

Case Report

Gastrointestinal Stromal Tumour with Synchronous Bone Metastases: A Case Report and Literature Review

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Keywords

Bone metastases · Gastrointestinal stromal tumours · Imatinib · *KIT* · Tyrosine kinase inhibitors

Abstract

Gastrointestinal stromal tumours (GISTs) are mesenchymal tumours of the digestive tract, derived from Cajal interstitial cells. Bone metastases are very rare, and there is no consensus regarding their treatment. Here, we present the unusual case of a 66-year-old man with a gastric GIST with synchronous bone and liver metastases, fully documented at the pathological and molecular levels with a *KIT* exon 11 mutation. After 9 months of imatinib, the scanner showed a 33% partial response of target lesions. We also review the literature and describe the characteristics, treatment, and outcome of all cases previously reported.

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Introduction

Gastrointestinal stromal tumours (GISTs) are the most frequent mesenchymal tumours of the digestive tract, derived from the Cajal interstitial cells [1]. They are characterised by the presence of a gain-of-function mutation of the *KIT* or *PDGFRA* oncogenes [2]. Their incidence remains low, around 5–20 per million in different population-based studies, but their prevalence has been increasing during the last decade thanks to the therapeutic progress related to the use of tyrosine kinase inhibitors (TKIs; imatinib, sunitinib, and regorafenib) [3]. GISTs can occur anywhere along the gastrointestinal tract, but the most frequent anatomical locations are the stomach (60%), jejunum, and ileum (30%), followed by the duodenum (5%), colorectum (<5%), and more rarely the oesophagus (1–2%) and the omentum [4]. About 40% of patients with GISTs will develop metastases, most commonly in the liver (65%) or the peritoneum (50%), and less frequently in the lung [5].

Bone metastases of GISTs are a very rare event. In the small series in the literature, their proportion is low (<5%) when compared with all secondary locations [5–8]. Biologically, little is known about bone metastases of GISTs, as these metastatic sites are rarely biopsied. Particularly, it is still unknown whether bone metastases keep the same *KIT*/*PDGFRA* mutations as the primary tumour or acquire new mutations. Here, we present a case of gastric GIST with synchronous liver and bone metastases that were fully documented by pathological and molecular analysis. We also provide a review of all cases reported in the literature.

Case Report

A 66-year-old man, a retired oenologist with histories of asthma, non-insulin-dependent diabetes mellitus, and bilateral genu valgum consulted his general practitioner in November 2015 for asthenia lasting more than 6 months and left posterior intercostal pain. A thoraco-abdomino-pelvic CT scan (Fig. 1a) revealed a 16-cm abdominal tumour lesion above the pancreas, associated with several suspect hepatic nodules, and multiple osteolytic lesions of the spine and pelvis. An oesogastroduodenal endoscopy found a cardiac ulceration whose biopsy was negative. The patient was thus referred to our institution in January 2016.

Clinically, the patient's weight was stable, and his WHO performance status was equal to 0. The left posterior intercostal pain was imperfectly controlled by 3 g/day of paracetamol, and the patient had no digestive symptoms. Physical examination found a painless voluminous tumour of the left hypochondrium; neurological examination was normal. Laboratory tests were normal, with the exception of a grade 1 increase in γ GT. Gastric endoscopic ultrasound revealed a voluminous intra-abdominal 17-cm tumour, in contact with the stomach, mainly necrotic, as well as multiple suspect hepatic lesions, all enhanced after injection. Pathological analysis of endoscopic ultrasound-guided fine-needle aspiration biopsies of the gastric tumour and 1 hepatic lesion revealed an epithelioid-cell gastric tumour and a spindle-cell liver tumour (Fig. 2a, b). In both specimens, tumour cells were characterised by few mitoses (<5/50 high-power fields), no necrosis, and an immunohistochemistry (IHC) staining strongly positive for CD117 and DOG1, weakly positive for AML, and negative for desmin and PS100. The gastric tumour was CD34-negative, whereas the hepatic lesion was CD34-positive (Table 1). No *KIT* or *PDGFRA* mutation was found in the hepatic metastasis, whereas

the gastric tumour harboured a *KIT* exon 11 mutation (c.1676_1714del, p.Val559_Ile571del), further confirming the diagnosis of gastric GIST with hepatic metastasis.

