

# Gastrointestinal (GI) leiomyosarcoma (LMS) case series and review on diagnosis, management, and prognosis

Lara Hilal<sup>1</sup> · Kassem Barada<sup>2</sup> · Deborah Mukherji<sup>3</sup> · Sally Temraz<sup>3</sup> · Ali Shamseddine<sup>3,4</sup>

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**Abstract** This review of 76 gastrointestinal (GI) leiomyosarcoma (LMS) cases that include 11 cases from the American University of Beirut Medical Center represents, to our knowledge, the largest number of combined GI LMS cases reported. The age range of GI LMS is variable, and the presentation is non-specific, making pathological diagnosis essential. LMSs usually lack CD117 and CD 34 mutations and are usually positive for smooth muscle cell markers. The review highlights surgery as the mainstay of treatment with negative margins attained most of the times. Adjuvant chemotherapy is used in around 7–27 % of the cases mainly for small intestinal and colorectal LMS. The relatively small

number of patients is a limitation on outcome analysis. However, LMS has a risk of recurrence reaching 39–80 % and secondary metastasis reaching 55–71 % in small intestinal and colorectal cases. In light of the high frequency of recurrence and metastasis, enrolling patients in clinical randomized trials to investigate the role of chemotherapy, radiation therapy, and targeted therapy is required for better control of this rare aggressive GI tumor.

**Keywords** Intraluminal gastrointestinal · Leiomyosarcoma · Pathological characteristics · Survival outcomes

✉ Ali Shamseddine  
as04@aub.edu.lb

Lara Hilal  
Lh54@aub.edu.lb

Kassem Barada  
Kb02@aub.edu.lb

Deborah Mukherji  
Dm25@aub.edu.lb

Sally Temraz  
st29@aub.edu.lb

- <sup>1</sup> Department of Radiation Oncology, Naef K. Basile Cancer Institute, American University of Beirut Medical Center, Beirut, Lebanon
- <sup>2</sup> Gastrointestinal Division, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon
- <sup>3</sup> Department of Internal Medicine, Naef K. Basile Cancer Institute, American University of Beirut Medical Center, Beirut, Lebanon
- <sup>4</sup> Hematology - Oncology Division, Tumor Registry, P.O.Box: 11-0236, Riad El Solh, Beirut 110 72020, Lebanon

## Introduction

Leiomyosarcomas (LMSs) account for 10–20 % of all soft tissue sarcomas. They most commonly originate in the uterus, retroperitoneum, and gastrointestinal (GI) tract [1]. Unlike the benign counterpart leiomyoma, LMS is a smooth muscle cell (SMC) tumor that usually has high mitotic counts, necrosis, and cytological atypia [2]. It differs from GI stromal tumors (GISTs) in its immunohistochemical (IHC) and clinicopathological profiles [3]. LMS usually lack CD117 and CD 34 mutations, which are positive in the majority of GISTs [4, 5]. On the other hand, LMS is usually positive for smooth muscle cell markers such as actin, desmin, and h-caldesmon [4, 5]. As for the pathological characteristics, GISTs arise from the interstitial cells of Cajal and the cellular morphology of GISTs ranges from spindle-shaped cells to epithelioid, whereas LMSs which originate from SMCs of the muscularis mucosa or propria, are usually composed of elongated cells with an abundant cytoplasm [6–8]. Clinically, the distinction between LMS and GISTs is important given the

activity of the tyrosine kinase inhibitor imatinib against GISTs as opposed to LMS [9].

The introduction of the IHC test for the KIT protein, a receptor tyrosine kinase (RTK) called CD117, made this distinction between GISTs and LMS possible [10]. However, 4–5 % of GISTs might be negative for CD117. In such cases, mutational analysis for the KIT gene, testing for activating mutations in another RTK called platelet-derived growth factor receptor alpha (PDGFRA), or mutational analysis for subunits of the enzyme succinate dehydrogenase (SDH) can be performed to confirm a diagnosis of GIST [11–13]. Historically, the most common site of LMS within the GI tract was the stomach followed by the small intestine and then the colon and rectum [14]. However, with the recent categorization of GIST as a separate disease entity from LMS, most of the GI mesenchymal tumors are being diagnosed as GIST. Thus, the real number of LMS, specifically gastric LMS, is way lower than it was previously reported [3]. LMSs are currently reported to occur mainly in the small and large intestine [15].

