American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2019; 20: 1942-1948
DOI: 10.12659/AJCR.918606

Received: 2019.07.10
Accepted: 2019.10.08
Published: 2019.12.26

Long-Term Survival After Multidisciplinary Treatment Including Surgery for Metachronous Metastases of Small Intestinal Gastrointestinal Stromal Tumors after Curative Resection: A Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 56-year-old
Final Diagnosis: Metachronous metastases of small intestinal gastrointestinal stromal tumors
Symptoms: Abdominal and/or epigastric pain
Medication: —
Clinical Procedure: Operation • chemotharapy
Specialty: Gastroenterology and Hepatology

Objective: Rare co-existance of disease or pathology

Background: Currently, 3 molecular targeted drugs are available for the treatment of unresectable and recurrent gastrointestinal stromal tumors (GISTs), and result in improved prognoses and rare occurrence of bone metastases. However, there is no established treatment guideline for bone metastases of GIST.

Case Report: The patient was a 56-year-old male who was diagnosed with leiomyosarcoma in 1997. Partial resection of the small bowel was performed. As part of post-operative follow-up in 2004, a computed tomography scan showed metastatic lesions in the liver and the right femoral neck. Accordingly, partial hepatectomy was performed, followed by artificial femoral head replacement. In 2006, bone metastases were detected in the sternum, cervical and thoracic vertebra, and the right upper arm; therefore, the patient was subjected to radiotherapy. However, further histopathological examination revealed positive findings for CD34+ and KIT cells, prompting a diagnosis of GIST. Imatinib was started. The disease remained stable. However, in 2010, metastasis to the right ilium was detected, after which there was an increase in metastatic lesions in the thoracic vertebra, prompting a diagnosis of progressive disease. Thus, treatment with sunitinib was initiated. In 2012, the patient experienced spinal paralysis due to metastasis in the eighth thoracic vertebra. In 2013, metastases in the right ilium, lungs, and liver were detected. In 2014, the patient died.

Conclusions: Multidisciplinary treatment via radiotherapy and surgery for GIST with bone metastases indicates the possibility of extending the overall survival further.

MeSH Keywords: Bone Diseases • Gastrointestinal Stromal Tumors • Liver Diseases • Piezosurgery

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/918606

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Background

Until June 2002, there was no effective drug therapy for gastrointestinal stromal tumors (GISTs), and surgery was the main treatment modality. Currently, there are 3 available drugs for the management of unresectable and recurrent GIST [1–3]; thus, patients' prognoses have improved. The extension of overall survival is accompanied by an increase in the number of reports of symptoms associated with bone metastasis. As bone metastasis can increase the risk of pathological fractures and impair the quality of life, its treatment is becoming an increasingly important issue. However, very few studies have reported on multidisciplinary treatment including surgery for GIST with bone metastasis. To our knowledge, this is the first such case; thus, we present it here along with a discussion.

Case Report

Medical history

A 56-year-old male complained of severe epigastric pain in August 1997, for which a careful examination was conducted, which revealed a 3 cm wide tumor of the jejunum. Accordingly, in September 1997, partial resection of the jejunum was performed. Histopathological examination revealed a leiomyosarcoma; therefore, a follow-up of the patient was conducted.

Progress

In June 2004, the patient underwent a regular computed tomography scan as part of the treatment-free follow-up. The scan detected metastasis in the S5 segment of the liver and the right femoral neck (Figures 1, 2). In August of the same year, the patient underwent partial hepatectomy. Artificial femoral head replacement was then performed in October of the same year due to the possibility of a pathological fracture secondary to metastasis in the right femoral neck. Macroscopic examination of the jejunal tumor revealed a 3×2 cm well-circumscribed white-yellow tumor below the submucosal layer; the hepatic tumor was a 2×1.5 cm well-circumscribed white-yellow nodule; and the femoral tumor was a 6.5×3 cm well-circumscribed white-yellow nodule (Figure 3). In May 2006, bone metastases were detected in the sternum, cervical and thoracic vertebrae, and the right upper arm; therefore, the patient was subjected to radiotherapy. In 2006, the patient was suspected to have a GIST, and not a leiomyosarcoma. Subsequently, further histopathologic examination showed positive findings for CD34+ and KIT cells in the initial metastatic site, liver, and right femoral neck, prompting a diagnosis of GIST (14.5/50 HPF, high-risk) (Figures 4, 5). Histologically, the various metastatic tumors were similar; they appeared as fascicles of spindle cells. In addition, immunohistochemically, the tumor cells were found to express c-kit and DOG-1. Thereafter, the patient was diagnosed with GIST. Thus, the initiation of chemotherapy was delayed.