A new staging was done in January 2016. CT scan showed an increase in size of both the abdominal tumour (19 cm) and the hepatic metastases as well as multiple osteolytic lesions involving notably the spine and the pelvis. ^{99m}Tc-labelled bone scintigraphy (Fig. 3) showed several bone uptakes located on the cervico-dorso-lumbar spine, sternum, scapula, pelvis (sacrum and left sacroiliac joint), rib cage (K5–K7), left femur, and right humerus. Magnetic resonance imaging of the spine (Fig. 1b, c) confirmed the vertebral bone lesions, and notably identified a T1 and T9 epiduritis and a mild medullar compression in C7, T1, and T9 without intramedullary lesion. A CT scan-guided biopsy of a lesion of the right posterior iliac bone confirmed the diagnosis of bone metastasis by a spindle-cell GIST showing the same morphological and IHC profile (Fig. 2c) as the hepatic metastasis, and the same *KIT* exon 11 mutation as the primary gastric tumour. The diagnosis of voluminous gastric GIST with synchronous liver and bone metastases was retained.

In February 2016, the patient started imatinib at 400 mg/day. No local treatment was initiated for the vertebral bone lesions because of the absence of any neurological symptoms, the expected efficacy of imatinib, and the control of dorsal pain by small doses of oxycodone. In May 2016, after 3 months of treatment, CT scan showed a regression of both the primary tumour (14 cm) and the hepatic and bone metastases. In August 2016, after 6 months of treatment, CT scan showed further regression of the primary tumour (12 cm) and the hepatic metastases (RECIST 1.1 partial response with 33% decrease in target lesions when compared to baseline) and stabilisation of bone metastases. In November 2016, after 9 months of imatinib, CT scan confirmed the partial response of the primary and hepatic lesions, which had become more necrotic, and stabilisation of the bone lesions. Currently, the patient continues imatinib, which is perfectly tolerated, without any digestive, bone, or neurological symptoms related to the tumour lesions.

Discussion

The classical metastatic locations of GISTs are the liver and peritoneum, whereas bone metastases are rare. We report here a case of gastric GIST with synchronous hepatic and bone metastases at diagnosis, documented in all sites with respect to histology and molecular biology. In epidemiologic terms, the true incidence of bone metastases remains unknown, but was reported to be between 3.2 and 5.5% in 4 retrospective series of 53–309 patients with metastatic GISTs [5–8]. To our knowledge, 37 cases, including the present case, have been reported in the English-language literature during the last decade, including 31 since 2011. The incidence seems to be growing thanks to the longer survival of metastatic patients due to the increasing use of TKIs, as observed in other cancers responding to medical therapies in their advanced stages. All 37 cases are summarised in Table 2 and Table 3.

Bone metastases mainly occurred in men ($n = 31/37$) and patients older than 50 years ($n = 29/37$). Like in our case, the location of the primary GIST was mainly the stomach ($n = 12/36$ informative cases), followed by the ileo-jejunum ($n = 10$), the rectum ($n = 8$), the duodenum ($n = 4$), the mesentery ($n = 1$), and the oesophagus ($n = 1$). Of note, rectal GISTs were overrepresented in that population of bone metastases, with 8/36 patients (22%), whereas

their frequency in overall GISTs is around 5% [4]. A likely explanation might be the haematogenous spread via the non-portal vein drainage from the rectum. Regarding the pathological characteristics, most of the primary tumours were spindle (11/20 informative cases) or mixed (7/20), and only 2 cases, including the present one, were purely epithelioid (2/20). Interestingly, contrary to our patient, most of the informative cases described a high number of mitoses of over 5/50 high-power fields ($n = 20/25$), suggestive of intermediate or high risk of relapse. All 31 informative cases showed KIT-positive IHC staining. The mutational status of the primary tumour was documented for only 5/37 cases and showed an exon 11 *KIT* mutation, which is the most frequent mutation found in GISTs before any treatment.

