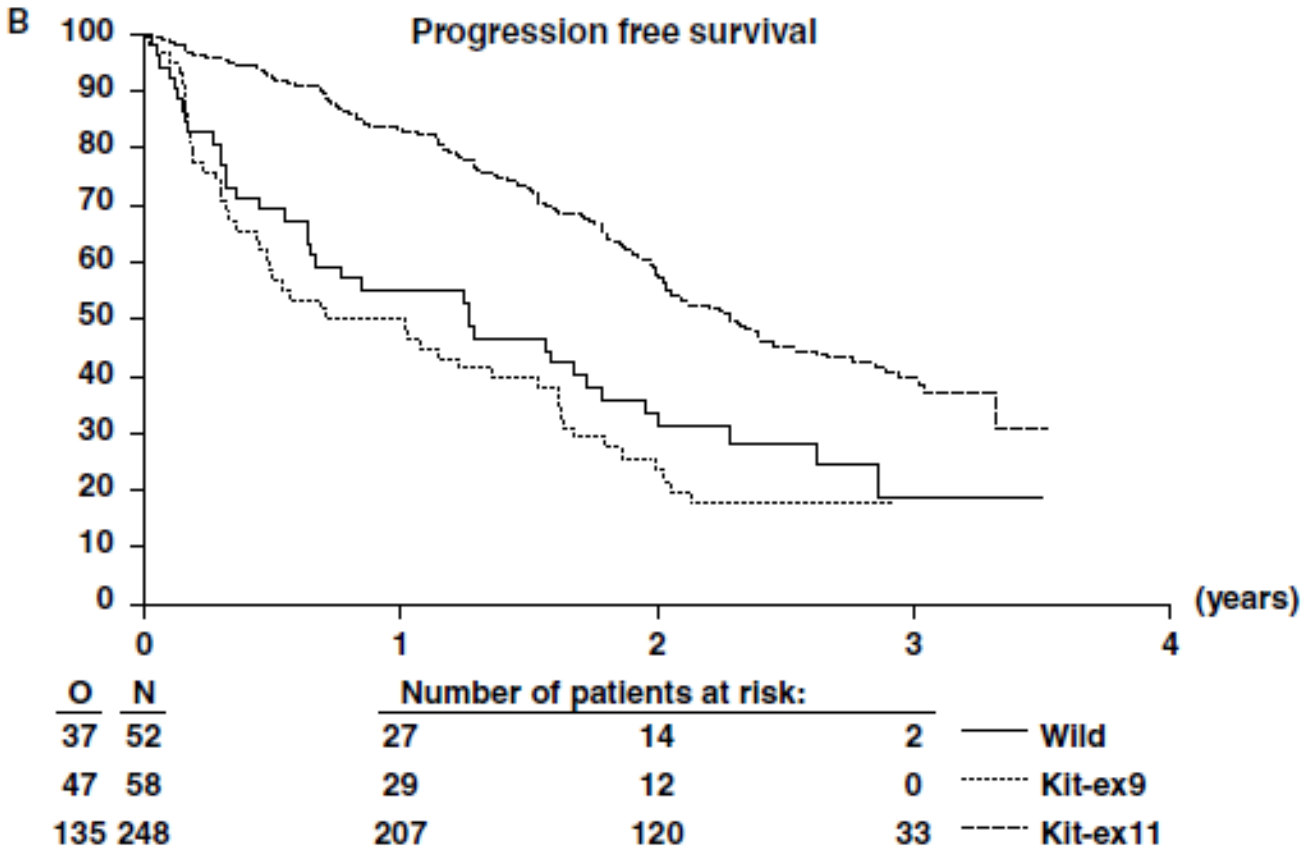


Figure 1. Kaplan–Meier Estimates of Overall Survival and Time to Treatment Failure for All Patients. Each arrowhead represents the point at which a patient's data were censored.

Demetri, Joensuu *et al*. (2002). *NEJM* 347 (7):472-80.

