Case Report

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

Yu Tung Lo, David Siu Kei Mak, Colum Patrick Nolan
Department of Neurosurgery, National Neuroscience Institute, Singapore.
E-mail: *Yu Tung Lo - yutung.lo@mohh.com.sg; David Siu Kei Mak - david.mak@mohh.com.sg; Colum Patrick Nolan - colum.nolan@singhealth.com.sg

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.[1,2] 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.

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 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.

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 neurological 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, liver, left fourth rib | 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 | None reported | 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..)
| Slimack et al. 2012<sup>[27]</sup> | 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 | Imatinib Adjuvant RT | Censored at 2 years | Pain resolution and ambulatory without difficulty |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Waterman et al., 2015<sup>[30]</sup> | 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 L2 to L4 | 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].

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/rectum (15%), and appendix (<1%). Metastases are observed in up to 30% of patients at diagnosis and are associated with decreased survival. When identified, the most common site of initial diagnosis is the liver, followed by the lung and bone.

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

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

| Treatment modality | Surgery | Nonsurgery | Univariate P-values |
|-------------------|---------|------------|---------------------|
| Number of patients | 9       | 20         | -                   |
| Age, median (IQR) | 54 (50–63) | 64 (58–70) | 0.08*               |
| Male, n (%)       | 6 (67)  | 15 (75)    | 0.64*               |
| Presenting symptoms, n (%) |         |            |                     |
| Asymptomatic      | 2 (22)  | 4 (29)     | 0.79*               |
| Neurological deficits | 4 (44) | 7 (50)     | 0.88*               |
| 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*               |
| Not reported       | 0 (0)   | 6 (30)     |                     |
| Involved vertebral segments, n (%) |         |            | 0.39*               |
| 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* |
| Residual deficits, n (%) | 1 (17)* | 2 (20)* | 0.87* |

*Treatment modality was unknown in four patients. Percentages reported excluded those that did not report the corresponding outcomes. *Mann–Whitney U test. *Chi-square test. *Log-rank test. *Neurological outcome was not reported in 1 patient. *Neurological outcome was not reported in six patients.
| 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 | 2 months following RT | Significant pain improvement after RT |
| Barrière et al., 2019 [3] | 57, Male | Lumbar | Clivus, rectum, liver, skull | Cauda equina syndrome and pain | None | 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 | 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 | Alive at 32 months | Pain significantly improved |
| Chu et al., 2009 [8] | 69, Male | L1, L3, sacrum | Stomach, pancreas, omentum, pelvis, femur | Right buttock pain and right thigh pain | (Percutaneous needle biopsy at L3 vertebral body) | Alive at 5 months | Pain significantly improved |
| Chou et al., 2010 [7] | 82, Female | T3 | Vulva, liver, rib | Bilateral lower limb weakness | None | 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 | Censored at 24 months | NA |

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 |
|-------------|-------------|--------------------|-----------------------------------------------|-----------------------------------|--------------------------------------|---------|----------------------|
| 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 |
| 58, Male | T1, T10 | Small intestine, sternoclavicular joint, liver | Weakness of lower limbs | None | Previous imatinib RT (15 Gy) | Censored at 10 months | Paraplegic |
| 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 |
| 50, Female | Sacrum | Not reported | Left lower limb pain and dysesthesia | Resection | Not reported | Not reported | Not reported |
| 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 post surgery | No neurological deficit |
| 58, Male | L5 | Small intestine, liver | Back pain | None | Imatinib RT (40 Gy) | Alive at 28 months | Good performance status |
| 55, Male | T9 | Small and large intestine mesentery, liver, skull, rib, pelvis | Generalized bony pain | None | Imatinib | Alive at 6 months | Not reported |

(Contd...)
| 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 |
| | 71, Male | Not reported | Rectum, liver, peritoneum, rib, pelvis, femur, humerus | Not reported | Not reported | Imatinib | Not reported |
| | 52, Female | Not reported | Stomach, liver, peritoneum, rib, pelvis | Not reported | Not reported | Imatinib | 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 | >5 years |
| Nakajima et al., 2008[21] | 76, Male | Thoracic, lumbar | Jejunum, liver | Bilateral lower limb numbness and pain | None | Previous imatinib, sunitinib RT (46 Gy) | Died at 6 months |
| | 50, Male | Thoracic | Colon | None reported | (CT-guided biopsy) | Imatinib | Improvement in pain and numbness |
| Rochigneux et al., 2017[23] | 66, Male | Cervical, thoracic, lumbar, pelvis (sacrum and left sacroiliac joint) | Colon, liver, left fourth rib Stomach, ribs, left femur, right humerus, liver | None reported | Resection of C7 lesion | Imatinib | Alive at 9 months |
| Sahin et al., 2014[24] | 62, Male | Both sacroiliac joints | Stomach, skull, ribs | Lower limb weakness | None | Imatinib | ~1.5 years |
| Shimizu et al., 2018[26] | 51, Male | L3 (isolated metastasis) | Rectum | Asymptomatic | En bloc L3 corpectomy via bilateral anterolateral retroperitoneal approaches | Imatinib | Not reported |
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 | 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[29] | 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, intrasional 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 |
Lo, et al.: Surgical management of metastatic vertebral GIST rectum (5%), and visceral organs (omentum) mesentery (5%). Metastases commonly involve the liver and peritoneum.

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.

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.

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