Regarding the bone metastases, they occurred in 23/31 informative cases during the follow-up of treated primary GISTs, within a median delay of 48 months (range, 4–120 months) after the diagnosis of the primary tumour. In 8 patients, including ours, the diagnoses of primary tumour and bone metastasis were synchronous, whereas 1 case corresponded to a prevalent bone metastasis. These rare observations suggest that bone metastasis can be the initial metastatic manifestation. Like in our patient, the bone metastases mainly occurred concomitantly with or after other metastatic sites like the liver ($n = 27$), peritoneum ($n = 8$), lung ($n = 4$), or soft tissues ($n = 2$), likely through haematogenous spread via vein drainage from these metastatic sites. Their topography was mainly the spine ($n = 17$), especially thoracic and lumbar, followed by the pelvis ($n = 11$), the ribs ($n = 11$), the femur ($n = 7$), and less frequently the shoulder ($n = 3$) or the humerus ($n = 2$). Interestingly, skull or face metastases were numerous ($n = 9$), including the temporal bone, clivus, or mandible, and led to complex diagnostic investigations and surgical procedures. The discovery of bone metastases was often based on clinical symptoms or was done incidentally during diagnostic or staging thoraco-abdomino-pelvic CT scan. The bone metastases in GIST patients are classically lytic and well-defined lesions [6]. With an expanded access to magnetic resonance imaging, it is likely that more bone metastases of GISTs will be diagnosed in the future. Furthermore, bone metastases have an intense fluorodeoxyglucose uptake; in case of response to TKIs, the standardised uptake value decreases very early after the beginning of treatment, which makes PET scanning an interesting option for follow-up [9]. Unfortunately, biopsy of bone metastases was done in only 17/37 cases. The pathological type was spindle cells in all 10 informative cases, similar to our case; all tested cases were KIT-positive by IHC, and only 3 cases were sequenced, showing *KIT* exon 11 mutation. Comparison between the primary tumour and the bone metastasis was possible for some pairs; the concordance was perfect for KIT IHC (12/12 pairs) and mutational analysis (2/2 pairs), suggesting clonal origin, whereas only 1 case (ours) showed discordant pathological type, with epithelioid type in the primary and spindle cells in the metastasis. The absence of mutation documented in the liver metastasis in our patient may reflect intratumour heterogeneity [10]. Because of the scarcity of data, it remains unclear whether a particular mutational status is associated with these unusual metastases. Efforts should be made to systematically re-biopsy such patients for mutational analyses.

The systemic treatment was based on TKIs, mainly imatinib ($n = 22$) used in 1st line, sunitinib used in 2nd line ($n = 8$), and less frequently nilotinib ($n = 2$) or sorafenib ($n = 1$), with several “stop-and-go” attitudes due to toxicity or long-term disease stabilisation, although not recommended today [11]. Regarding the local treatment of bone metastases, the literature review showed that surgery ($n = 8$) was realised for oligometastatic patients for

different skeletal localisations, or patients with functional impairment, sometimes associated with graft or prosthesis. Some of these patients who underwent complex surgical bone resections with R0 margins benefitted from long-term disease-free survival [12, 13]. Palliative radiotherapy was delivered to 11 patients. Even if GISTs, like soft tissue sarcomas, are often considered radio-resistant, external beam radiotherapy was associated with a significant improvement of bone pain in most of the cases. Interestingly, 1 case report described the concomitant use of imatinib during radiotherapy, with good tolerance [14]. Bisphosphonates were used in 5 patients (zoledronic acid), and 1 case of jaw osteonecrosis was described after imatinib and zoledronic combination [15]. The clinical outcome after the diagnosis of bone metastasis was available in 26/37 patients: 9 patients died after a median time of 11 months (range, 1–103), whereas 17 remained alive with a median follow-up of 19 months (range, 2–187). Thus, although bone metastases occurred preferentially in high-risk metastatic GISTs, their prognosis was not particularly dreadful.