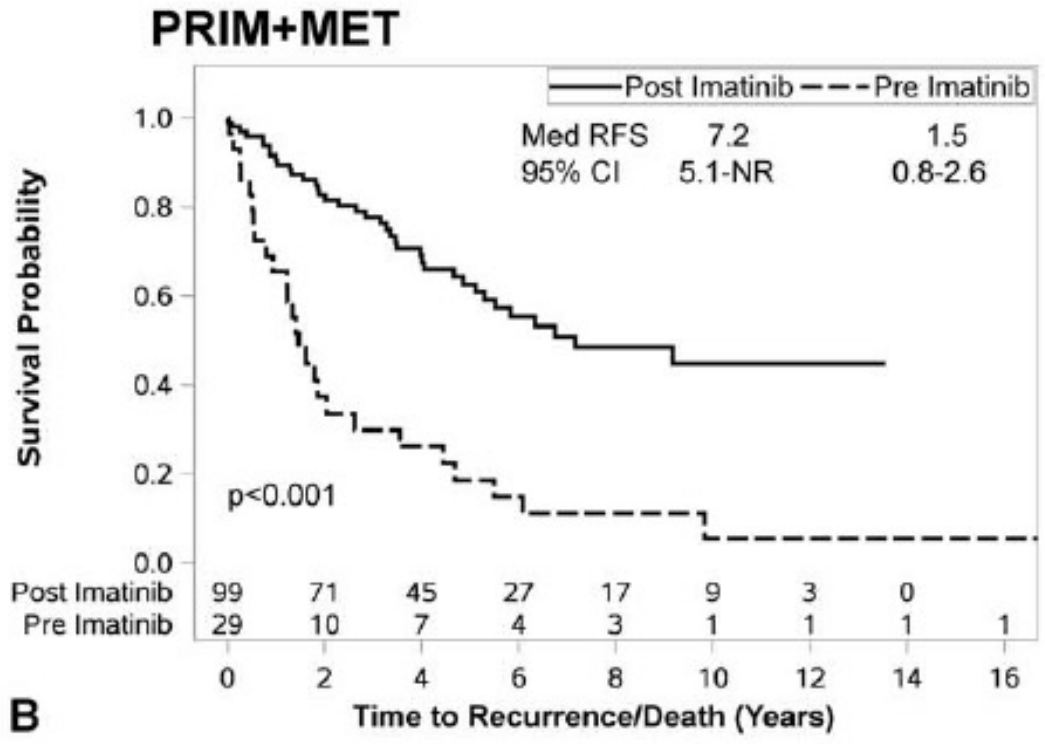
Secondary resistance develops in metastatic GIST that initially responds to imatinib

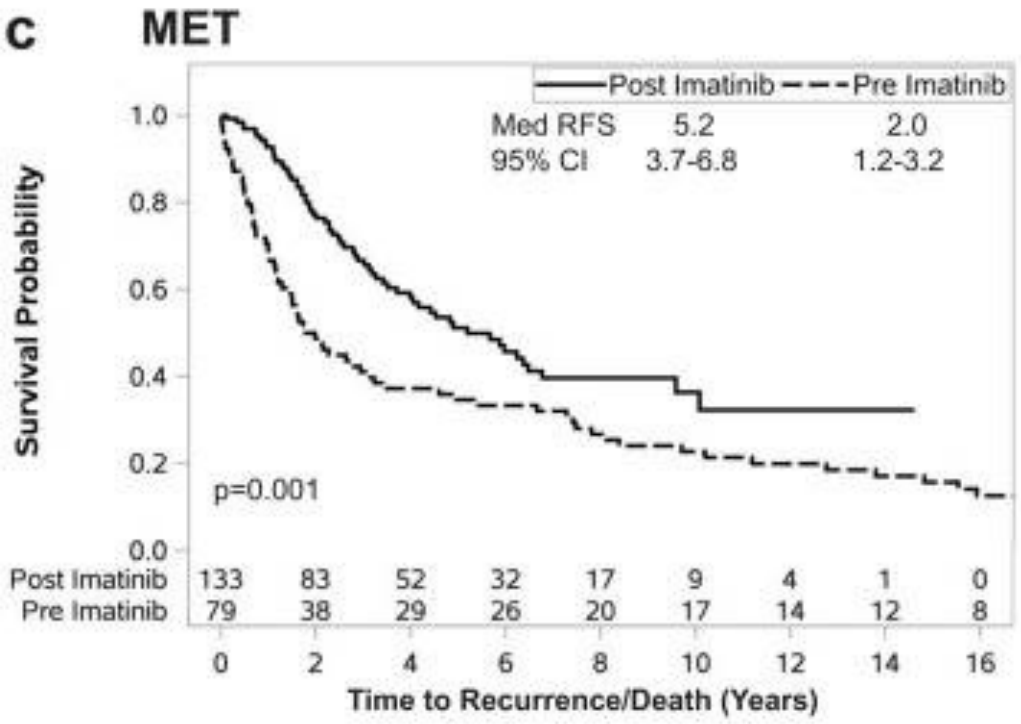


Debiec-Rychter, Judson, *et al.* (2006) *Eur J Cancer* 42:1093-1103

Options for treatment in secondary resistance – Surgery in the context of metastatic or multi-focal disease in the imatinib era