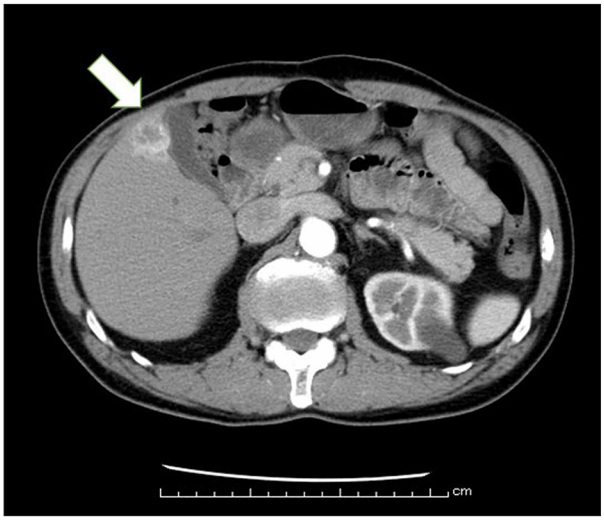

Figure 1. Abdominal computed tomography scan showing liver metastasis.

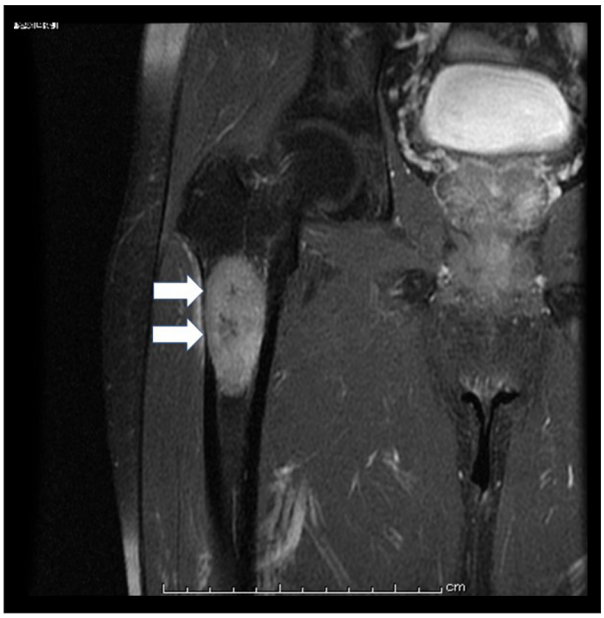

Figure 2. Right femoral neck with metastasis.

In July of the same year, the patient commenced a treatment course of orally administered imatinib at 400 mg/day. The imatinib reduced metastasis in the sternum, but stable bone disease continued in the other metastatic sites. In June 2010, metastasis to the right ilium was detected, and in September, metastasis in the thoracic vertebra increased, prompting a diagnosis of progressive disease. In October 2010, the patient was commenced on a course of sunitinib at 50 mg/day. Owing to the occurrence of watery diarrhea, the dose was reduced to 37.5 mg/day, but stable bone disease persisted. In June 2012,

