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Case Report

Surgical management of vertebral metastatic gastrointestinal stromal tumor: Case illustration, literature review, and pooled analysis

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ABSTRACT

Background: Gastrointestinal stromal tumors (GISTs) very rarely metastasize to the vertebrae. Tyrosine kinase inhibitors (TKIs) confer favorable long-term survival and durable disease control for metastatic disease. Here, we reviewed a case and the literature to determine the various management options, and neurological outcomes for these patients.

Case Description: A 63-year-old Chinese female with metastatic jejunal GIST previously treated with various TKIs presented with the left lower limb weakness and a sensory level at T10. MRI revealed a T9 vertebral body tumor with cord compression. The tumor was excised and surgical fixation was performed. She received 30Gy of fractionated adjuvant radiotherapy. She achieved near-complete neurological recovery but died 2 months later from systemic disease progression.

Conclusion: Based on this case and a review of the literature, surgical intervention and treatment with TKIs with adjuvant RT can lead to comparable survival and neurological outcomes.

Keywords: Gastrointestinal stromal tumor, Spine metastasis, Spine surgery, Vertebral metastasis

INTRODUCTION

Metastasis of gastrointestinal stromal tumor (GIST) to the vertebral column is very rare; there are only a handful of reported cases in the literature. Tyrosine kinase inhibitors (TKIs) (e.g., imatinib mesylate) have significantly prolonged survival in metastatic GIST,[2] with response rates in excess of 80%.[11] Responses have been reported as rapid and durable, with a median time-to-response of 13 weeks, lasting for more than 46 weeks.[10] Unlike many other common metastatic malignancies, survival beyond 6 years can be expected for patients with metastatic GISTs.[4,22] These are important considerations, as radiotherapy (RT) for symptom relief and TKIs for tumor control may also be reasonable nonsurgery-based alternatives.

Here, we report a case of metastatic vertebral GIST, and provide a summary of the current literature regarding treatment options, and long-term survival/neurological outcomes for these patients.

METHODS

Literature review

PubMed and MEDLINE were searched using the term "(GIST OR (gastrointestinal AND stromal)) AND (spine OR spinal OR vertebral)" on April 11, 2019. It yielded 47 results; Chinese, Japanese, and English articles were assessed. Patient characteristics were identified and summarized. Kaplan–Meier analysis was used to estimate the median overall survival, 1-year and 2-year survivals by pooling outcome data from individual case reports or series. Python version 3.7, and the lifelines package were used to perform survival analyses.[9]

CASE REPORT

History, examination, and imaging

A 63-year-old Chinese female presented with 1-week history of progressive thoracolumbar back pain and left leg weakness with a T10 sensory level with preservation of sphincter function. She had been diagnosed with jejunal GIST 5 years previously and had known metastases to the liver, mesenteric lymph nodes, pelvis, and bladder. She had already received multiple lines of TKIs (imatinib, sunitinib, regorafenib, and dasatinib). The holospinal MR revealed a T9 enhancing lesion with an associated pathological fracture, spinal cord compression, and cord edema [Figure 1]. Small asymptomatic enhancing lesions were also noted involving the L5 vertebral body and L1 spinous process [Figure 2].

Operation

She underwent a T9 decompressive laminectomy for tumor excision and an instrumented fusion from T7 to T11; the diseased left T9 pedicle was excised. The tumor was gray, soft, friable, and hyper-vascular. The extradural component anterior to the cord was removed, and the cord was adequately decompressed.

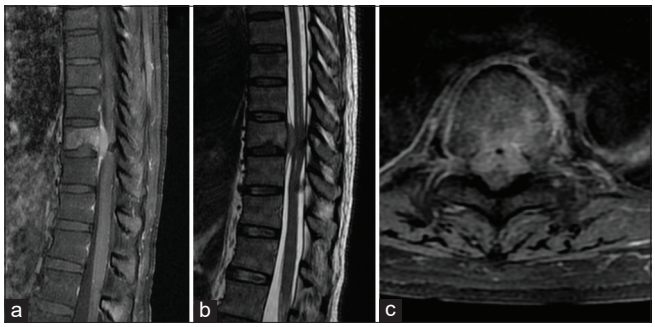

Figure 1: (a) Postcontrast T1 sagittal, (b) T2 sagittal, and (c) T1 axial MRI images showing anterior compression of the spinal cord from epidural extension of the lesion at the T9 vertebra.