The aim of this study was to review our cases of intraluminal GI LMS seen at the American University of Beirut Medical Center (AUBMC), a leading tertiary care referral center in the Middle East. We present 11 cases of primary intraluminal GI LMS with a review of the current literature on the diagnosis, management, and prognosis of this rare disease at its different GI sites.

## Methods

After obtaining an institutional review board (IRB) approval to access protected health information, we reviewed all the cases of GI LMS diagnosed at AUBMC from 1999 to 2014. Pathology reports were read to check that the histopathological staining and IHC staining were compatible with a LMS diagnosis as opposed to leiomyoma or GIST. The IHC staining was performed at AUBMC local pathology laboratory. The department of Pathology and Lab Medicine at AUBMC is certified by the College of American Pathologists (CAP). Patients' medical charts, pathology records, and radiographic images were reviewed for clinicopathological details, treatment modalities, and outcome data. Descriptive statistics were used to analyze the tumors' clinical and pathological characteristics as well as treatment outcomes.

## Results

### Case series

We found a total of 11 intraluminal GI LMS. The tumors were located mainly in the colon ( $n = 4$ ), at 36.3 %,

followed by the small intestine ( $n = 3$ ), at 27.3 %, the rectum ( $n = 2$ ), the esophagus ( $n = 1$ ), and the stomach ( $n = 1$ ). Table 1 shows the patients' clinicopathological characteristics. We found an almost equal percentage of males and females. Age ranged between 24 and 76 years with a median age of 56 years. The patients mainly presented with weight loss or abdominal pain. All the tumors that we found measurements for were greater than or equal to 5 cm in size with a mean of  $9.7 \text{ cm} \pm 4.3 \text{ cm}$ . Grossly, the tumors appeared as lobulated, pedunculated, or ulcerated lesions. Microscopically, most of the tumors were high-grade LMS, and most showed necrosis. All of them had cytological atypia with a wide range of mitosis per 50 high power field (HPF), from 2 to 250 with a median of 100 mitotic counts per 50 HPF. The only patient who did not have the mitotic counts reported on him had a Ki67 of 60 %. On IHC, all the tumors were negative for CD 117 and CD 34 and were positive for smooth muscle actin (SMA) and desmin. All 5 tumors tested for vimentin were positive.

As for the treatments offered, all patients had surgical resection with negative margins. Only two out of eleven (18.2 %) underwent adjuvant chemotherapy. None had radiotherapy. Out of the two patients who received chemotherapy in our case series, one had metastatic disease to the liver at diagnosis (case 2). She received adjuvant doxorubicin and then passed away 3 years after treatment. The second patient (case 11) received adjuvant chemotherapy after resection of non-metastatic small intestinal tumor that recurred a year and a half later with pancreatic infiltration necessitating neoadjuvant chemotherapy followed by resection. Unfortunately, the patient had another recurrence a year from the second surgery and was then lost to follow-up. Out of the patients with available outcome data, 6 out of 10 had local recurrence, 4 out of 10 had metastasis (liver lesions) upon presentation that was surgically resected, and 3 patients out of 9 developed metastasis later on after surgery. Seven out of the 9 patients who had adequate follow-up (77.8 %) were deceased at 5 years (Table 2).

### Literature review

For a more comprehensive review of GI LMS, we combined our 11 cases to the cases of GI LMS published in the English literature since 2000, the year when GIST was recognized as separate from LMS. Including our cases, we analyzed a total of 8 esophageal LMS, 7 gastric, 30 small intestinal, and 31 colorectal LMS cases (Tables 3, 4, 5, 6).

Out of the esophageal LMS, 71.4 % were males and 28.6 % females. The ages ranged between 40 and 78 years with a median of 60. Out of the two patients whose symptoms were reported, both had dysphagia at

