effective. To our knowledge, this study is the first to describe the non-invasive visualisation of small-bowel motility in a patient group.

The reduced distension did not impede the visualisation of the small-bowel wall as it was outlined by either air or gastrointestinal liquid. It had the added advantage of not affecting the bowel function by placing tubes or filling the bowel. Four distinct motility patterns could be distinguished in our patients: paralysis, shivering, uncoordinated motion and sinusoidal motion. A previous study on motility with healthy volunteers⁹ observed only the sinusoidal pattern, suggesting a clear difference in the motility patterns between postoperative patients and healthy volunteers. It may be hypothesised that motility recovers along a defined path during postoperative convalescence starting with slight shivering, changing into irregular movements and finally developing into full sinusoidal motion. Many factors may influence postoperative bowel motility, but the effect and relevance of each are complex and remain to some extent unknown.^{9,10}

The MRI technique described here is not limited to postoperative treatment, but can be applied to a wide range of motility diseases⁷ and common intestinal disorders with unknown pathomechanisms. Non-invasive MRI assessment of peristaltic motion allows rapid and reliable localisation and diagnosis of motility problems and thus could have a beneficial impact on treatment and recovery.

Michael A Patak

Institute of Diagnostic Radiology, Inselspital, University Hospital, Bern, Switzerland

Michael A Patak, Johannes M Froehlich, Constantin von Weymarn

MR-Research Group, Institute of Radiology, Cantonal Hospital, Winterthur, Switzerland

Stefan Breitenstein

Department of Surgery, University Hospital Zurich, Switzerland

Christoph L Zollkofer, Klaus-Ulrich Wentz

MR-Research Group, Institute of Radiology, Cantonal Hospital, Winterthur, Switzerland

Correspondence to: Dr M A Patak, Institute of Diagnostic Radiology, Inselspital, University Hospital, 3010 Bern, Switzerland; michael.patak@insel.ch

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Double resistance to imatinib and AMG 706 caused by multiple acquired *KIT* exon 17 mutations in a gastrointestinal stromal tumour

Gastrointestinal stromal tumours (GISTs) are rare mesenchymal neoplasms that arise in the wall of the gastrointestinal tract and originate from the interstitial cells of Cajal.¹ The tumours are characterised by the expression of the receptor tyrosine kinase *KIT* (CD117, c-Kit). Activating mutations of the *KIT* proto-oncogene are known to be associated with the tumorigenesis of most GIST.² The standard treatment for primary GIST is surgical resection, as GISTs are resistant to conventional

chemotherapy. The multitargeted tyrosine-kinase inhibitor (MKI) imatinib mesylate (Gleevec, Novartis, Basel, Switzerland) revolutionised the treatment for advanced disease. Although most patients benefit from imatinib, many subsequently develop acquired resistance.³ In patients developing resistance to imatinib, other MKIs provide clinical benefit. Sunitinib malate (Sutent, Pfizer, New York, USA) has demonstrated activity in patients with imatinib-resistant GIST,⁴ and other MKIs are currently in development, including AMG 706, an inhibitor of *KIT*, all vascular endothelial growth factor receptors and platelet-derived growth factor receptor. Preliminary data from recent clinical trials with AMG 706 showed an encouraging clinical benefit rate in patients with advanced high-dose imatinib-resistant GIST.⁵

We report on a 64-year-old woman with a 20 mm GIST of the small bowel (fig 1A, table 1), which was removed in September 2002.

In October 2003, peritoneal and liver metastases were recognised and treatment with imatinib (400 mg/day) was started, resulting in a complete metabolic response (on [¹⁸F] fluorodeoxyglucose positron emission tomography) 8 weeks later. Owing to the presence of a subsequent progressive mesenteric mass, the imatinib dose was increased (800 mg/day) in July 2004, leading to growth arrest. In April

Figure 1 (A) Histopathology of the high mitotic primary spindle cell type gastrointestinal stromal tumour (arrows: mitoses, H&E $\times 400$). (B) *KIT* exon 17 point mutation c.2466T→A (G) found in three specimens of the imatinib/AMG 706-resistant progressive tumour leading to Asn822Lys. (C) *KIT* exon 17 point mutations c.2453A→G, c.2467T→G, and c.2433T→C (silent) found in additionally investigated four specimens of the tumour relapse leading to Tyr823Asp and Lys818Arg.

Table 1 Tumour characteristics

	Primary GIST	Regressive GIST	Progressive GIST
Gross pathology			
Localisation	Jejunum	Peritoneal	Mesenterial
Size (mm)	20	15–55	95
Histopathology			
GIST type	Spindle cell	Spindle cell	Spindle cell
Vital tumour (%)	100	20	100
Mitoses/50HPF*	43	0	114
Risk profile†	High risk	—	—
Immunohistochemistry			
KIT	+	Variable	+
CD34	+	+	+
Actin	—	—	+
MIB-1+ cells (%)	25	<1	25
Mutation analysis			
KIT exon 9	Wt	Wt	Wt
KIT exon 11	Tyr553_Lys558del	Tyr553_Lys558del	Tyr553_Lys558del
KIT exon 13	Wt	Wt	Wt
KIT exon 17	Wt	Wt	Mutations P1: c.2466T/A or G (Asn822Lys) P2: c.2453A/G (Lys818Arg) c.2467T/A (Tyr823Asp) c.2433T/A or G (silent mutation)
PDGFRA exon 12	Wt	Wt	Wt
PDGFRA exon 18	Wt	Wt	Wt

HPF, high power field; GIST, gastrointestinal stromal tumour; P1, mutation profile 1; P2, mutation profile 2; Wt, wild-type; +, present; —, absent.