Histopathology

The histopathology confirmed the diagnosis of metastatic GIST. It revealed lamellar bone fragments with nests and cords of epithelioid cells accompanied by moderate anisonucleosis, fair amounts of cytoplasm, and gland-like spaces in some areas. Background myxoid features were also noted. The tumor stained weakly for KIT (CD117), strongly for DOG-1, and negative for S-100, HMB45, desmin, CD31, ERG, Cam5.2, and AE1/3.

Postoperative course

Following surgery, she had no surgery-related complications, and nearly-completely recovered neurological function with a short rehabilitation stay. Adjuvant RT of 30 grays over ten fractions was administered from T7 to T11. Some residual back pain was noted and treated with oral analgesics. Postoperative X-rays demonstrated adequate location of instrumentation and preservation of alignment [Figure 3]. Two months later she developed disease progression with peritoneal carcinomatosis with ascites, and expired.

RESULTS

Patient demographics

From literature search, we identified nine patients (including this case) with metastatic vertebral GIST who were treated surgically. Four of these had neurological deficits: 2 motor, 1 sensory, and 1 malignant cord compression presenting with cauda equina syndrome [Table 1].

There were "20 patients" managed non-surgically, whose baseline clinical characteristics were similar to the surgical patient population. Interestingly, they averaged 10 years older than the surgical patients (64 years old vs. 54 years old,

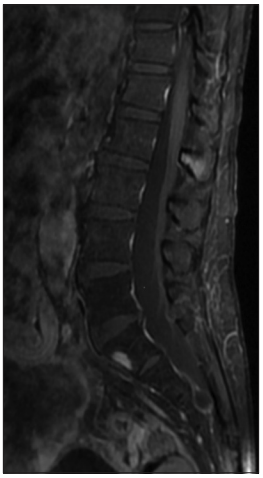

Figure 2: Asymptomatic enhancing lesions at the L1 spinous process and L5 vertebral body.

Table 1: Summary of surgically managed metastatic GIST to the vertebra published in the literature (excluding percutaneous biopsies). Gy: Gray (cGy: centi-Gray). RT, radiotherapy.

	Age, gender	Spinal sites	Extraspinal sites	Presenting complaints for vertebral metastases	Surgical treatment for spinal lesion	Non-surgical treatment for spinal lesion	Survival	Neurological outcomes
Bor-Ren *et al.*, 2008[3]	83, Male	C3 to C5	Sigmoid colon	Neck pain and weakness in his bilateral upper arms	C3-5 laminectomy with tumor excision and posterior fusion	RT (300 cGy for 10 doses)	Died 2 months later	Pain and power improved post-operatively
Chang *et al.*, 2018[6]	71, Female	Sacrum	Stomach, liver, right piriformis, gluteus	Right buttock pain, right leg radiating pain	Sacral laminectomy and tumor removal	Imatinib, sunitinib RT (20Gy single fraction, 36 Gy in 4 fractions)	Alive at 32 months	Pain significantly improved
Gong *et al.*, 2009[14]	50, Female	Sacrum	Unknown primary (Detailed imaging and endoscopy were negative)	Left lower limb pain and dyschesia	Resection	Not reported	Not reported	Not reported
Ishi *et al.*, 2014[15]	54, Male	Cervical (craniovertebral junction)	Small bowel, liver, peritoneum	Severe neck pain	Extensive tumor resection, prophylactic ipsilateral occipital artery-posterior inferior cerebellar artery (OA-PICA) bypass	Prior imatinib, sunitinib. Started on sorafenib, regorafenib	Alive 22 months post-surgery	No neuro-logical deficit and working at 22 months
Lo *et al*, *current study*	63, Female	T9 (symptomatic), L1 and L5 (asymptomatic)	Jejunum, liver, mesenteric lymph nodes, pelvis, bladder	Left leg weakness, thoracolumbar back pain	T9 decompressive laminectomy, tumor excision and instrumentation from T7 to T11	Prior imatinib, sunitinib, regorafenib, dasatinib. Adjuvant RT (30 Gy over 10 fractions)	Died 2 months post-surgery from systemic disease progression	Able to ambulate independently for short distances. Residual back pain.
Nakajima *et al.*, 2008[21]	50, Male	C7	liver, left fourth rib	None reported	Resection of C7 lesion	Imatinib	Alive at 9 months	NA
Shimizu *et al.*, 2018[26]	51, Male	L3 (isolated metastasis)	Rectum	Asymptomatic	En bloc L3 corpectomy and L2 to L5 fusion via bilateral anterolateral retroperitoneal approaches	Imatinib	Not reported	NA

(*Contd...*)

Table 1: (*Continued*).