- Progression free survival on sunitinib or regorafenib is less than 6 months.
- Study of 1000 patients treated surgically for GIST at MSKCC
- Outcomes stratified by whether surgery was performed before or after treatment with imatinib.



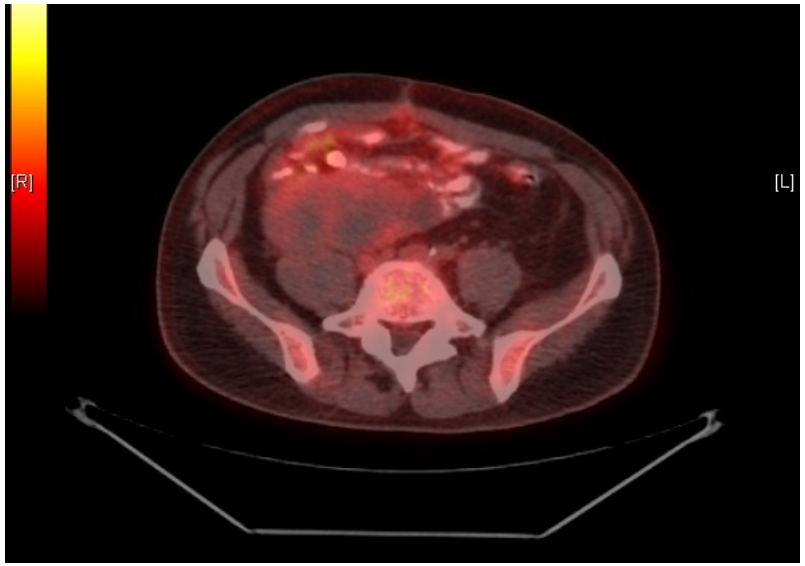


Cavnar, DeMatteo, *et al*. (2021) *Ann Surg* 273 (1):128-38.

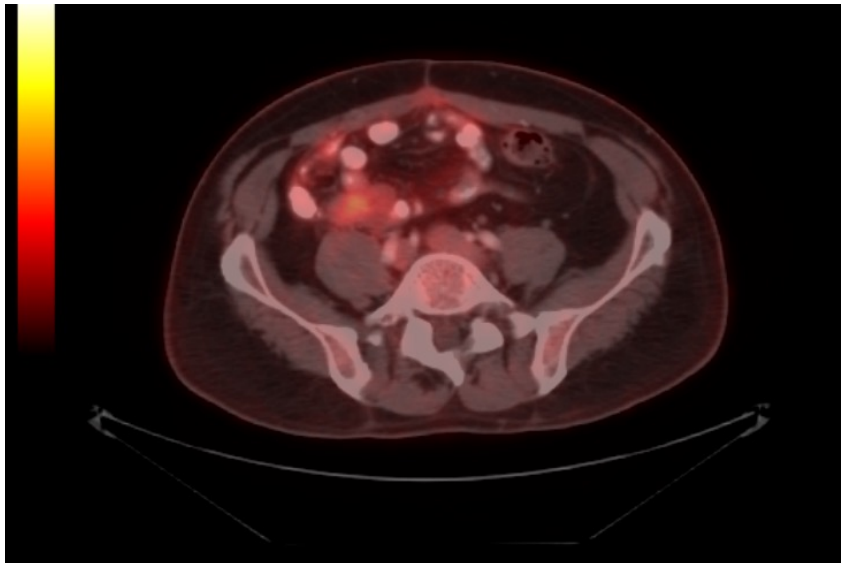
A case of secondary resistance

- 53yo man initially presented with primary small bowel GIST
- Surgical exploration showed unresectable, multifocal peritoneal disease and pathology demonstrated 6 base pair deletion in *CKIT* exon 11
- Initiated on a course of imatinib with partial response; imaging showed progression of solitary site after 7 years
- Underwent surgical resection and reinitiated on imatinib therapy