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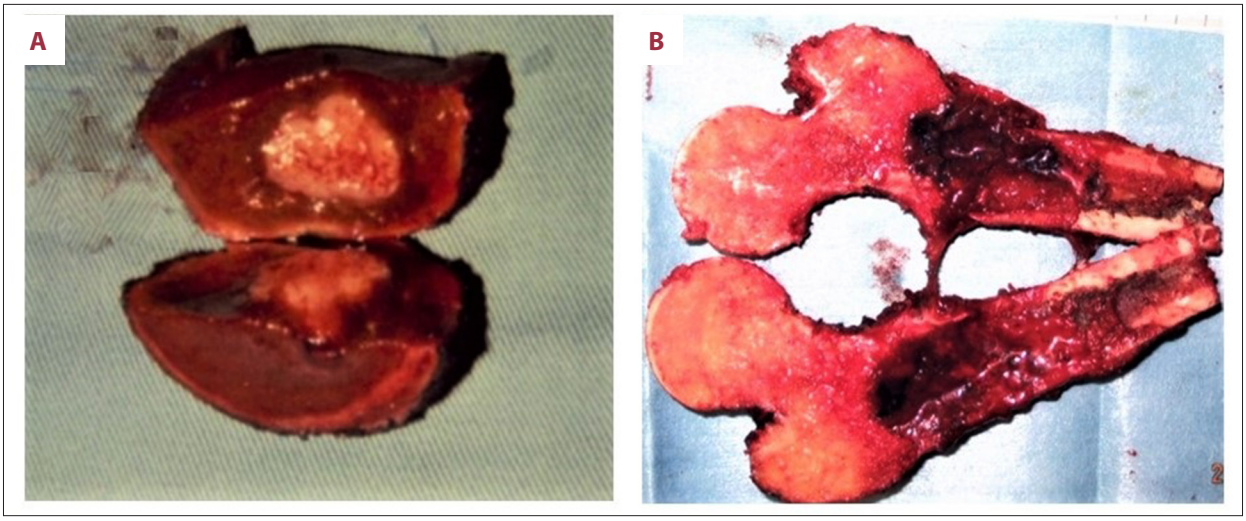

Figure 3. Macroscopic findings of metastases. (**A**) Liver, (**B**) right femur neck.

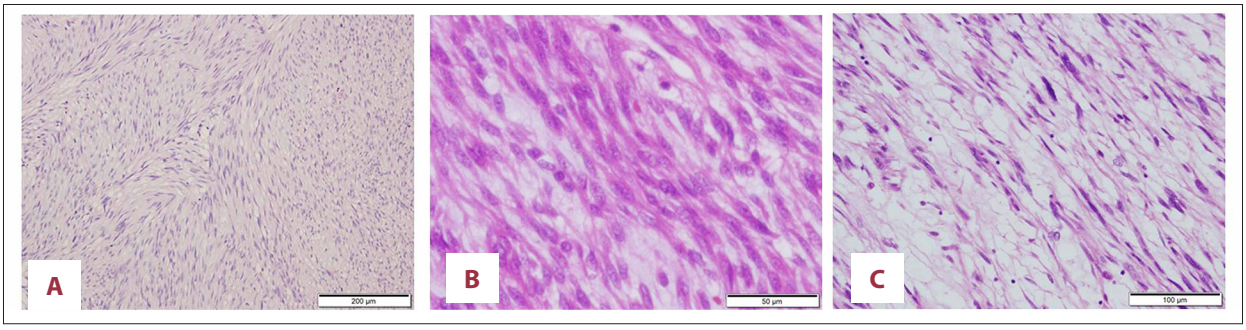

Figure 4. Histological appearance of lesions obtained in the (**A**) jejunum, bar=200 µm, (**B**) liver, bar=100 mm, and (**C**) femur, bar=100 mm.