**Table 1** Demographic, clinical, and histopathological characteristics, and IHC stains of our LMS patients

Case	Age	Gender	Site	Gross appearance	Presenting symptoms	Size (cm)	Mitosis/50HPF	Necrosis	Atypia	Grade	CD 117	CD 34	SMA	Desmin	Vimentin
1	41	Male	Esophagus	Missing	Dysphagia	5	8	Yes	Yes	Intermediate	Neg	Neg	Pos	Pos	NR
2	68	Female	Transverse colon	Pedunculated	Abdominal pain	20	150	Yes	Yes	High	Neg	Neg	Pos	Pos	NR
3	74	Male	Gastric	Lobulated	Weight loss	8	2	Yes	Yes	Low	Neg	Neg	Pos	Pos	NR
4	75	Male	Rectum	Ulcerated lesion	GI bleeding	5	100	Yes	Yes	High	Neg	Neg	Pos	Pos	NR
5	56	Female	Small intestine	Lobulated	GI bleeding	8	3	No	Yes	Low	Neg	Neg	Pos	Pos	Pos
6	38	Male	Cecal	Ulcerated lesion	Abdominal pain	12	100	Yes	Yes	High	Neg	Neg	Pos	Pos	NR
7	76	Male	Small intestine	Pedunculated	Weight loss	10	250	Yes	Yes	High	Neg	Neg	Pos	Pos	Pos
8	24	Female	Sigmoid	Pedunculated	Abdominal pain	9	100	Yes	Yes	High	Neg	Neg	Pos	Pos	NR
9	47	Female	Rectum	Ulcerated lesion	Asymptomatic		150	Yes	Yes	High	Neg	Neg	Pos	Pos	Pos
10	69	Male	Sigmoid	Pedunculated	Weight loss	9	250	Yes	Yes	High	Neg	Neg	Pos	Pos	Pos
11	51	Female	Small intestine	Lobulated	Palpated mass	11	100	Yes	Yes	High	Neg	Neg	Pos	Pos	Pos

NR not reported, Pos positive, Neg negative

presentation. The mean tumor size was 10.2 cm ± 4.5. All tumors showed cytological atypia, and the median mitotic rate was the lowest among other sites of GI LMS, 50 per 50 HPF. On IHC, all tumors were CD117 negative and SMA positive. Out of the patients with available treatment data, all had surgical resection of the tumor (4 out of 4) with negative margins (3 out of 3). None of the 3 patients with reported adjuvant data received chemotherapy or radiotherapy. Only one patient was reported to have no local recurrence or metastasis. Out of the 6 patients with available outcome data, 3 were alive and 3 deceased with a median follow-up of 21 months (Table 3).

Gastric LMS cases were the fewest. As in esophageal LMS, 71.4 % were males and 28.6 % females. However, the median age was the youngest among other sites of LMS at 37 years. The most common presenting symptom was GI bleeding, followed by abdominal pain, weight loss, and gastro esophageal reflux. The mean tumor size was 6.45 cm ± 3.7. The gross appearances of the tumors were variable including fungating, lobulated, polypoid, or ulcerated lesions. Out of those reported, all had cytological atypia and necrosis. The median mitotic rate was double that of the esophageal LMS with 100 mitosis/50 HPF, but the four reported grades were equally divided between low and high grade. On IHC, all tumors were CD 117 negative, CD 34 negative, and SMA positive. All patients had surgical resection with negative margins, and none had chemotherapy or radiotherapy. Out of the 4 patients with available local recurrence or metastasis data, all had no metastasis at presentation and developed no local recurrence. However, one patient developed metastasis later that was not resected. Out of the 6 patients with available outcome data, 66.7 % (n = 4) were alive and 33.3 % (n = 2) were dead of disease with a median follow-up of 6.5 months only.

Thirty patients were reported to have small intestinal LMS, 8 of which have no site specified. As for the remaining 22, duodenal LMS was the most common, followed by ileal LMS and then jejunal LMS. Unlike the gastric and esophageal, they were divided equally between the two genders. The age range was variable between 18 and 80 years with a median of 58.5 years. The two most common presenting symptoms were intestinal obstruction and GI bleeding, followed by weight loss, abdominal pain, anemia, and a palpable mass. The mean tumor size was 10.6 cm ± 6. Grossly, out of the thirteen that are reported, a lobulated mass was the most common appearance, followed by an ulcerated lesion, polypoid lesion, and intramural nodule. Microscopically, out of the patients with available data, all exhibited cytological atypia and most had necrosis. The median mitotic rate was high at 100 per 50 HPF. On IHC, all tumors showed negative CD117 and positive SMA. Twenty-seven out of 28 tumors (96 %) were reported to have small intestinal LMS.