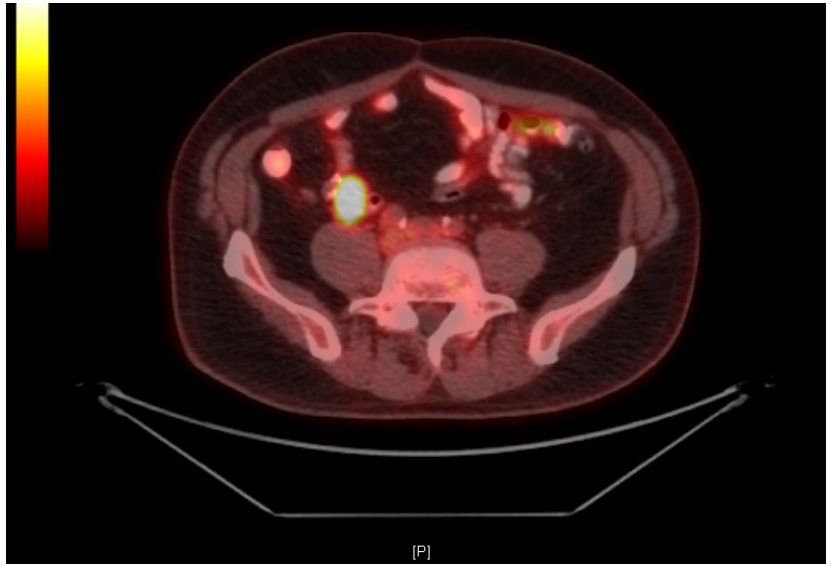
2013



2014



2020



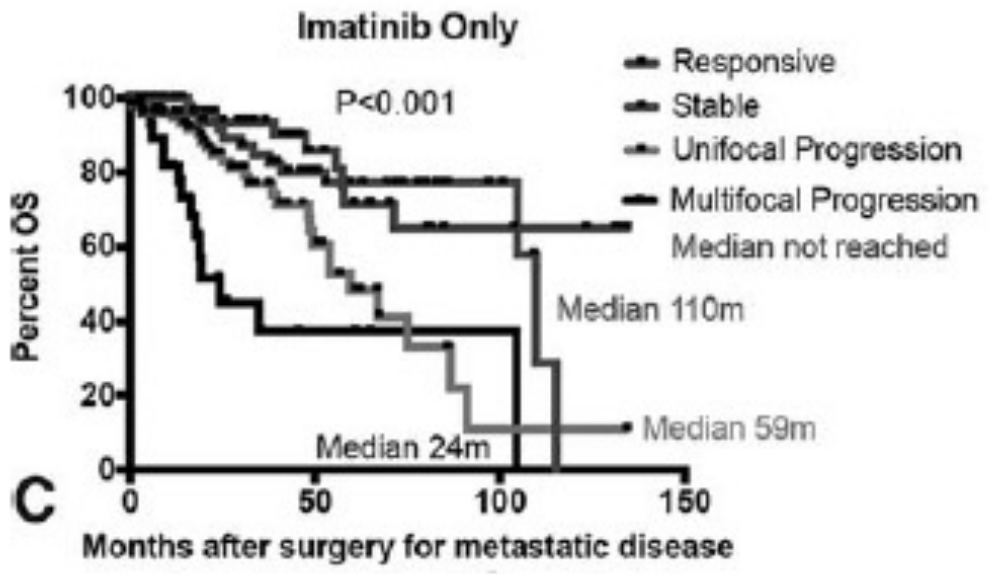
Theoretical reasons to consider cytoreductive therapy in resistant disease

