Clinical characteristics and prognosis of gastrointestinal stromal tumors with rare site metastasis (Review)

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Received August 13, 2022; Accepted September 27, 2022

DOI: 10.3892/ol.2022.13573

Abstract. Gastrointestinal stromal tumors (GIST) are the most common stromal-derived tumors of the gastrointestinal tract and have a potential metastatic capacity in almost half of all cases, with the most common sites of metastasis being the liver and peritoneum. However, there is evidence that GIST metastasizes to sites other than the liver and peritoneum, which poses challenges for clinical diagnosis and treatment. Therefore, the Cochrane and Medline databases were searched via PubMed in July 2022 using relevant keywords to acquire the literature associated with the metastasis of GIST to rare sites published since from 2000 onwards. Study data comprising age, sex, primary location, metastatic site, mean survival time, clinical signs and symptoms, imaging, pathological features immunohistochemical indices, treatment and prognosis were recorded and analyzed. The 118 metastases at rare sites reported in the literature included bone (n=31), lung (n=10), lymph nodes (n=13), intracranial sites (n=13), skin and subcutaneous tissue (n=10), heart (n=7), skeletal muscle (n=7), orbit and choroid (n=6), pancreas (n=3), spleen (n=2), bone marrow (n=1), testis (n=3), scrotum (n=1), epididymis (n=1), penis (n=1), ovary (n=2), cervix (n=1), kidney (n=1), bladder (n=1), adrenal gland (n=2) and thyroid gland (n=2). From the reviewed studies, it may be concluded that when metastases from gastrointestinal stromal tumors occur at rare sites, the initial symptoms may help in the identification of these sites. In addition, the site-dependent imaging of different metastatic locations may further define the metastases, and the findings of pathological or immunohistochemical analyses may be used to confirm the diagnosis.

Contents

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Key words: gastrointestinal stromal tumor, rare metastatic site, tyrosine kinase inhibitor, clinical characteristics, prognosis

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most frequently occurring potentially malignant mesenchymal-derived tumors of the gastrointestinal tract, which are derived from interstitial cells of Cajal or their precursors and have an annual incidence of 10-15 cases per million (1-3). The pathogenesis of GIST is closely associated with mutations in the type III tyrosine kinase receptor gene KIT and the platelet-derived growth factor receptor a (PDGFRA) gene, which are associated with nearly 95% of cases (4,5).

The most common primary sites of GIST are the stomach, accounting for 60-70% of cases, and the small intestine accounting for 20-30% (6). Since the introduction of imatinib for the treatment GIST in 2002, the survival rate of patients with gastrointestinal stromal tumors has improved (7-9). However, GIST cells with the PDGFRA D842V mutation have since been found to have primary resistance to imatinib, and some cells in a non-proliferative quiescent state acquire secondary resistance during long-term treatment with this drug (5,10-13). Consequently, during the course of imatinib treatment, disease progression may occur, resulting in metastases outside the primary site. GIST commonly metastasizes to the liver (50-60%) (14) and peritoneum (20-43%), but less frequently to other sites, with metastases to lymph nodes, lungs and bone being relatively rare (15-18). Nevertheless, the ability to identify these rare sites of metastasis early is essential, as subsequent functional impairment at metastatic sites may occur, affecting clinical outcomes and leading to a poor prognosis. Since, to the best of our knowledge, no systematic review of the literature of rare metastatic sites for GIST other than the liver or peritoneum yet exists in the literature, the occurrence of these rare metastatic GIST sites and their metastatic characteristics are not yet clear. Therefore, the present study aimed to provide a systematic review of the rare sites of metastatic GIST, in order to enrich understanding of this type of stromal tumor and to improve the prognosis of patients with GIST metastasis in rare sites.

2. Materials and methods

Inclusion criteria. Literature published from 2000 onwards on GIST in humans with metastases to sites other than the liver or peritoneum following an initial diagnosis of GIST, treated or not, were included. The papers were required to have viewable abstracts online and full text that it was possible to download.