**Table 2** Treatment modalities and outcomes of LMS patients in our case series

Case	Surgery	Surgical margins	Chemotherapy	Radiotherapy	Primary Mets	Surgery for Mets	LR	Secondary mets	Outcome (F/U period)
1	Yes	Negative	No	No	NR	NR	NR	NR	NR
2	Yes	Negative	Yes (doxorubicin)	No	Yes	Yes	Yes	No	DOD (3 years)
3	Yes	Negative	No	No	No	NR	No	No	DUC (9 years)
4	Yes	Negative	No	No	No	No	Yes	Yes	DOD (1 month)
5	Yes	Negative	No	No	No	NR	No	No	Alive (16 years)
6	Yes	Negative	No	No	No	NR	No	No	Alive (11 months)
7	Yes	Negative	No	No	Yes	No	No	No	DUC (2 years)
8	Yes	Negative	No	No	Yes	Yes	Yes	No	DOD (3.5 years)
9	Yes	Negative	No	No	No	Yes	Yes	Yes	DOD (11 years)
10	Yes	Negative	No	No	Yes	Yes	Yes	Yes	DOD (7 months)
11	Yes	Negative	Yes	No	No	NR	Yes	NR	NR

NR not reported, LR local recurrence, Mets metastasis, DOD dead of disease, DUC dead of unknown cause, F/U follow-up

showed negative CD34. Concerning the treatment modalities, out of 29 patients with treatment data, 93.1 % underwent surgical resection; all except one patient had negative margins. Two patients received adjuvant chemotherapy, and none had radiation therapy. Among the few patients with available local recurrence or metastasis data, 8 out of 10 (80 %) suffered from a local recurrence including the patient who had a positive surgical margin. Six out of 11 (54.5 %) developed a secondary metastasis. Twenty percentage (3 out of 12) presented initially with metastatic lesions, one of them surgically resected. As for the outcomes, 28 patients had reported data. With a median follow-up duration of 56.5 months, most of the patients passed away; 32 % died of an unknown cause, 25 % died of LMS, and 7.1 % died of other causes. 17.9 % of the patients were alive, and 17.9 % lost to follow-up.

As for the colorectal LMS, we found 31 reported cases distributed as follows: around half in the rectum, followed by sigmoid colon, cecum, ascending colon, transverse colon, and descending colon. Like the small intestinal LMS, they were almost equally divided among males and females. The ages ranged between 24 and 79 with a median of 65 years. Only nine patients had presenting symptoms reported; abdominal pain was the most common followed by GI bleeding. One patient had weight loss, and one was asymptomatic. The mean tumor size was  $6.7 \pm 5$  cm, smaller than the small intestinal and esophageal LMS, but close to the gastric. Grossly, polypoid tumor appearance was the most common. Few patients had available data on their microscopic appearance: All had cytological atypia and necrosis. The six patients whose grade was reported had high-grade tumors. The median mitotic rate was 100 per 50 HPF, similar to the small intestinal and gastric

counterparts. On IHC, all the patients with available data had negative CD117, negative CD34, positive SMA, and positive vimentin. Treatment information was limited to only 11 patients; 100 % had surgical resection of the tumor with negative margins, 27.3 % had chemotherapy, and none had radiotherapy. Four out of 19 patients (21 %) presented with metastatic lesions. Out of 13 patients with recurrence data, 5 (38.5 %) experienced a local recurrence and 12 out of 17 (70.6 %) developed metastasis later on. Metastasectomy was performed in 5 cases. Concerning the outcomes, data were reported for 26 out of 31 patients. With a median follow-up of 90 months, 30.8 % of the patients remained alive and most passed away; 38.5 % died of disease, 19.2 % died of unknown causes, and 11.5 % died of other causes.

## Discussion

The number of patients in our case series of LMS over 15 years is consistent with the literature on the rarity of this tumor, especially in the stomach. In a series of 262 smooth muscle neoplasms over an 11-year period at a German center, only 3 cases were true leiomyosarcomas [15]. Weight loss and abdominal pain are common non-specific symptoms of LMS originating in the gastrointestinal tract. Other symptoms include vomiting, palpable mass, GI bleeding, and perforation [37].

In all the above-reported cases of LMS, data were collected retrospectively after retrieving the cases from the pathology records of the corresponding institutions. There is no mention, however, of whether the diagnosis was suspected preoperatively or it was only made postoperatively.