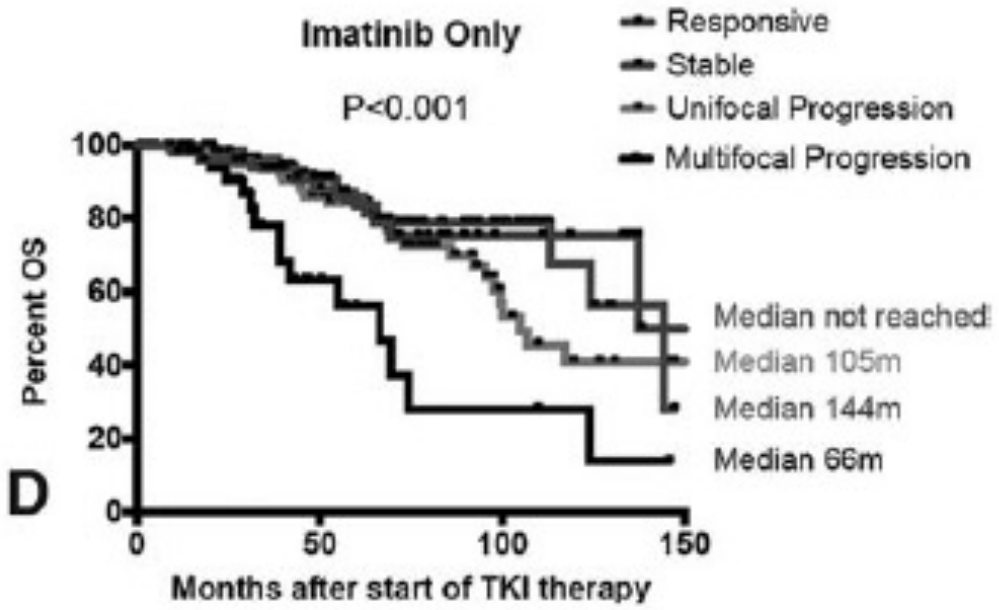
- Removal of the resistant site will allow for continued therapy with lower toxicity tyrosine kinase inhibitors
  - But does it improve overall survival as compared to second or third line treatments?

- Debulking of non-resistant disease will reduce the number of GIST cells *in situ* that may develop additional resistance

Cytoreductive surgery in metastatic GIST is associated with improved outcomes when not in the context of multifocal progression

- 400 operations on 323 patients with metastatic GIST taking TKIs.
- At Dana Farber Cancer Institute and MSKCC.





- Consider similar factors when prescribing hepatic artery embolization, radiation, etc.

Fairweather, Raut, *et al*. (2018) *Ann Surg* 268(2): 296-302.

Outcomes after surgery are better for patients being managed with imatinib as opposed to second line sunitinib