Search strategy. Cochrane and Medline databases were searched via PubMed) using the following query: ['gastrointestinal stromal tumor' (Title/Abstract) OR 'GIST' (Title/Abstract)] AND ['metastasis' (Title/Abstract)]. A total of 969 articles were retrieved, and based on the inclusion criteria, 88 articles with 98 cases were finally obtained. Considering that the literature published prior to 2000 did not include complete clinical patient information, only articles published on or after 2000 were selected, with a search deadline of July 31, 2022 for published literature. The screening flow chart is shown in Fig. 1.

Statistical analysis. The included articles were analyzed to record the basic data used for the analysis. Study data included age, sex, primary site, metastatic site, immunohistochemical staining for CD117 and CD34, treatment of metastases and mean survival time. Given the differences in management and the limited number of cases identified, descriptive analyses were used and data were expressed as mean or median values.

3. Rare metastatic sites and basic characteristics of patients

It has been reported in the literature that >70% of GISTs originate from the stomach or small intestine and 1-5% from the colon and esophagus (19). The primary GIST sites found in the present review included the stomach and small intestine in 69 cases (70.41%), the rectum in 14 cases (14.29%), the esophagus in two cases (2.04%), the colon in one case (1.02%), the retroperitoneum in two cases (2.04%), the mesentery in one case (1.02%), the perisacrum in one case (1.02%), the liver in one case (1.02%), the pelvis in one case (1.02%) and unknown origin in six cases (6.12%). The non-liver/peritoneum sites to which GIST metastasized are shown in Fig. 2 and are similar to those reported in the literature (19). Since several metastatic sites were reported in some cases, the 98 cases included 118 metastatic sites. The 118 metastasis sites included in the present review comprised: Bone (n=31), lung (n=10), lymph nodes (n=13), intracranial sites (n=13), skin and subcutaneous tissue (n=10), heart (n=7), skeletal muscle (n=7), orbit and choroid (n=6), pancreas (n=3), spleen (n=2), bone marrow (n=1), testis (n=3), scrotum (n=1), epididymis (n=1), penis (n=1), ovary (n=2), cervix (n=1), kidney (n=1), bladder (n=1), adrenal gland (n=2) and thyroid gland (n=2). The primary and metastatic sites are summarized in Table I (20-88). The mean age of the patients was 59.83 years (range, 17-85 years) and the median age of GIST onset was 55-65 years (89,90). The patients included 61 males and 36 females, with a male-to-female ratio of 1.743. However, the sex of one case could not be verified in the text (64).

4. Diagnosis of rare site metastasis of GIST

The diagnosis of GIST with rare metastases is based on clinical symptoms and signs, appropriate imaging and ultrasound to determine the site of the lesion, and the results of puncture or postoperative biopsy with molecular testing (6,91).

Clinical signs and symptoms of different rare metastatic sites. In cases of GIST with metastasis at rare sites, the symptoms will vary according to the organ affected by the metastatic lesion. In cases with synchronous unusual site metastases alongside the diagnosis of the primary GIST, the manifestations of the metastatic site are often dominant. For example, when intracranial GIST metastasis occurs, it usually affects the nervous system, resulting in dizziness, headache, memory impairment, loss of sensation and inability to move a single limb, the inability to maintain body balance and abnormal gait and posture, along with a series of neurological crements (27, 32,35,40,51,61,70,87,87,92,93). In cases of bone metastasis, pain manifests in the affected bone area (29,37,48,52,53,63, 69,75,80,94,95), in cases of skeletal muscle involvement, a mass can be palpated in the affected area (34,49,71,72,79), and when metastasis occurs deep in the bone marrow, anemia may be present (96). Furthermore, when GIST metastasizes to the lungs, signs and symptoms that may be observed include dyspnea, blood in the sputum, coughing and shortness of breath (18,85,88,97). When metastasis to superficial lymph nodes, skin or subcutaneous tissue occurs, a mass may be superficially palpable (28,42,45,55,68,68,73,98). However, when GIST metastasizes to the heart, although no clinical signs are evident in the early stages (24,82,83,99,100), the late stages may manifest as cardiogenic shock (43). When GIST metastasizes to the orbit, a mass may be palpable around the orbit (60) and may manifest as periorbital pain (101), and with involvement of the choroid, vision loss or diplopia may occur (44,48,51,67). Menstrual flow may increase when there is metastasis in the cervix (102), and when the testicles, penis or scrotum are involved, swelling of the testicles and scrotum, difficulty in achieving an erection and obstruction of the urinary tract are typical manifestations (21,38,64,74). When GIST metastasizes to the adrenal gland, the secretion of catecholamine hormones may become abnormal, and symptoms of hypertension may occur (59,103). In cases of metastasis to the thyroid gland, systemic manifestations such as weight loss, weakness and respiratory distress can be observed (23). The presence of rare site GIST metastasis may be initially discovered by the observation of the aforementioned early symptoms.