In conclusion, bone metastases of GIST are rare but likely underdiagnosed, and their frequency is increasing because of the improvement of imaging techniques and of patients' survival. Physicians in charge of GIST patients should be aware of this unusual metastatic site during the prolonged natural history of GISTs in the TKI era. We recommend attention notably in case of GISTs >5 cm, with a high mitotic index or with a rectal location. If bone metastasis remains a palliative disease, multiple therapeutics options (like surgery, radiotherapy, TKIs, and bisphosphonates) are available to improve symptoms and prolong survival.

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Statement of Ethics

We thank the patient who kindly gave his informed consent. The study was approved by our institutional review board.

Disclosure Statement

The authors declare no conflict of interest.

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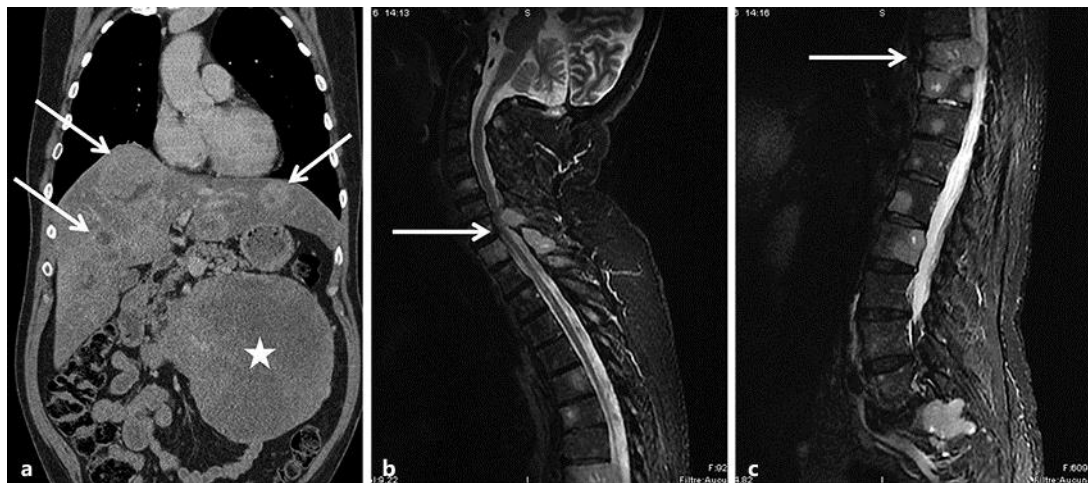


Fig. 1. Gastrointestinal stromal tumour (GIST) with liver and bone metastases: radiological aspects. **a** Thoraco-abdomino-pelvic CT scan in the coronal plane showing the huge gastric GIST (star) and multiple bilateral liver metastases (arrows). **b, c** Magnetic resonance imaging of the spine in the sagittal plane, T2 sequence, showing the multiple bone vertebral lesions (notably in C7, T1, and T9), the sacrum, and a T1 and T9 epiduritis (arrows).

