Pretreatment mutational analysis of *KIT* and *PDGFRA* optimizes down-sizing imatinib therapy of gastrointestinal stromal tumors

Per Hedenström, Carola Andersson, Henrik Sjövall, Fredrik Enlund, Ola Nilsson, Bengt Nilsson, Riadh Sadik

Sahlgrenska University Hospital, Gothenburg, Sweden Correspondence: per.hedenstrom@vgregion.se

Pretreatment EUS-guided biopsy sampling followed by immediate sequencing of *KIT* and *PDGFRA* in the acquired tumor tissue is highly valuable for the guidance of down-sizing imatinib therapy in GIST.

This approach will optimize the chance of tumor response induced by therapy and can be recommended to centers responsible for the care of GIST-patients.

Introduction

Imatinib, a tyrosine kinase inhibitor (TKI), has radically improved the prognosis in high risk gastrointestinal stromal tumors (GIST). Moreover, preoperative down-sizing imatinib increases the chance of organ-preserving, radical resection in selected patients. However, imatinib is effective only in genetic subsets of tumors with specific mutations in any of the two proto-oncogenes *KIT* and *PDGFRA.* Until now, down-sizing imatinib has often been initiated by chance without knowledge of the underlying tumor mutation in *KIT* and *PDGFRA*.

The aim of the study to evaluate sequencing of *KIT* and *PDGFRA* in pretreatment GIST-tissue acquired by EUS to guide down-sizing therapy and improve tumor response induce by such therapy.

Methodology

All patients eligible for down-sizing TKI-therapy of suspected GISTs during January 2006 – June 2017 were included in this prospective, single-center study. The reference cohort (**RC**, 2006–2013) underwent routine work-up. The immediate sequencing cohort (**ISC**, 2014–2017) was subjected to pretreatment endosonography-guided fine-needle biopsy sampling (EUS-FNB**, Image 1**) followed by immediate sequencing (<2 weeks) of the acquired tumor material.

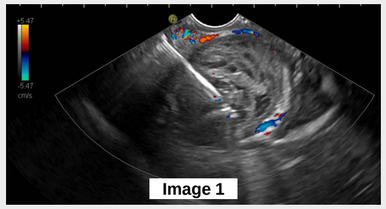
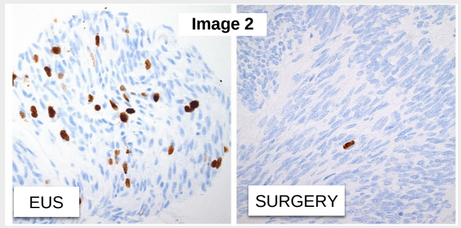


Image 1

The tumor response induced by standard dose imatinib therapy (400 mg) was evaluated by pretreatment and follow-up CT-scan (tumor size reduction, %) and Ki-67-indexing of pretreatment EUS-biopsies and posttreatment surgical specimens (Ki-67-index reduction, %), **Image 2**.



Results

A study total of 106 patients were included – (**ISC**, n=59, and **RC**, n=47). Pretreatment sequencing of GIST-tissue was successful in all but two patients during 2014-2017. Consequently the correct down-sizing therapy was more frequently initiated in the **ISC** compared with the **RC**, 57/59 (97 %) *vs* 33/47 (70 %), p<0.001. **Table 1**.

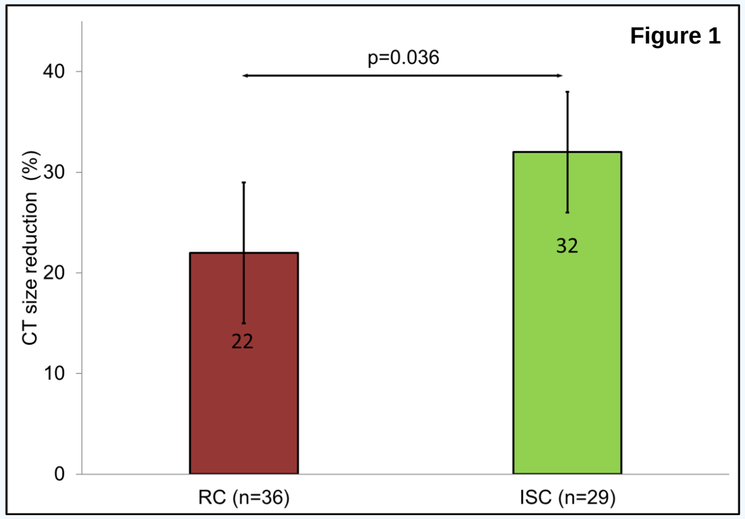
Table 1

	Standard IMA [a]	High IMA	Alternative TKI [b]	No TKI therapy
ISC				
KIT exon 11[c]	40			**1**
KIT exon 13 (p.K642E)	1		1	
PDGFRA exon 12	2			
KIT exon 9	**1**	1		
Wild type			2	2
KIT exon 11 (p.L576P)				1
KIT exon 17 (p.Y823D)				1
PDGFRA exon 18 (p.D842V)				6
RC				
KIT exon 11[c]	31			
KIT exon 13 (p.K642E)	2			
PDGFRA exon 12	-			
KIT exon 9	**2**			
Wild type	**3**			
KIT exon 11 (p.L576P)	**2**			
KIT exon 17 (p.Y823D)	-			
PDGFRA exon 18 (p.D842V)	**7**			

Bold text = case given incorrect therapy or incorrectly abstained from therapy; white background= mutations indication full sensitivity to imatinib; grey background= mutations indicating reduced sensitivity or resistance to imatinib; standard IMA = 400 mg daily; high IMA = 800 mg daily

[a]) IMA = imatinib; [b]) TKI = tyrosine kinase inhibitor; [c]) all mutations in *KIT* exon 11 except p.L576P

The tumor response was higher in the **ISC** compared with the **RC**, both regarding the tumor size reduction measured by **CT scan, Figure 1:**



and regarding the **Ki-67-index reduction**, **Figure 2:**