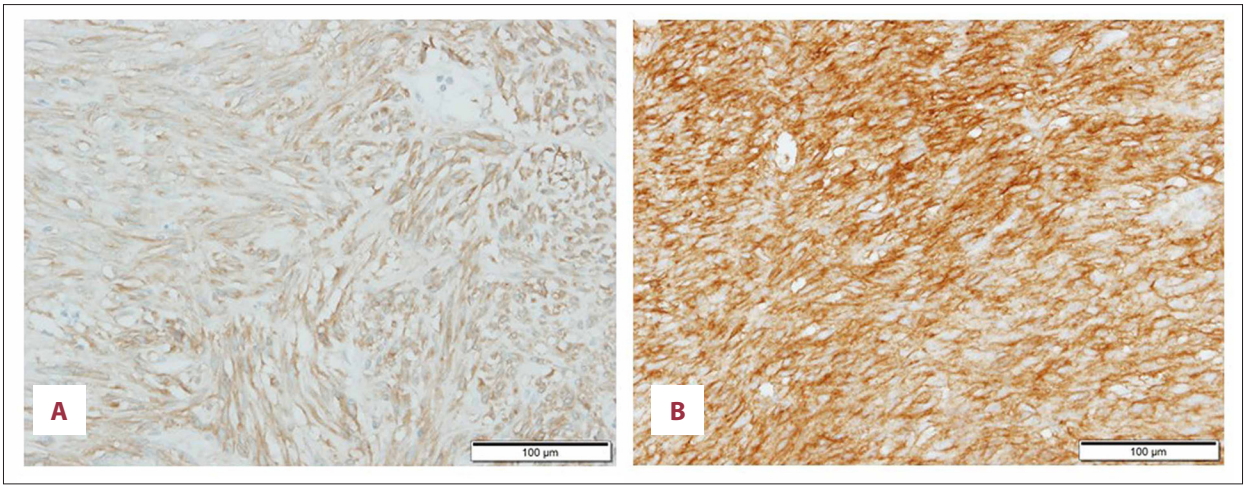

Figure 5. Immunohistological images of samples obtained in the (**A**) jejunum, c-kit bar=100 mm and (**B**) liver, DOG-1 bar=100 mm.

the patient experienced spinal paralysis due to metastasis in the eighth thoracic vertebra, prompting the onset of a neurological disorder, which made it difficult for the patient to walk. The patient underwent radiotherapy (37.5 Gy for 15 sessions) due to a possible risk of complete paralysis when undergoing decompression surgery. At this time, regorafenib had not yet been approved; therefore, the sunitinib regimen was administered orally. Metastasis in the right ilium was detected in February 2013; thus, the patient was subjected to another course of radiotherapy (37.5 Gy for 15 sessions). In April 2013,

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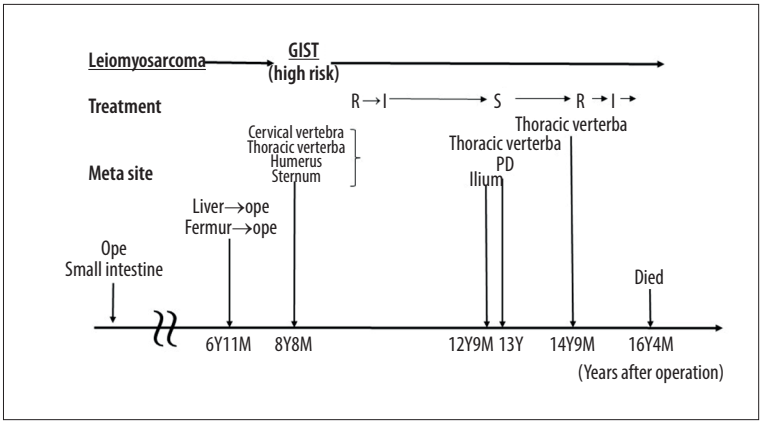

Figure 6. Treatment course. R – radiation; I – imantinib; S – sunitinib; GIST – gastrointestinal stromal tumor.

the patient was again started on orally administered imatinib; however, metastases to the lungs and liver were detected. Accordingly, in September 2013, a best supportive care policy was adopted. In January 2014, the patient died (Figure 6).

Genetic test

Verbal informed consent was obtained from the next of kin as the patient had died. Total RNA was extracted from a formalin-fixed tumor sample, and polymerase chain reaction was performed using a method and primers previously reported for the amplification of human KIT cDNA [4]. The entire coding region for KIT was sequenced directly as described in the previous publication. Molecular analysis of the small intestine and liver metastasis showed a *c-kit* mutation at exon 11 (Leu576Pro, substitution-missense). However, the bone metastasis site could not be identified because the polymerase chain reaction amplification failed due to DNA recovery failure. Genetic testing was performed at the Department of Surgical Pathology, Hyogo College of Medicine, and approved by the Ethics Committee of Tokyo Medical University Hachioji Medical Center (H-206).