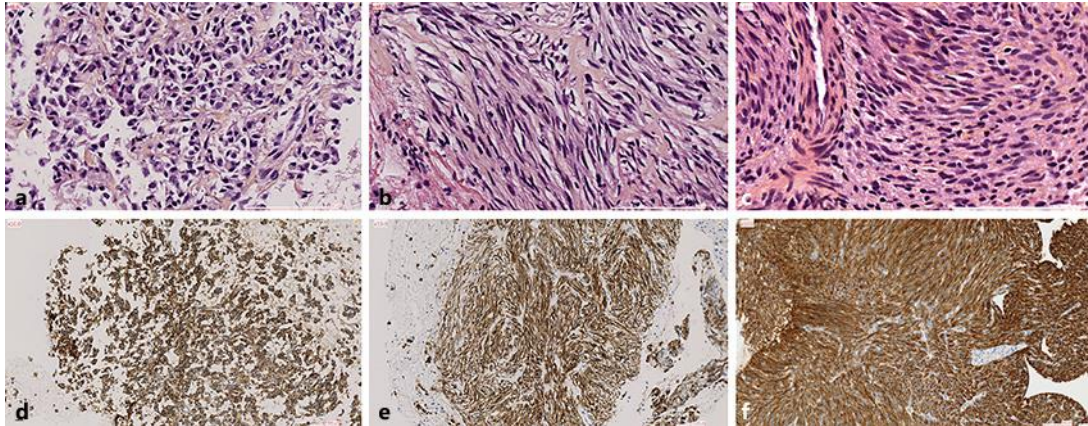


Fig. 2. Gastrointestinal stromal tumour (GIST) with liver and bone metastases: pathological aspects. **a–c** HES microphotographies showing 2 distinctive morphological patterns of GIST: epithelioid cells on gastric biopsy (**a**) as well as spindle cells on hepatic (**b**) and bone (**c**) metastases. **d–f** Immunohistochemistry staining showing expression by tumour cells (epithelioid and spindle cells) of CD117/KIT (**d–f**) and DOG1 (**e**).

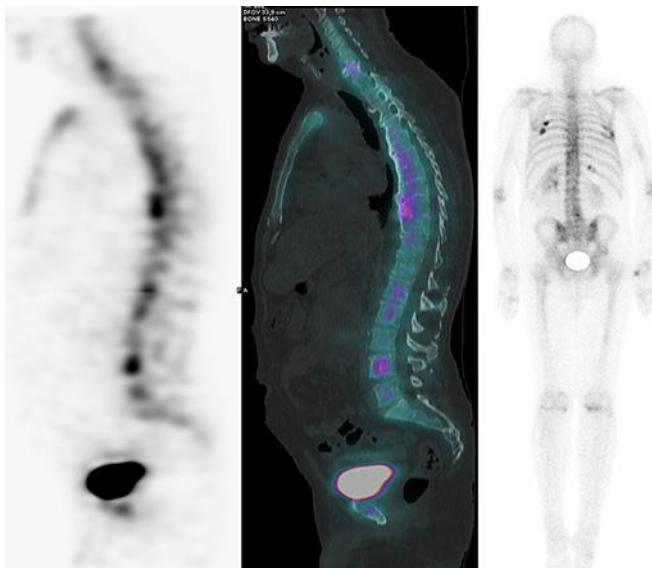


Fig. 3. ^{99m}Tc -labelled bone scintigraphy showing multiple lesions (bone uptakes) of the cervico-dorso-lumbar spine, the pelvis, the ribs, and the clavicles.

Table 1. Pathological and molecular characteristics of the primary tumour and the metastases

Characteristics	Gastric tumour	Liver metastasis	Bone metastasis
Morphology	epithelioid	spindle cells	spindle cells
Mitotic index	<5/50 HPFs	<5/50 HPFs	<5/50 HPFs
IHC staining	CD34– CD117/KIT+ DOG1+	CD34+ CD117/KIT+ DOG1+	CD34+ CD117/KIT+ DOG1+
<i>KIT</i> mutational status	exon 11 c.1676_1714del	wild type	exon 11 c.1676_1714del
<i>PDGFRA</i> mutational status	wild type	wild type	wild type

HPFs, high-power fields; IHC, immunohistochemistry.