Imaging of rare metastatic sites. In cases of extrahepatic/extraperitoneal GIST metastasis, imaging examinations can be performed according to the individual patient's symptoms and signs to clarify the site of metastasis; however, the imaging manifestations vary depending on the site. For example, when GIST metastasizes to the intracranial area, computed tomography (CT) scans show high density with cerebral edema and enhancement scans show homogeneous enhancement. The magnetic resonance imaging (MRI) of cranial GIST metastasis shows equivocal masses in T1- and T2-weighted terms, with circumferential enhancement in T1-weighted sequences and inhomogeneous enhancement in T2-weighted sequences (40,61,70,104), while

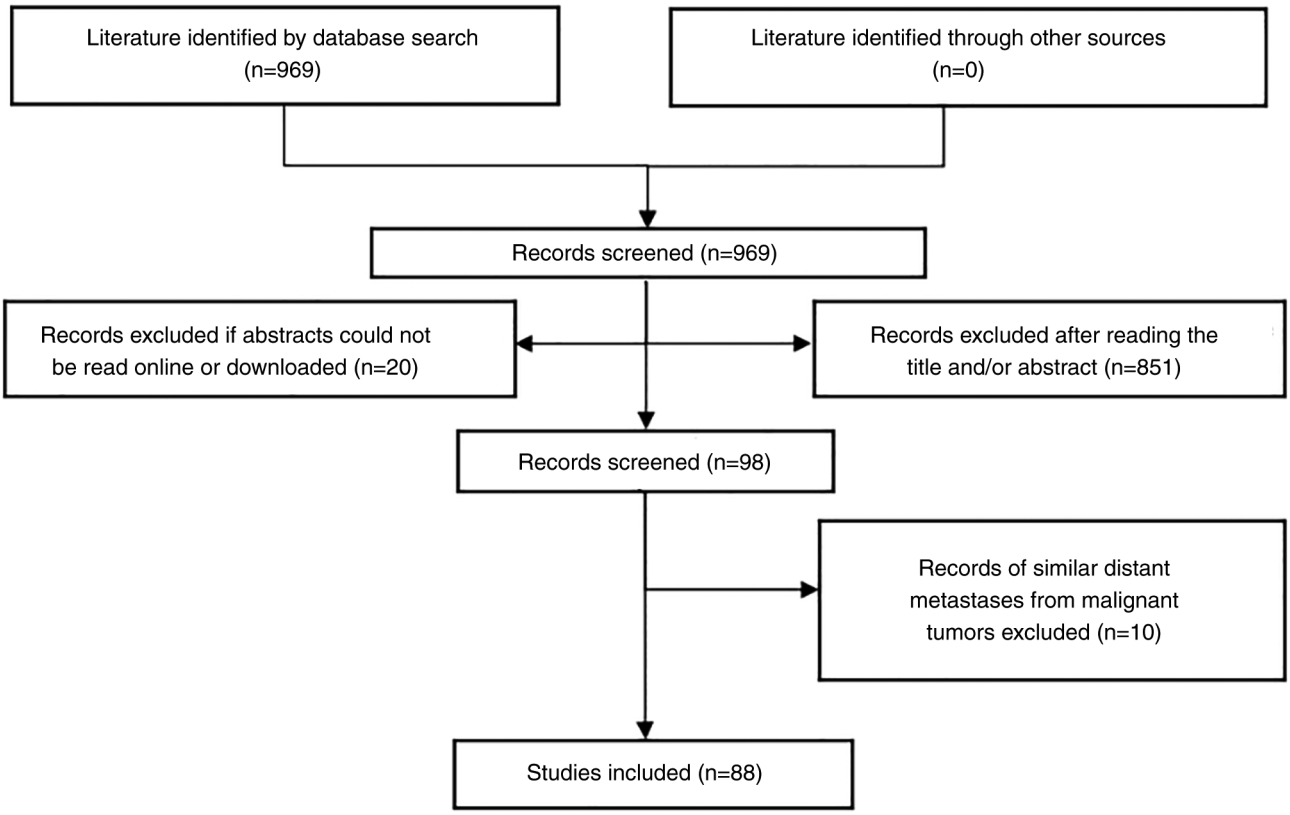

Figure 1. Flow chart of the literature screening process.