	Age, gender	Spinal sites	Extraspinal sites	Presenting complaints for vertebral metastases	Surgical treatment for spinal lesion	Non-surgical treatment for spinal lesion	Survival	Neurological outcomes
Slimack *et al.* 2012[27]	37, Male	T3, L3	Duodenum, liver	Bilateral scapular tightness and pain, mild low back discomfort, paresthesia in the right groin and anterior thigh	1) Decompressive laminectomies at T2, T3, T4 with T3 corpectomy and tumor resection via lateral extracavitary approach, posterior C5-T9 instrumentation and fusion, trapezius muscle flap and paraspinal muscle advancement flap 2) Anterolateral L3 corpectomy with resection of psoas muscle lesion, anterior interbody fusion from L2-L4, posterior pedicle instrumentation from L2-L4	Imatinib Adjuvant RT	Censored at 2 years	Pain resolution and ambulatory without difficulty
Waterman *et al.*, 2015[30]	56, Male	T10-11, lumbar	Posterior mediastinum, esophagus, ribs	Severe low back pain, loss of motor and sensory levels below T12, absence of sphincter tone	Emergent multilevel, posterior decompression, T10 and T11 corpectomy with interbody fusion, intralesional biopsy, and posterior instrumentation from T6 to L1	Imatinib	~1-2 months	Marginal interval improvement with only partial recovery of anal sensation and no further neuro-motor return

respectively), and seven presented with motor/sensory deficits, while 11 had pain alone. There were no other statistically significant differences in baseline clinical characteristics between the surgical and non-surgical groups [Table 2]; [Table 3 for a summary of non-surgically treated patients].

Pattern of vertebral metastasis

The lumbar (39%) and thoracic (39%) regions were the most common sites, followed by the sacrum (24%), and lastly, the cervical (15%) spine. Twenty (61%) of these patients also had bone metastases mainly involving the axial skeleton. In addition, 26 patients (79%) had visceral involvement, and 23 patients (70%) had liver metastasis. GIST tumors arose from a variety of locations: eleven from the small intestinal (33%), ten gastric (30%), six colorectal (18%), and six from extra-gastrointestinal sites [Table 3].

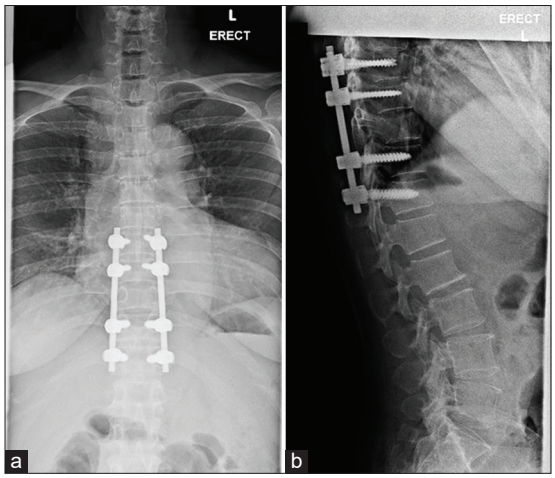

Figure 3: T7 to T11 instrumentation and fixation, T9 laminectomy and excision of tumor. (a) Anterior-posterior film and (b) lateral film.

Survival outcomes

The median overall survival of 27 patients, from time of diagnosis of vertebral GIST, was 34 months; 1-year survival was 74%, and 2-year survival was 56%. The survival curves for those managed surgically versus "non-surgically" did not differ significantly; in the surgical cohort, the median survival was 24 months, while in the nonsurgery cohort, it was 34 months [Figure 4].

Neurological outcomes

Rates of residual neurological deficits were comparable between the two groups [Table 1].

DISCUSSION

Metastatic GIST

GISTs are rare mesenchymal tumors and constitute 0.1%–3% of all gastrointestinal neoplasms. They most commonly involve the stomach (60%), small intestine (15%), colon/

Table 2: Comparison of surgically managed and non-surgically managed patients.