Table 2. Literature review of 37 patients with primary GIST and bone metastases: characteristics of primary GIST

Ref. No.	Sex, age	Site	Pathological type	Mitosis (/HPFs)	KIT IHC	Mutational status
Our case	M, 66	stomach	epithelioid	<5/50	positive	<i>KIT</i> exon 11 (c.1676_1714del)
16	M, 56	jejunum, ileum	epithelioid + spindle	12/50	positive	NA
16	M, 70	ileum	epithelioid + spindle	20/50	positive	NA
12	M, 78	stomach	NA	NA	NA	NA
12	M, 41	rectum	NA	NA	positive	NA
17	M, 76	rectum	spindle	20/50	NA	NA
17	M, 43	jejunum	spindle	19/50	NA	NA
17	M, 50	rectum	spindle	15/50	NA	NA
17	M, 50	jejunum	spindle	15/50	NA	NA
18	M, 62	stomach	epithelioid + spindle	7/50	positive	NA
19	M, 58	jejunum	spindle	low	positive	NA
6	M, 49	stomach	NA	27/50	positive	NA
6	M, 71	rectum	NA	41/50	positive	NA
6	F, 52	stomach	NA	40/50	positive	NA
6	M, 48	stomach	NA	12/50	positive	NA
6	M, 51	stomach	NA	22/50	positive	NA
6	M, 60	jejunum	NA	6/50	positive	NA
20	M, 54	rectum	spindle	NA	positive	NA
13	M, 37	duodenum	NA	NA	positive	NA
21	F, 57	jejunum	spindle	<5/50	positive	NA
22	M, 83	rectum	NA	NA	positive	NA
23	M, 55	mesentery	epithelioid + spindle	10–15/50	positive	NA
24	M, 70	stomach	spindle	21/50	positive	NA
25	M, 26	duodenum	epithelioid	<5/50	positive	NA
15	M, 62	ileum	NA	NA	NA	NA
15	F, 82	stomach	NA	16/50	positive	<i>KIT</i> exon 11 (c.1696_1718del)
15	F, 54	duodenum	NA	>5/50	positive	<i>KIT</i> exon 11 T>A 69429
26	M, 26	duodenum	NA	NA	positive	NA
27	F, 48	ileum	NA	>10/50	positive	<i>KIT</i> exon 11 (c.1657_1674del)
28	M, 62	stomach	spindle	NA	positive	<i>KIT</i> exon 11 (codons 557/558)
29	M, 38	stomach	spindle	>5/50	positive	NA
30	M, 53	oesophagus	NA	5–10/50	positive	NA
14	M, 57	rectum	spindle	NA	positive	NA
31	M, 65	rectum	spindle	NA	positive	NA
9	M, 73	stomach	epithelioid + spindle	NA	positive	NA
32	F, 50	NA	NA	NA	NA	NA
33	M, 68	ileum	epithelioid + spindle	<5/50	positive	NA

GIST, gastrointestinal stromal tumour; HPFs, high-power fields; IHC, immunohistochemistry; NA, not available.

Table 3. Literature review of 37 patients with primary GIST and bone metastases: characteristics of bone metastases