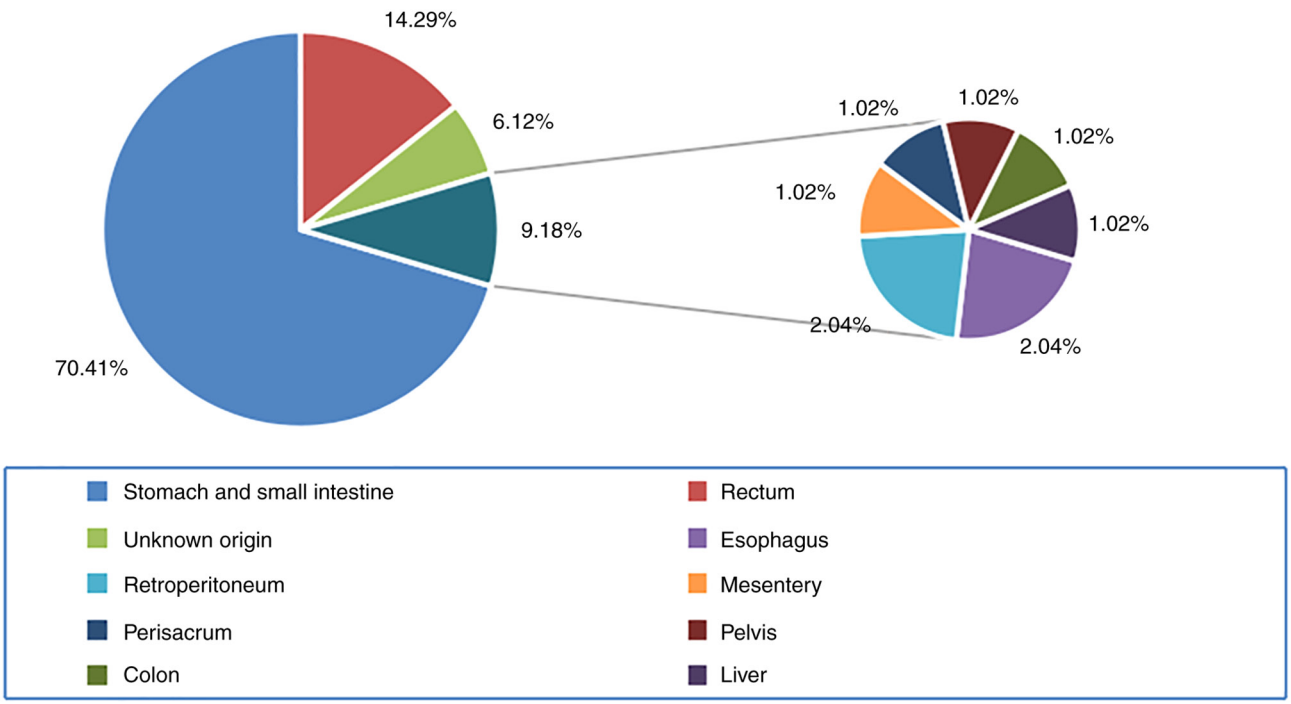

Figure 2. Percentage of primary sites of gastrointestinal stromal tumors. The dark teal wedge in the first chart represents the rare sites that are presented in the second chart.

the intracranial aggregation of ^{18}F-fluorodeoxyglucose is not reported as being visible when examined using positron emission tomography (PET) (27,86,87,92). When GIST metastasizes to bone, it is primarily present in the spine (17), with CT plain scanning showing osteolytic bone destruction of the vertebral ody (29,31,37,47,52,53,69,76,78,81,84,94,95). Additionally, MRI reveals dural protrusion and compression of the spinal cord, usually with spinal stenosis, T1 and T2 high signals on

Table I. Primary and metastatic sites of gastrointestinal stromal tumors.