	Treatment modality[a]		Univariate *P*-values
	Surgery	Nonsurgery	
Number of patients	9	20	-
Age, median (IQR)	54 (50–63)	64 (58–70)	0.08[b]
Male, *n* (%)	6 (67)	15 (75)	0.64[c]
Presenting symptoms, *n* (%)			
Asymptomatic	2 (22)	4 (29)	0.79[c]
Neurological deficits	4 (44)	7 (50)	0.88[c]
Motor	2 (22)	4 (29)	
Sensory	1 (11)	3 (19)	
Cauda equina/cord compression	1 (11)	1 (7)	
Pain	7 (78)	11 (79)	0.99[c]
Not reported	0 (0)	6 (30)	
Involved vertebral segments, *n* (%)			0.39[c]
Cervical	3 (33)	2 (10)	
Thoracic	3 (33)	10 (50)	
Lumbar	3 (33)	10 (50)	
Sacral	2 (22)	7 (35)	
Overall survival (months), median (95% CI)	24 (0 – not reached)	34 (16 – not reached)	0.56[d]
Residual deficits, *n* (%)	1 (17)[e]	2 (20)[f]	0.87[b]

[a]Treatment modality was unknown in four patients. Percentages reported excluded those that did not report the corresponding outcomes. [b]Mann–Whitney U test. [c]Chi-square test. [d]Log-rank test. [e]Neurological outcome was not reported in 1 patient. [f]Neurological outcome was not reported in six patients

Table 3: Summary of all available case reports of metastatic GIST to the vertebra in the literature.

	Age, gender	Spinal sites	Extra spinal sites	Presenting complaints for vertebral metastases	Surgical treatment for spinal lesion	Nonsurgical treatment for spinal lesion	Survival	Neurological outcomes
Aktan *et al.*, 2015[1]	56, Male	L1, L3	Small intestine, liver, right femur	Back pain	None	Previous imatinib palliative RT (3 Gy with total dose of 30 Gy on bone metastasis in the right femur and L1-3 vertebral body) IV zoledronic acid 4 mg	2 months following RT	Significant pain improvement after RT
	70, Male	L2	Small intestine, liver	Back pain	None	Previous imatinib palliative RT (total dose of 30 Gy) IV zoledronic acid 4 mg	45 days following RT	Significant pain improvement after RT
Barriére *et al.*, 2019[3]	57, Male	Lumbar	Clivus, rectum, liver, skull	Cauda equina syndrome and pain	None	Nilotinib (previous imatinib and sunitinib) palliative RT	17 months	No improvement in cauda equina syndrome
Bor-Ren *et al.*, 2008[5]	83, Male	C3 to C5	Sigmoid colon	Neck pain and weakness in his bilateral upper arms	C3-5 laminectomy with tumor excision and posterior fusion	RT (300 cGy x 10 doses)	Died 2 months later	Pain and power improved postoperatively
Chang *et al.*, 2018[6]	71, Female	Sacrum	Stomach, liver, right piriformis, gluteus	Right buttock pain, right leg radiating pain	Sacral laminectomy and tumor removal	Sunitinib (previous imatinib) RT (20Gy single fraction, 36 Gy in 4 fractions)	Alive at 32 months	Pain significantly improved
	69, Male	L1, L3, sacrum	Stomach, pancreas, omentum, pelvis, femur	Right buttock pain and right thigh pain	(Percutaneous needle biopsy at L3 vertebral body)	Previous imatinib palliative SRS (36 Gy in 4#)	Alive at 5 months	Pain significantly improved
Chou *et al.*, 2010[7]	82, Female	T3	Vulva, liver, rib	Bilateral lower limb weakness	None	RT	Not reported	Near-complete motor recovery
Chu *et al.*, 2009[8]	73, Male	T6, sacrum	Stomach, jejunum, spleen, pancreas, clavicle, rib, pelvis	Asymptomatic (detected on PET images)	None	Imatinib (continued)	Censored at 24 months	NA

(*Contd...*)

Table 3: (*Continued*).