Discussion

The incidence rate of bone metastasis among patients with GIST ranges from 3.2–6% [5,6]. However, this has a tendency to increase alongside advances in drug therapy. The frequency of bone metastases, which has not been observed so far, has increased because the prognosis has been improved by advances in drug therapy. Positron emission tomography scans are an effective means of diagnosing bone metastasis and determining therapeutic efficacy; the standardized uptake value would decrease if treatment causes a reduction [6,7]. A great majority of bone metastases are from primary tumors in the lower rectum and esophagus, which are known to enter the greater part of the circulatory system into diverse metastatic trajectories [8,9]. Furthermore, bone metastasis may occur in cases of extragastric primary tumor and are, thus, highly likely to recur, those in which liver metastasis occurs from the outset, and those involving long-term survival [10,11]. In the case reported here, the primary tumor was in the small intestine and bone metastasis was detected during the patient's long-term survival. Accordingly, multidisciplinary treatment was continued. Ultimately, bone metastases occurred at 6 sites. Regarding drug therapy for bone metastasis, imatinib therapy is associated with 1-year and 2-year survival rates of 92% and 78%, respectively [1,12] and is reportedly effective when used concomitantly with zoledronic acid [13]. Surgery should be performed to remove resectable tumors and to prevent the deterioration of quality of life due to pathological fractures or spinal cord injury [14,15]. Heinrich et al. reported that radiotherapy was ineffective due to its poor response [16]; however, other authors reported that it is a valid treatment option as it is effective as desensitization therapy [17,18]. Conversely, a combination of radiation and drug therapy yielded a complete response in some cases [19]. Therefore, radiotherapy can be considered an effective treatment option in cases in which surgery is not possible, but more data are needed to demonstrate its efficacy.

Applying the search terms "GIST" and "bone metastasis" yielded 35 papers and 54 case reports in PubMed and content from the Japan Medical Abstracts Society. Bone metastasis was treated by surgery in 13 of these cases [14,15,20–28] and our case (Table 1). Of these cases, 10 were men, and the median age at the time of disease onset was 57 years (range, 26–78 years). The median duration to first metastasis was 72 months (12–468 months). Given that metastasis presents relatively late in life, long-term follow-up is required. The primary site was the rectum in 4 cases, the stomach in 3 cases, the duodenum in 3 cases, the small intestine in 2 case, and the esophagus in 1 case. GIST that originates in the lower digestive tract (small and large intestines) has a higher grade of malignancy than GIST that originates in the upper digestive tract (esophagus and stomach). This observation is further validated by the present case in which the rectum accounted for

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Table 1. Gastrointestinal stromal tumors with bone metastasis treated by surgery.

Case	Age	Sex	Primary site	Primary resection	First metastatic site	Duration to first metastasis (month)	First bone metastatic site	Duration to bone metastasis (month)	Reference
1	67	M	Rectum	Yes	Liver	29	Rib, scapula	79	[20]
2	26	M	Duodenum	No	Liver	0	Skull	60	[21]
3	57	F	Small Intestine	Yes	Liver	14	Humerus	49	[22]
4	26	M	Duodenum	No	Liver	0	Skull	72	[23]
5	62	M	Stomach	Yes	Femur	23	Femur	23	[14]
6	67	F	Stomach	Yes	Vertebra	12	Vertebra	12	[24]
7	70	F	Rectum	Yes	Femur	471	Femur	468	[25]
8	57	M	Esophagus	Yes	Humerus	101	Humerus	101	[26]
9	54	M	Rectum	Yes	Scapula	108	Scapula	108	[27]
10	37	M	Duodenum	Yes	Liver, vertebra	36	Vertebra	36	[28]
11	78	M	Stomach	Yes	Femur	60	Femur	60	[15]
12	41	M	Rectum	Yes	Local	84	Rib	120	[15]
13	56	M	Small Intestine	Yes	Liver, femur	81	Femur	81	Our case