Primary site	Metastatic site	(Refs.)
Small intestine	Bone, lung, ovary, lymph nodes, heart, skeletal muscle, intracranial sites, skin and subcutaneous tissue, orbit, thyroid, scrotum, testes, bladder and choroid	(18,20-53)
Stomach	Bone, lung, ovary, lymph nodes, heart, intracranial sites, skin and subcutaneous tissue, orbit, thyroid, adrenal gland, pancreas, spleen and choroid	(23,28,33,54-73)
Rectum	Bone, lung, skeletal muscle, heart, lung, kidney, eye socket, epididymis and penis	(37,63,74-84)
Retroperitoneum	Skin and lung	(45)
Pelvis	Lung	(85)
Perisacrum	Intracranial sites	(86)
Esophagus	Intracranial sites and lung	(87)
Colon	Lung	(88)
Liver	Adrenal gland	(84)

enhancement scans and partial necrosis and non-uniform enhancement of the lesion (29,31,48,63,76,78,81,95). The PET-CT imaging of bone metastasis shows hypermetabolic changes at the site of a vertebral lesion (37,47,62,63,69,75,76). In cases with the involvement of skeletal muscle, T2-weighted images show a mass with high signal intensity (71,72). When GIST metastasizes to the lungs, a dense mass is visible in one or both lungs (18,85,88,97), and in the lymph nodes, GIST metastasis appears on CT images as a hypodense mass with no enhancement when examined using enhanced MRI (39,57,58) and as a hypoechoic cystic or solid mass when examined using ultrasound (28,33,29). No enhancement is seen on chest enhancement CT images when GIST metastasizes to the heart (85,100), and PET-CT reveals high ^{18}F-fluorodeoxyglucose accumulation in the mass (24,83), with echocardiograms showing a hypoechoic mass in the ventricle or atrium (24,83,99,100). When GIST metastasizes to the orbit, CT shows a hypodense mass with well-defined lesions, and enhanced MRI shows uniform enhancement (20,60), Optical coherence tomography may reveal edema of the optic disc and retinal neuroepithelia (44), while MRI presents a well-defined round nodule with isointensity to eye muscles in T1-weighted sequences and high signal T2-weighted sequences (44,82) and enhancement scans show homogeneous enhancement (20). Ultrasonography of metastasis to the orbit also shows a well-defined homogeneous hypoechoic mass around the orbit without retinal detachment (44). In cases of choroidal involvement, funduscopic examination may reveal an enlarged choroidal mass surrounded by a flat retinal detachment, while ultrasonography reveals a choroidal mass with moderate-to-low reflectivity (51,67). When GIST metastasizes to the ovaries, transvaginal ultrasound detects a solid pelvic hypoechoic mass with irregular margins, and energy Doppler ultrasound presents a grade 3 blood flow signal (41). In ovarian metastasis, the presence of a mass in the pelvis may also be detected by CT, and enhanced CT shows heterogeneous enhancement of the mass (41,102). When GIST metastasizes to the male genital system, metastatic GIST in the scrotum appears as a vascular-rich hypoechoic mass on ultrasound (38). In addition, CT may reveal multiple satellite nodules distributed along the spermatic cord (74,77), while contrast-enhanced T1-weighted MRI does not show mass enhancement (64). Lastly, when GIST metastasizes to the spleen, a low-density mass in the spleen is shown using abdominal CT and enhancement is observed on enhanced scans (59).

Pathological features and gene mutation detection. Upon pathological examination, GIST can be morphologically classified into three types: Spindle cell (70%), epithelioid (20%) and mixed spindle and epithelioid types (10%) (14,19,105). Spindle cells are microscopically viewed as spindle-shaped with uniform cytoplasm, eosinophilic cytoplasmic staining, ovoid nuclei and juxtaposed nuclear vesicles (106). Epithelioid cells are round with round or oval nuclei (107), and mixed types are observed as a mixture of epithelial and spindle cells within pathological sections, or as a transitional pattern between the two (91). In the present review, 57 cases (58.16%) were of spindle cell type, 15 cases (15.31%) were of epithelial cell type, 12 cases (12.24%) were of mixed cell type and 14 cases were of unknown type and 14 cases (14.29%) were of unknown type. A total of 69 cases were immunohistochemically tested, with 62 cases being positive for CD117 and 54 cases being positive for CD34, revealing that the latter is less often positive. In addition, bone marrow biopsy is essential for the analysis of gastrointestinal stromal tumors that have metastasized to the bone marrow (96).