*1HPF = 0.23 mm².

†Based on the NIH workshop held in April 2001.

2005 the lesion again showed slow progression, and additionally an adjacent nodule with increasing size appeared. In June 2005, AMG 706 therapy (125 mg/day) was started in a clinical trial, resulting in apparent growth arrest with tumour shrinkage (minor response) within the first 8 weeks, but after 3 months a radiological measurable increase in size occurred once again and both tumours started to fuse, subsequently presenting as a mass measuring 950 mm in January 2006, which was surgically removed because of small bowel obstruction. Additionally, multiple stable regressive peritoneal lesions were resected (table 1). Because of delayed wound healing, AMG 706 therapy was interrupted 4 weeks after surgery. At 11 weeks after surgery, the wound was completely healed and imatinib (800 mg/day) was administered again, which resulted in a lack of tumour growth (no change) until August 2006. The subsequently observed progression of some liver lesions was treated by administration of sunitinib (50 mg/day for 4 weeks, then 2 weeks off).

Mutation analysis of *KIT* exons 9, 11, 13 and 17 and *PDGFRA* exons 12 and 18 (table 1) of the primary tumour, as well as from progressive and responding lesions, were carried out by PCR amplification (Primus 25 Thermocycler, MWG, Ebersberg, Germany) followed by direct sequencing of both forward and reverse strands with an ABI 3130 Genetic Analyzer (Applied Biosystems, Foster City, California, USA).

The primary tumour, as well as the regressive and progressive metastases, showed a deletion of 18 bp in exon 11 of *KIT* (c.1656_1673del18), resulting in loss of Tyr553 to Lys558. In addition, we found multiple secondary exon 17 point mutations of *KIT* in seven specimens of the peritoneal

relapse. Three samples had one mutation (c.2466T→A or c.2466T→G) resulting in Asn822Lys (fig 1B). The other four showed a combination of three mutations (c.2433T→C, c.2453A→G, and c.2467T→A or G). Although the first mentioned mutation represents a silent mutation, the others lead to Lys818Arg and Tyr823Asp, respectively (fig 1C).

Secondary *KIT* mutations are the most common cause of KIT-dependent resistance. Point mutations of *KIT* exon 17 may occur in multiple form, and are found exclusively between aspartate-816 and tyrosine-823.^{6,7} The distal TK domain of KIT contains the kinase activation loop (A-loop), a hinged region that must assume a particular conformation for full kinase activation. A-loop mutations are generally resistant to imatinib, because of conformation changes resulting in an insufficient imatinib binding.^{3,8} The reported case suggests that exon 17 A-loop mutations are responsible for imatinib resistance and also for resistance to AMG 706. The preliminary reported activity of AMG 706 in patients with imatinib-resistant GIST⁹ may therefore be due to a response of tumours with secondary *KIT* mutations other than exon 17—for example, proximal TK domain mutations of *KIT* (exon 13 or 14).⁶ Hence, this patient might have benefited from a (combination) therapy with a more potent inhibitor of KIT activation loop mutants or by targeting downstream signalling molecules of KIT. Recently, Schittenhelm *et al*⁹ reported that dasatinib (BMS-354825) has potent activity against KIT A-loop mutations of GIST.

The complexity of imatinib resistance indicates the need for a precise understanding of the nature and timing of molecular events in resistant GIST. Detection of secondary *KIT* mutations may be the clue to guide and adapt

individual second-line therapies with alternative MKIs or agents against targets of KIT signalling.

Florian Grabellus

Department of Pathology and Neuropathology,
University Hospital of Essen, Essen, Germany

Peter Ebeling

Department of Internal Medicine (Cancer Research),
University Hospital of Essen, Essen, Germany

Karl Worm, Sien-Yi Sheu

Department of Pathology and Neuropathology,
University Hospital of Essen, Essen, Germany

Gerald Antoch

Department of Diagnostic and Interventional Radiology,
University Hospital of Essen, Essen, Germany

Andrea Frilling*

Department of General Surgery and Transplantation,
University Hospital of Essen, Essen, Germany

Kurt W Schmid*

Department of Pathology and Neuropathology,
University Hospital of Essen, Essen, Germany

Correspondence to: Dr F Grabellus, Department of
Pathology and Neuropathology, University Hospital
Essen, Hufelandstrasse 55, 45122 Essen, Germany;
florian.grabellus@uk-essen.de

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*Member of the West German Cancer Center Essen
(WTZE).

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