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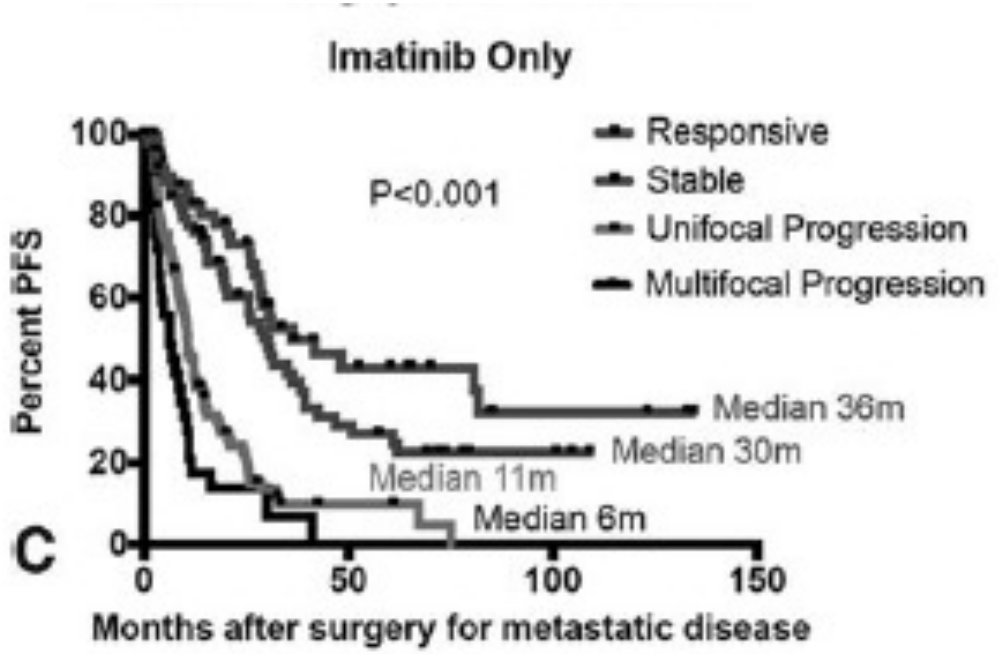
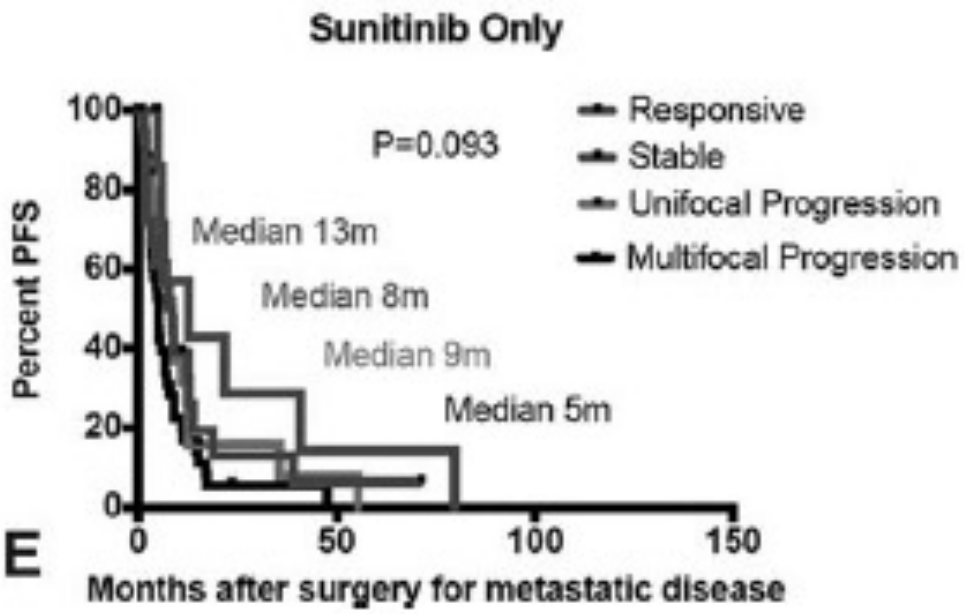
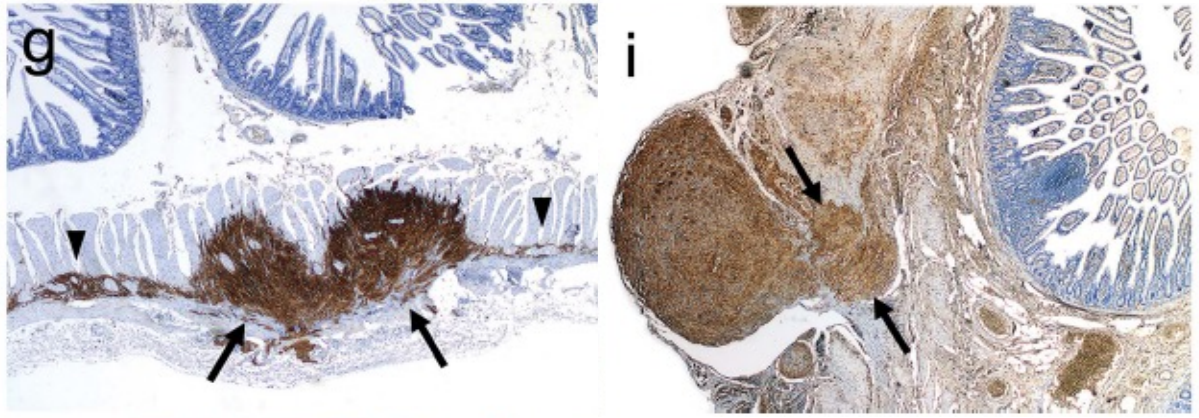




Fairweather, Raut, *et al*. (2018) *Ann Surg* 268(2): 296-302.

NF1-associated GIST is less responsive to systemic therapy but indolent at baseline so may be appropriate for surgery despite imatinib resistance

- Develop in context of interstitial cell of Cajal hyperplasia, autopsy results suggest develop in ~25% of NF1 patients
- Commonly have spindle cell morphology, low mitotic rate
- Series of 45 NF1 GIST patients
  - only 2 died of disease after median 13 month follow-up
  - 2 from post-op complications
- Three of 4 patients with metastatic GIST, had primary resistance to imatinib is small series