5. Therapy and prognosis for rare site GIST metastases

Treatment and prognosis details described in the literature for rare metastatic sites of GIST are shown in Table II (18,20-27,29-41,43,44,46,47,50-54,56-67,69-72,74,75,77-80,82-88,92,94-101,103,104,108-112). Treatment modalities included TKIs alone, surgical treatment or resection alone, radiotherapy alone, resection with TKIs, resection with radiation therapy, radiation therapy with TKIs, and resection with radiation therapy and TKIs. Surgical resection was performed at the primary site in 87 cases (92.31%). Among

Table II. Treatments and mean survival times of patients with gastrointestinal stromal tumors at rare metastatic sites.

Metastatic site	Therapies for metastases	Mean survival time, months	(Refs.)
Bone	R, TKIs, RT, R + RT + TKIs, R + TKIs and R + RT	63.50	(26,29,31,36,37,46,47,52,53,62, 63,66,69,75,77,78,80,84,94,95)
Bone marrow	TKIs	8.00	(96)
Skeletal muscle	R, R + TKIs and RT+TKIs	38.00	(25,34,43,71,72,79)
Lymph nodes	R and R + TKIs	33.20	(22,23,27,30,33,39,54,57,58,108)
Heart	R and R + TKIs	76.50	(24,83,99,100)
Lung	R + TKIs	80.00	(18,50,56,85,88,97)
Intracranial sites	R, R + TKIs, R + RT, R + RT + TKIs	35.81	(27,32,35,40,51,61,70, 86,87,92,104)
Skin or subcutaneous tissue	R + TKIs	60.00	(42,45,55,68,73,98)
Orbit or choroid	R, R + TKIs and R + RT	72.00	(20,44,51,60,67,82,101,109)
Thyroid	R	9.00	(23)
Pancreas	R + TKIs	57.00	(65,110)
Inferior vena cava	R + TKIs	14.00	(111)
Spleen	R + TKIs	43.00	(59,110)
Kidney	R + TKIs	187.00	(37)
Adrenal gland	R + TKIs	12.50	(59,103)
Ovary	R + TKIs	NA	(41,112)
Scrotum	TKIs	24.00	(38)
Testicle	R and TKIs	NA	(21,74)
Penis	R + TKIs	48.00	(64)
Bladder	R + TKIs	62.00	(46)

R, resection; TKIs, tyrosine kinase inhibitors; RT, radiation therapy; NA, not available.

these cases, 17 had surgical resection of both primary and metastatic sites diagnosed at the same time, 67 had postoperative metastases from rare sites, 52 had surgical resection of rare metastatic site, and 39 cases had liver or peritoneal metastases prior to the surgical resection of rare sites, of which 21 cases had surgical treatment. Notably, a recent study by Pantuso *et al* (113) confirmed that positive surgical margins had no effect on the overall and recurrence-free survival of GIST patients. Therefore, surgical resection is an important treatment modality for GIST. In addition to surgical treatment, TKIs are also very valuable in pre- or postoperative adjuvant therapy. The TKI drugs imatinib, sunitinib, regorafenib and ripretinib have been approved for the first-, second-, third- and fourth-line treatment of GIST, respectively (114). A multicenter randomized controlled trial clearly demonstrated that imatinib treatment at a dose of 400 mg/day achieved objective remission in 81.6% of patients with unresectable or metastatic GIST (115). Further, other studies have confirmed that preoperative imatinib can effectively prevent tumor rupture and reduce the incidence of surgical complications (116,117). However, when patients experience imatinib resistance or intolerable adverse effects, treatment with the second-line drug sunitinib at a dose of 50 mg/day for 4 weeks followed by 2 weeks without treatment, or at 37.5 mg/day continuously is recommended (76,78). One study demonstrated improved patient compliance for continuous once-daily 37.5 mg sunitinib dosing compared with intermittent sunitinib dosing in patients following imatinib failure (118). Furthermore, sunitinib may achieve greater efficacy as a first-line therapy in patients with intracranial GIST metastases due to the inability of imatinib to cross the blood-brain barrier (BBB) (119,120); sunitinib can cross the BBB and achieve a sufficient drug concentration for improved therapeutic outcomes (35,121). While imatinib and sunitinib are clinically beneficial for the majority of patients with metastatic GIST, some patients experience progression as well as intolerable adverse effects following treatment. The third-line treatment regorafenib and the fourth-line treatment ripretinib have been demonstrated to be effective in such patients (50,77,85), Therefore, for patients with GIST at rare metastatic sites, TKIs used alone or in combination can be selected or replaced according to efficacy. In addition, radiotherapy may be used as an adjuvant treatment when GIST metastasizes to the skull and bone. At a typical dose of 30 Gy daily, radiation can effectively reduce tumor size and alleviate symptoms, while creating optimal conditions for surgery (40,61,62,78). The administration of 4 mg zoledronic acid intravenously has also been shown to reduce bone destruction in GIST bone metastases (36,75).