**Table 3** Esophageal leiomyosarcoma cases, demographic, histopathological, and IHC characteristics, treatment, and outcome data

Cases	References	Age	Gender	Size	Mitosis/ 50HPF	CD 117	CD 34	SMA	Desmin	Surgery	Surgical margins	Chemo	XRT	LR	Secondary mets	Outcome
1	Our series, 2015	41	Male	5	8	Neg	Neg	Pos.	Pos.	Yes	Neg.	No	No	NR	NR	NR
2	Stelow et al. [16]	67	Female	14.5	NR	Neg	Neg	Pos.	Pos.	NR	NR	NR	NR	NR	NR	NED, 2 months
3	Miettinen et al. [6]	56	Male	9.16	>50	Neg	Pos (40 %)	Pos.	Pos.	Yes	NR	NR	NR	NR	NR	DOD
4	Miettinen et al. [6]	62	Male	9.16	>50	Neg	Neg	Pos.	Neg.	NR	NR	NR	NR	NR	NR	DOD
5	Miettinen et al. [6]	78	Female	9.16	>50	Neg	Neg	Pos.	Neg.	NR	NR	NR	NR	NR	NR	DOD
6	Lindenmann et al. [17]	60	Male	NR	NR	Neg	Neg	Pos.	Pos.	Yes	Neg.	No	No	NR	NR	NED, 21 months
7	Zhu et al. [18]	NR	NR	4	Few	Neg	Neg	Pos.	Pos.	NR	NR	NR	NR	NR	NR	NR
8	Pramesh et al. [19]	40	Male	NR	NR	Neg	NR	Pos.	NR	Yes	Neg.	No	No	No	No	NED, 7 years

NR not reported, Neg negative, Pos positive, LR local recurrence, NED no evidence of disease, DOD dead of disease, XRT radiotherapy, LR local recurrence

**Table 4** Gastric leiomyosarcoma cases, demographic, clinical, and histopathological characteristics

Case	References	Age	Gender	Presenting Sxs	Mitosis/ 50HPF	CD 117	CD 34	SMA	Desmin	Local recurrence	Secondary Mets	Outcome
1	Our series, 2015	74	Male	Weight loss	2	Negative	Negative	Positive	Positive	No	No	DUC (9 years)
2	Insabato et al. [20]	65	Male	NR	100	Negative	Negative	Positive	Positive	No	Yes	DOD (24 months)
3	Soufi et al. [21]	16	Female	Hematemesis	NR	Negative	Negative	Positive	NR	NR	NR	Alive (18 months)
4	Pauser and Grimm [22]	37	Male	Reflux	20	Negative	Negative	Positive	NR	No	No	Alive, 3 years
5	Aggarwal et al. [57]	26	Male	Abd pain and black stools	100	Negative	Negative	Positive	Positive	NR	NR	Alive, 1 month
6	Masuzawa et al. [23]	29	Female	Abd pain and black stools	500	Negative	Negative	Positive	Positive	NR	NR	NR
7	Insabato et al. [24]	51	Male	Weight loss and anemia	250	Negative	Negative	Positive	Positive	No	No	Alive, 10 months

NR not reported, XRT radiotherapy, LR local recurrence, DUC dead of unknown cause, DOD dead of disease

**Table 5** Small intestine leiomyosarcoma cases, demographic, histopathological, and IHC characteristics, treatment, and outcome data