	Age, gender	Spinal sites	Extra spinal sites	Presenting complaints for vertebral metastases	Surgical treatment for spinal lesion	Nonsurgical treatment for spinal lesion	Survival	Neurological outcomes
Di Scioscio *et al.*, 2011[25]	62, Male	Not reported	Ileum, liver, pelvis, ribs	Acute lumbar back pain	None	Imatinib, then sunitinib zoledronic acid RT (T12-L2 with total dose of 3000 cGy)	34 months	Pain improved
	82, Female	Thoracolumbar spine	Stomach, liver, pelvis	Asymptomatic (detected on CT)	None	Imatinib, then sunitinib zoledronic acid	3 years 8 months	NA
	54, Female	Sacrum	Duodenum, liver, iliac wings, ribs	No spine-related pain (presented with right intercostal pain prompting a CT)	None	Restarted sunitinib (previous imatinib, sunitinib, nilotinib)	Died 1 year 4 months from diagnosis of spine metastasis	NA
Feki *et al.*, 2012[12]	58, Male	T1, T10	Small intestine, sternoclavicular joint, liver	Weakness of lower limbs	None	Previous imatinib RT (15 Gy)	Censored at 10 months	Paraplegic
Fujisawa *et al.*, 2013[13]	70, Male	T6, T12, L1, sacrum	Stomach, liver	Back and lower limb numbness and pain, difficulty in walking	None	Imatinib RT denosumab	Censored at 20 months from symptom onset	Improvement in pain and numbness
Gong *et al.*, 2009[14]	50, Female	Sacrum	Not reported	Left lower limb pain and dyschesia	Resection	Not reported	Not reported	Not reported
Ishi *et al.*, 2014[15]	54, Male	Cervical (craniovertebral junction)	Liver, peritoneum	Severe neck pain	Extensive tumor resection, prophylactic ipsilateral occipital artery- posterior inferior cerebellar artery (OA-PICA) bypass	Prior imatinib, sunitinib. started on sorafenib, regorafenib	Alive 22 months postsurgery	No neurological deficit
Ishikawa *et al.*, 2006[16]	58, Male	L5	Small intestine, liver	Back pain	None	Imatinib RT (40 Gy)	Alive at 28 months	Good performance status
Jain *et al.*, 2011[17]	55, Male	T9	Small and large intestine mesentery, liver, skull, rib, pelvis	Generalized bony pain	None	Imatinib	Alive at 6 months	Not reported

(*Contd...*)

Table 3: (*Continued*).

	Age, gender	Spinal sites	Extra spinal sites	Presenting complaints for vertebral metastases	Surgical treatment for spinal lesion	Nonsurgical treatment for spinal lesion	Survival	Neurological outcomes
Jati *et al.*, 2012[18]	49, Male	Not reported	Stomach, liver, spleen, peritoneum, LN, soft tissue, rib, pelvis, femur, humerus	Not reported	Not reported	Imatinib	Not reported	Not reported
	71, Male	Not reported	Rectum, liver, peritoneum, rib, pelvis, femur, humerus	Not reported	Not reported	Imatinib	Not reported	Not reported
	52, Female	Not reported	Stomach, liver, peritoneum, rib, pelvis	Not reported	Not reported	Imatinib	Not reported	Not reported
	48, Male	Not reported	Stomach, liver, peritoneum	Not reported	Not reported	Imatinib	Not reported	Not reported
Kaku *et al.*, 2006[19]	68, Female	Lower lumbar, sacrum / presacral	Lumbar spine, sacrum, intracranial, ureter	Severe back pain	None for the recurrent vertebral tumor (resection of the initial presacral tumor)	RT to sacrum imatinib for subsequent lumbar spine local recurrence	>5 years	Pain improved and able to walk
Nakajima *et al.*, 2008[21]	50, Male	Thoracic, lumbar	Jejunum, liver	Bilateral lower limb numbness and pain	None	Previous imatinib, sunitinib RT (46 Gy)	Died at 6 months	Improvement in pain and numbness
	76, Male	Thoracic	Colon	None reported	(CT-guided biopsy)	Imatinib	Alive at 3 years and 7 months	NA
	50, Male	C7	Colon, liver, left fourth rib	None reported	Resection of C7 lesion	Imatinib	Alive at 9 months	NA
Rochigneux *et al.*, 2017[23]	66, Male	Cervical, thoracic, lumbar, pelvis (sacrum and left sacroiliac joint)	Stomach, ribs, left femur, right humerus, liver	Asymptomatic (detected on CT)	None	Imatinib	11 months	NA
Sahin *et al.*, 2014[24]	62, Male	Both sacroiliac joints	Stomach, skull, ribs	Lower limb weakness	None	Imatinib	~1.5 years	Not reported
Shimizu *et al.*, 2018[26]	51, Male	L3 (isolated metastasis)	Rectum	Asymptomatic	En bloc L3 corpectomy via bilateral anterolateral retroperitoneal approaches	Imatinib	Not reported	NA

(*Contd...*)

Table 3: (*Continued*).