Based on the limited information reported in the literature, the mean survival time for patients with GIST at rare metastatic sites was >61.50 months, with a mean survival time of 59.59 months for men and 63.78 months for women. Among all

the reported cases, 21 (15.31%) had a disease course ending in death. When intracranial metastases were present, patients had a poor prognosis with a mean survival time of 35.81 months, which may have been associated with the inability of imatinib to penetrate the BBB and maintain an effective therapeutic concentration. However, this point requires confirmation by future randomized controlled studies. The mean survival time of patients was 32.75 months for those treated with TKIs alone, 73.11 months for resection alone, 65.17 months for radiotherapy alone, 86.33 months for resection with TKIs, 36.4 months for resection with radiotherapy and 49.17 months for resection with radiotherapy and TKIs. The lower survival rate for patients whose treatment included radiotherapy may have been due to patients requiring radiotherapy being more symptomatic and unable to undergo surgery in a timely manner. Also, if the radiotherapy was administered as a palliative treatment, this may have resulted in a lower mean survival time compared with that for other treatment modalities. Although the mean survival times of patients with GIST metastases in the thyroid, adrenal gland and scrotum were markedly lower compared with those in other sites, the number of cases was small and the representative times may be higher in clinical practice; however, this pends confirmation with additional studies.

6. Summary and prospects

In addition to the liver and peritoneum, GIST can metastasize to rare sites, namely the bone, bone marrow, lungs, lymph nodes, intracranial area, skin, subcutaneous tissue, heart, skeletal muscle, orbit, pancreas, spleen, testes, scrotum, epididymis, penis, ovaries, cervix, kidneys, bladder, adrenal glands and thyroid. Based on the symptoms of the patients along with imaging and ultrasound examinations, the primary and metastatic site can be determined on a basic level; however, diagnosis must be confirmed by the immunohistochemical detection of CD117 and CD34. For primary localized GIST, surgery is the most important treatment, sometimes combined with pre- or postoperative neo-/adjuvant treatment, but for metastatic GIST, TKIs are the principal treatment. TKIs may be combined with surgery and/or with radiotherapy as an adjuvant treatment in cases of bone and intracranial metastases. In patients with a poor prognosis due to intracranial metastases, the use of sunitinib as the first-line treatment may improve prognosis; however, further studies are needed to confirm this.

The present review was constrained by the low incidence of GIST and the limited number of cases collected, unpublished data and associated literature not being available in the English language. However, rare metastatic sites of GIST other than the liver and peritoneum were summarized and reviewed, which may assist with their diagnosis and serve as a reference for selection of the appropriate treatment modality and estimation of prognosis. In addition, more high-quality research evidence such as large-sample, blinded randomized controlled trials is required, to improve clinicians' understanding of the management of GISTs with rare metastases.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

XY, XL and KW conceived the study and drafted the manuscript. XY made substantial contributions to the interpretation of the data, drafting the manuscript and revising it critically for important intellectual content. XL helped to organize the data collected, helped to collect information regarding the survival time of the patients and helped to write the manuscript. All authors revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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