Case	Another site metastasis	Liver/ bone metastasis	Imatinib therapy	Sunitinib therapy	OS (month)	Duration after bone metastasis (month)	Dead or alive	Reference
1	Liver	Liver first	Yes	No	91	12	Alive	[20]
2	Liver	Liver first	Yes	Yes	72	12	Alive	[21]
3	Liver, Lung	Liver first	Yes	Yes	55	6	Dead	[22]
4	Liver, lung	Liver first	Yes	Yes	72	1	Alive	[23]
5	None		Yes	No	35	12	Alive	[14]
6	None		Yes	No	24	12	Alive	[24]
7	Local		Yes	No	480	9	Alive	[25]
8	Lung		Yes	No	126	25	Alive	[26]
9	Liver	Liver first	Yes	Yes	108	6	Alive	[27]
10	Liver	Synchronous	Yes	No	60	24	Alive	[28]
11	None		Yes	No	108	48	Alive	[15]
12	Liver, kidney	Bone first	Yes	No	204	84	Alive	[15]
13	Liver	Synchronous	Yes	Yes	196	115	Dead	Our case

M – Male; F – Female; OS – overall survival.

a large proportion of bone metastases. In all 13 cases, bone metastasis was metachronous. The first site of bone metastasis was the femur in 4 cases and the vertebra, humerus, rib, skull, and scapula in 2 cases each. Primary resection was performed in 11 cases (synchronous hepatic metastasis occurred in 1 of these cases). Primary resection was not performed in the 2 cases with GISTs of the duodenum, due to synchronous hepatic metastasis. Metastasis was limited to only the bone in 11 cases, and synchronous bone and liver metastasis occurred in 2 cases. Surgery as local treatment and simultaneous resection at multiple sites might be an effective multidisciplinary treatment; however, as bone metastasis is generally a constitutional disease, drug therapy is probably more effective than surgery. In 8 cases (62%), distant metastasis occurred

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at a site other than the bone, suggesting that GIST presented as a constitutional disease. Hepatic metastasis occurred in all of these 8 cases. The liver was the first site of metastasis in 5 cases (38%) i.e., the majority of the 8 cases. Of the 3 remaining cases of hepatic metastasis, synchronous metastasis occurred in 2 cases (15%) and first occurred in the bone in 1 case (7%). Both cases of synchronous hepatic metastasis underwent simultaneous hepatic metastasis resection. Vital prognosis of the metachronous cases after metastasis to both the liver and bone occurred but did not significantly differ from the synchronous cases (P=0.52). Among the 5 cases (38%) in which hepatic metastasis did not occur, 4 cases (31%) were cases of primary occurrence and recurrence was limited to the bone, and in 1 case (7%), bone metastasis occurred after local recurrence and 8 surgical operations. The sites of metastasis were the lung and kidney in 3 cases (23%) and 1 case (7%), respectively, of distant metastasis to sites other than the liver. As no peritoneal metastasis occurred in these cases, these may be GIST cases characterized by malignancy with hematogenous metastasis.

Regarding treatment after primary resection, 5 cases were treated with imatinib, 2 cases with sunitinib, 1 case with nilotinib, 1 case with chemotherapy (no details provided), and 4 cases were left untreated. Further, in 3 cases (23%), metastasis to another site occurred within 2 years of bone metastasis resection. The median vital prognosis for cases in which surgery for bone metastasis was not performed was 3 years (range, 3 months to 6 years) [6], and the prognosis after bone metastasis was poor [29]. However, looking at the 13 cases investigated in this report, the 5-year survival rate after surgery for bone metastasis was favorable (91.7%). Thus, for cases of bone metastasis in 2 resectable sites, surgical treatment is recommended via a multidisciplinary approach.