Ref. No.	Sex, age	Chronology ^a	Site	Patho-logical type	KIT IHC	Mutational status	Other metastasis ^b	Treatment	Outcome ^c
Our case	M, 66	synchronous	spine, pelvis	spindle	pos	<i>KIT</i> exon 11 (c.1676_1714del)	L	I	alive: 9 m
16	M, 56	4 m	spine (L1–L3), femur	NA (NB)	NA	NA	L	I+RT+Bi	death: 2 m
16	M, 70	5 m	spine (L2)	NA (NB)	NA	NA	L	I+RT+Bi	death: 1.5 m
12	M, 78	60 m	femur	spindle	pos	NA	no	Surg (prosthesis)+I	alive: 48 m
12	M, 41	84 m	rib (K4)	spindle	pos	NA	no	Surg+I	alive: 120 m
17	M, 76	49 m	spine (thoracic)	NA	NA	NA	no	I	death: 103 m
17	M, 43	81 m	spine (cervical/lumbar)	NA (NB)	NA	NA	L	Sun	alive: NA
17	M, 50	108 m	spine (cervical), rib	NA (NB)	NA	NA	L	I	alive: 187 m
17	M, 50	104 m	spine (thoracic/lumbar)	NA (NB)	NA	NA	L, P	no	death: 1 m
18	M, 62	6 m	skull, rib, sacroiliac	NA (NB)	NA	NA	no	I	alive: NA
19	M, 58	28 m	sternoclavicular, T1–T10	spindle	pos	NA	L	I+RT	alive: 19 m
6	M, 49	NA		NA (NB)	NA	NA	L, S, P, LN, ST	NA	NA
6	M, 71	NA	spine (n = 4)	NA (NB)	NA	NA	P, L	NA	NA
6	F, 52	NA	pelvis (n = 4)	NA (NB)	NA	NA	P, L	NA	NA
6	M, 48	NA	ribs (n = 4)	NA (NB)	NA	NA	P, L	NA	NA
6	M, 51	NA	femur (n = 3)	NA (NB)	NA	NA	L, P, ST	NA	NA
6	M, 60	NA		NA (NB)	NA	NA	L	NA	NA
20	M, 54	120 m	scapula	spindle	pos	NA	L	Surg+Sun	alive: 24 m
13	M, 37	36 m	spine (thoracic/lumbar)	NA	pos	NA	L	Surg+I+RT	alive: 24 m
21	F, 57	49 m	humerus	spindle	pos	NA	L, Pl	Sun+RT	death: 7 m
22	M, 83	12 m	hip/femur	NA	NA	NA	L	I+RT+Bi	alive: NA
23	M, 55	36 m	skull, rib, spine (T9–T10)	NA (NB)	NA	NA	L	I	alive: 6 m
24	M, 70	synchronous	clivus, ribs	NA	pos	NA	L, Lg	I	alive: 2 m
25	M, 26	72 m	temporal bone/orbit	NA	pos	NA	L	Surg+RT+Nilo	NA
15	M, 62	synchronous	spine, ribs, pelvis	NA (NB)	NA	NA	L	I/Sun+RT+Bi	death: 34 m
15	F, 82	synchronous	spine, pelvis	NA	NA	NA	L	I/Sun+Bi	alive: 44 m
15	F, 54	84 m	spine, pelvis, ribs	NA (NB)	NA	NA	L	Sun	death: 16 m
26	M, 26	72 m	skull (frontotemporal)	NA (NB)	NA	NA	L	Surg+I/Sun+RT	alive: 4 m
27	F, 48	46 m	clavicle	NA (NB)	NA	NA	P	Soraf+RT	alive: 12 m
28	M, 62	28 m	femur	spindle	pos	<i>KIT</i> exon 11 (codons 557/558)	no	Surg (graft)+I	alive: 12 m
29	M, 38	38 m	skull (frontoparietal)	spindle	pos	NA	L, LN	NA	NA
30	M, 53	synchronous	humerus	NA (NB)	NA	NA	Lg	I	alive: NA
14	M, 57	synchronous	clivus, temporal bone	spindle	pos	NA	L, Lg	I/Sun/Nilo+RT	death: 17 m
31	M, 65	synchronous	frontoparietal skull	NA (NB)	NA	NA	L	I	NA
9	M, 73	6 m	spine (T6), pelvis, clavicle	NA (NB)	NA	NA	L, P, S, PC	I	NA
32	F, 50	prevalent	sacrum	spindle	pos	<i>KIT</i> exon 11 (del 15 bp, position 100)	no	Surg	NA
33	M, 68	synchronous	mandible	NA	pos	NA	no	I	death: 11 m

Bi, bisphosphonates; I, imatinib; L, liver; Lg, lung; LN, lymph node; m, month(s); NA, not available; NB, no biopsy; Nilo, nilotinib; P, peritoneum; PC, pancreas; Pl, pleural; pos, positive; RT, radiotherapy; S, spleen; Soraf, sorafenib; ST, soft tissue; Sun, sunitinib; Surg, surgery. ^a Time in months between the diagnosis of primary gastrointestinal stromal tumour and bone metastasis. ^b Other metastasis before or at the diagnosis of bone metastasis. ^c Outcome in months from the diagnosis of bone metastasis.