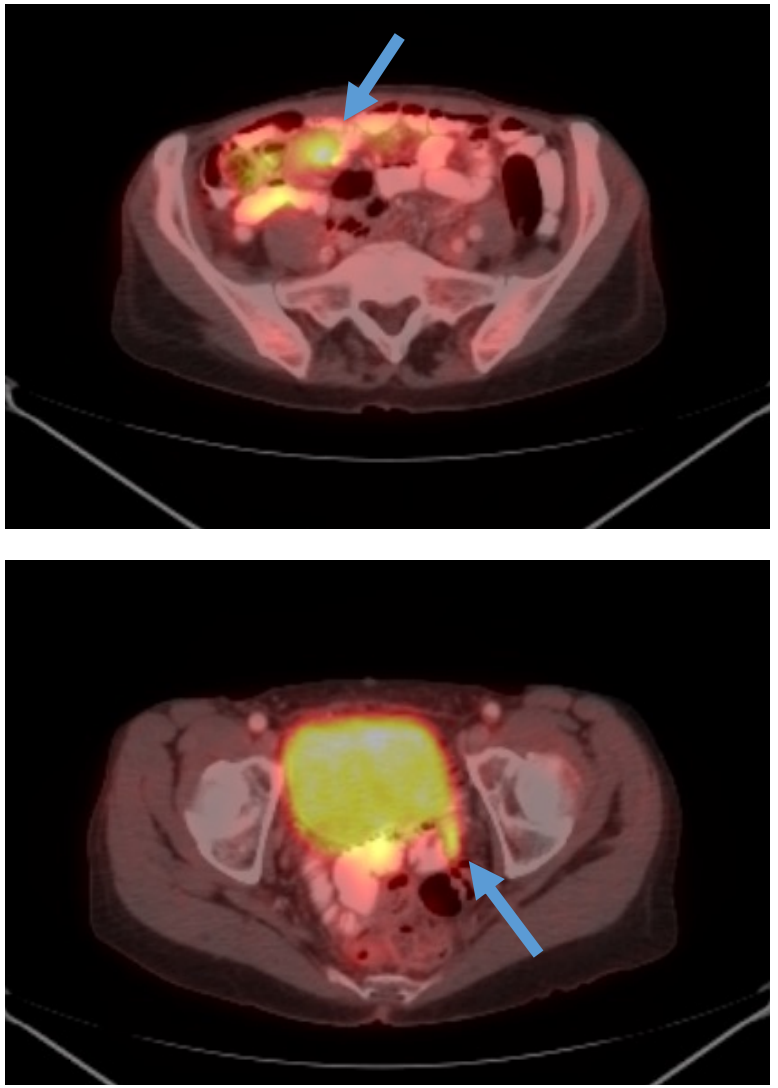
	Miettinen series n=45 (%)	Published series n=64 (%)
Mean age (y.o., range)	49 (23-72)	50 (10-86)
Female	26 (58)	35 (55)
Presenting symptoms		
GI bleeding	20/32 (63)	23/47 (49)
Obstruction	2/32 (6)	4/47 (9)
Incidental	7/32 (22)	17/47 (36)
Individual sites		
Gastric	1 (2)	8 (13)
Duodenal	10 (22)	20 (31)
Jejunal	24 (53)	38 (59)
Ileal	4 (9)	11 (17)
Small bowel (NOS)	16 (36)	2 (3)
Multifocal disease	28 (62)	38 (59)
Mean tumor size (cm, range)	4 (0.4-29)	3.0 (0.2-27)

Miettinen, Lasota *et al*., (2006) *Am J Surg Pathol* 30(1): 90-6.
Andersson, Kindbloom *et al*. (2005) *Am J Surg Pathol* 29(9): 1170-6.
Mussi, Hohenberger *et al*. (2008) *Clin Cancer Res* 14(14):4550-5.

68y.o. patient with NF1

- Underwent resection of what was thought to be a bleeding fibroid 2 years prior
- Intra-operative tumor rupture
- TKI treatment deferred due to cardiac co-morbidities, relative decreased response rate, dominant lesion growing in RLQ with intermittent obstruction
- Operative findings
    - Multifocal disease throughout small bowel
    - Most lesions ~1cm
    - Dominant 6cm mass resection right lower quadrant with final pathology showing mitotic rate of 36/50hpf
    - Smaller pelvic lesion 1.7cm with mitotic rate of 1/50hpf

- ***No radiographic recurrence 4 years later***
- ***Similar approach considered for symptomatic patients with SDH deficient GIST***



Conclusions

- Historically, surgery for metastatic GIST was associated with poor outcomes
- Patients undergoing surgical debulking for metastatic GIST have significant improvement in outcomes in the era of imatinib
- Removing resistant clones may prolong the benefit of imatinib in patients with metastatic GIST or other TKIs
- Resection is also an option to assist in management of patients with certain subtypes of wild-type GIST

Thank you!