	Age, gender	Spinal sites	Extra spinal sites	Presenting complaints for vertebral metastases	Surgical treatment for spinal lesion	Nonsurgical treatment for spinal lesion	Survival	Neurological outcomes
Slimack *et al.*, 2012[27]	37, Male	T3, L3	Duodenum, liver	Bilateral scapular tightness and pain, mild low back discomfort, paraesthesia in the right groin and anterior thigh	Decompressive laminectomies at T2, T3, T4, with T3 corpectomy and tumor resection through lateral extracavitary approach, posterior C5-T9 instrumentation and fusion, trapezius muscle flap and paraspinal muscle advancement flap Anterolateral L3 corpectomy with resection of psoas muscle lesion, anterior interbody fusion from L2-L4, posterior pedicle instrumentation from L2-L4	Previous imatinib adjuvant RT	Censored at 2 years	Pain resolution and ambulatory without difficulty
Takeda *et al.*, 2014[28]	62, Female	Not reported	Duodenum, liver	Not reported	None	Regorafenib (Previous imatinib, sunitinib)	7	NA
Waterman *et al.*, 2015[30]	56, Male	T10-11, lumbar	Esophagus, posterior mediastinum, ribs	Severe low back pain, loss of motor and sensory levels below T12, absence of sphincter tone	Emergent multilevel, posterior decompression, T10 and T11 corpectomy with interbody fusion, intralesional biopsy, and posterior instrumentation from T6 to L1	Imatinib	~1–2 months	Marginal interval improvement with only partial recovery of anal sensation and no further neuro-motor return
Zhang *et al.*, 2018[31]	66, Male	C7, T1	Left first rib	Progressive lower limb numbness and weakness	None (resection of a previous cervical paravertebral mass)	Imatinib for local recurrence	Censored at 10 months	Significant improvement in symptoms

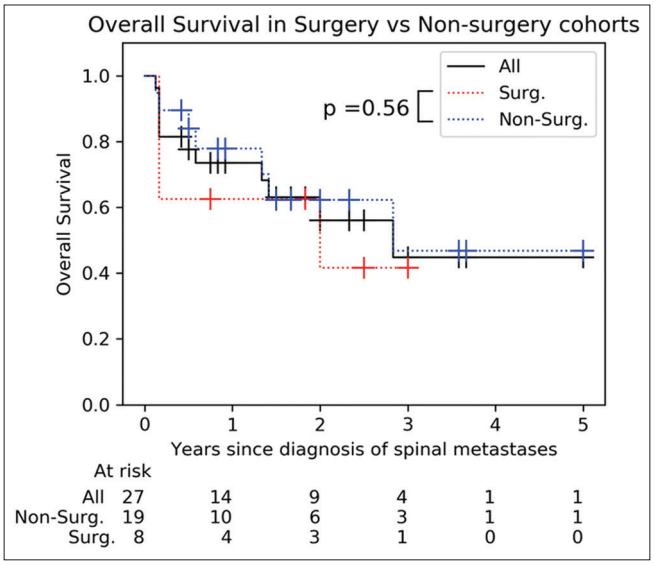

Figure 4: Kaplan-Meier plot of pooled survival data from literature review of all 27 reported cases of GIST with spinal metastases.

rectum (5%), and visceral organs (omentum) mesentery (5%).[29] Metastases commonly involve the liver and peritoneum.[29]

Genetics and chemotherapy

Most GISTs stain positive for KIT (CD117) and DOG-1. The identification of driver mutations in the KIT or PDGFRA (platelet-derived growth factor receptor alpha) genes led to the development of TKIs such as imatinib and sunitinib which significantly improved the survival of these patients.[20] In some studies, metastatic GIST in general is expected to survive for over 6 years following treatment with TKIs. In our case, vertebral metastases developed despite four lines of TKIs, which likely contributed to the rapid disease progression following surgery.

Treatment considerations

Most vertebral GIST metastases are symptomatic; 80% present with pain, and 38% with neurological deficits.

Comparison of all reported cases failed to show a significant difference in the median overall survival (24 vs. 34 months, $P = 0.56$) or neurological outcome (17% vs. 20% residual deficits, $P = 0.87$) between those managed surgically versus "non-surgically" (e.g., with TKIs and RT).

CONCLUSION

Metastatic GIST to the vertebral bodies is rare, and these patients have median survivals of 34 months. Successful treatment may include surgical and nonsurgical (TKIs and RT) options.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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