The efficacy of drug therapy varies depending on the type of mutation. Heinrich et al. reported that primary imatinib therapy yielded a better response in the *KIT* exon 11-mutant genotype than in the *KIT* exon 9-mutant and wild-type genotypes (complete response/partial response, 71.7% versus 44.4% [P=0.007] and 44.6% [P=0.0002], respectively), as well as favorable time to tumor progression (median, 24.7 versus 16.7 months and 12.8 months, respectively) and overall survival (median, 60.0 versus 38.4 months and 49.0 months, respectively) [30]. Sunitinib as secondary therapy prolongs the survival of cases of imatinib-resistant GIST. According to Demetri et al., the median time to tumor progression was 27.3 weeks (95% confidence interval: 16.0–32.1) among patients receiving sunitinib and 6.4 weeks (95% CI: 4.4–10.0) among those on placebo (hazard ratio 0.33, P<0.0001) [2]. Sunitinib exhibited a better life-prolonging effect among exon 9-mutant cases. This implies that exon 11-mutant cases, among whom imatinib exhibits strong efficacy, require a longer course of imatinib treatment, thereby increasing the chances of secondary mutations occurring in the ATP binding pocket of the KIT tyrosine kinase region, the imatinib binding site [31]. According to Hopkins et al., imatinib inhibits the aberrant tyrosine kinase, and imatinib therapy in metastatic disease has shown significant clinical benefits. However, resistance typically develops within 2 years, and patients require further therapy [31]. However, in cases in which GIST was diagnosed histologically and no neoadjuvant/adjuvant therapy was performed, *KIT* (versus *PDGFRA* or wild-type) was an independent predictor of poor event-free survival, but its effect size was smaller than that of the existing prognostic factors (such as mitotic index, tumor diameter, and site). In addition, Joensuu et al. performed the same analysis but with exon 9-, 11-, 13-, and 17-mutants as covariates and found that each exon was a significant independent predictor of recurrence-free survival [32]. While the type of mutation can predict treatment efficacy, it does not seem to have an impact on progression-free survival. Also, an issue here is that currently, it is not possible to conduct a comprehensive examination of all related genes under health insurance-based treatment. Therefore, there is a need to examine how the efficacy and prognosis of drug treatment can be improved based on differences in the mutation type at the time of recurrence/unresectability.

In the case presented here, metastases to the liver and bone occurred 6 years and 9 months after primary resection; therefore, radical resection was performed. One year and 7 months after resecting the recurrent liver and bone metastasis, the patient experienced multiple bone metastases and was, thus, diagnosed with high-risk GIST. Long-term control of his condition was achieved using imatinib as the primary treatment and sunitinib as the secondary treatment; the courses of both treatments were 3 years and 9 months and 1 year and 8 months, respectively. These drug treatments were satisfactorily efficacious against the bone metastasis. GIST with bone metastasis is a constitutional disease; however, for sing metastasis, such as the primary bone metastasis in the present case, prognosis can probably be improved further by performing complete resection and maintaining the patient on drug therapy thereafter. Given the present circumstances, it is important to treat bone metastasis via three approaches: drug therapy, surgery as local treatment, and radiotherapy to prevent pathological fractures and control pain. In the case presented here, even after recurrence, the patient survived for 9 years and 7 months. To our knowledge, this is the first report of a case in which surgery was performed on the primary GIST site and the hepatic and bone metastasis sites and in which drug therapy comprising imatinib and sunitinib was administered. Using such a multidisciplinary treatment, the patient survived for 16 years and 4 months after primary resection and 9 years and 7 months after recurrence.

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Conclusions

Herein, we have described a case in which long-term survival was achieved using aggressive multidisciplinary treatment for GIST. Advances in drug treatments have led to prolonged vital prognosis of unresectable/recurrent GISTs, and thereby an increase in bone metastasis rates. By examining the optimal timing and appropriateness of radiotherapy and surgery within a multidisciplinary treatment framework, it should be possible to further prolong overall survival. Mutation scanning is also essential as it provides useful information for drug therapy. It is necessary to accumulate more cases with further examination to establish an appropriate treatment plan for bone metastasis of GIST.

Acknowledgements

We deeply appreciate the many orthopedic doctors who operated on this patient with bone metastasis of GIST. We would also like to thank Editage (*www.editage.com*) for English language editing.

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