Case	References	Age	Gender	Site	Presenting Sxs	Size (cm)	Mitosis/50HPF	CD 117	CD 34	SMA	Desmin	Surgery	LR	Secondary mets	Outcome
1	Our series, 2015	56	Female	Ileum	GI bleed	8	3	Neg	Neg	Pos	Neg	Yes	No	No	Alive
2	Our series, 2015	76	Male	Duodenum	Weight loss	10	250	Neg	Neg	Pos	Pos	Yes	No	No	Dead
3	Our series, 2015	51	Female	Duodenum	Palpated mass	11	100	Neg	Neg	Pos	Pos	Yes	Yes	NR	NR
4	Miettinen et al. [25]	59	Male	Ileum	Intestinal obstruction	15.9	<5	Neg	Neg	Pos	Pos	Yes	Yes	Yes (abd)	DUC (192 months)
5	Miettinen et al. [25]	60	Male	Jejunum	Intestinal obstruction	NR	>100	Neg	Neg	Pos	Pos	Yes	NR	NR	DUC (148 mo)
6	Miettinen et al. [25]	69	Female	Jejunum	Intestinal obstruction	7	35	Neg	Neg	Pos	Pos	Yes	NR	NR	dead other causes (129 mo)
7	Miettinen et al. [25]	74	Male	Jejunum	Intestinal obstruction	8	>100	Neg	Neg	Pos	Pos	Yes	NR	NR	DUC (122 mo)
8	Miettinen et al. [25]	63	Female	NR	Intestinal obstruction	7	55	Neg	Neg	Pos	Pos	Yes	NR	NR	LFU (84 mo)
9	Miettinen et al. [25]	40	Female	NR	GI bleed	15	45	Neg	Neg	Pos	Pos	Yes	NR	NR	DUC (64 mo)
10	Miettinen et al. [25]	67	Female	Ileum	GI bleed	5	>100	Neg	Neg	Pos	Pos	Yes	NR	NR	DUC (49 mo)
11	Miettinen et al. [25]	18	Female	Jejunum	GI bleed	12	100	Neg	Neg	Pos	Pos	Yes	NR	NR	DOD (33 mo)
12	Miettinen et al. [25]	49	Male	NR	Perforation	20	55	Neg	Neg	Pos	Pos	Yes	NR	Yes (liver and lungs)	DOD (27 mo)
13	Miettinen et al. [25]	80	Male	ILEUM	Abd pain	17	45	Neg	Neg	Pos	Pos	Yes	NR	NR	DUC (18 mo)
14	Miettinen et al. [25]	78	Male	NR	Weight loss	11	75	Neg	Neg	Pos	Pos	Yes	NR	NR	DOD (9 mo)
15	Miettinen et al. [25]	50	Male	NR	Hernia	8	35	Neg	Neg	Pos	Pos	Yes	NR	NR	DUC (6 mmo)
16	Miettinen et al. [25]	41	Male	NR	NR	4	95	Neg	Neg	Pos	Pos	Yes	NR	NR	LFU
17	Miettinen et al. [25]	48	Male	NR	NR	9	>100	Neg	Neg	Pos	Pos	Yes	NR	NR	LFU
18	Miettinen et al. [25]	63	Female	Jejunum	NR	29	>100	Neg	Neg	Pos	Pos	Yes	NR	Yes (liver)	LFU
19	Miettinen et al. [25]	67	Female	Ileum	NR	6	>100	Neg	Neg	Pos	Pos	Yes	NR	NR	LFU
20	Miettinen et al. [7]	61	Male	Duodenum	GI bleed	10	80	Neg	Neg	Pos	Pos	Yes	NR	NR	DOC (175 mo)
21	Miettinen et al. [7]	55	Male	Duodenum	NR	19	30	Neg	Neg	Pos	Pos	Yes	No	yes (liver)	DOD (147 mo)
22	Miettinen et al. [7]	58	Female	Duodenum	NR	13.8	>100	Neg	Neg	Pos	Pos	Yes	NR	NR	DUC (141)

**Table 5** continued

Case	References	Age	Gender	Site	Presenting Sxs	Size (cm)	Mitosis/50HPF	CD 117	CD 34	SMA	Desmin	Surgery	LR	Secondary mets	Outcome
23	Miettinen et al. [7]	46	Male	Duodenum	Anemia	13	>100	Neg	Neg	Pos	Pos	Yes	NR	NR	DUC (75 mo)
24	Miettinen et al. [7]	51	Female	Duodenum	Abd mass	12	>100	Neg	Neg	Pos	Pos	Yes	No	Yes (liver)	DOD (37 mo)
25	Insabato et al. [20]	50	Male	Ileum		7	100	Neg	Neg	Pos	Pos	Yes	No	No	Alive (72 mo)
26	Kefalas et al. [26]	65	Female	Duodenum	Recurrent pancreatitis	1.4	NR	Neg	NR	Pos	Pos	No (endoscopic papillectomy)	No	No	Alive (18 mo)
27	Agaimy and Wunsch [3]	77	Female	Ileum	Abd pain	NR	100	Neg	NR	Pos	Pos	Yes	Yes	No	Alive (4 months)
28	Pahwa et al. [27]	23	Male	Duodenum	Cutaneous lesions	NR	NR	Neg	Neg	Pos	NR	No	NR	NR	DOD (9 mo)
29	Lee et al. [58]	50	Female	Jejunum	NR	6	Multiple	Neg	Neg	Pos	NR	NR	NR	NR	NR
30	Jabr and Skeik [28]	80	Female	Small intestine	Anemia	3	NR	Neg	Neg	Pos	Pos	Yes	No	No	Alive, 24 mo

NR not reported, Neg negative, Pos positive, LR local recurrence, DUC dead of unknown cause, DOD dead of other causes, LFU lost to follow-up

On imaging, LMS should be considered in the differential of a large circumscribed and heterogeneous abdominal mass [38]. When compared to GISTs that appear as solid smoothly contoured masses, LMSs typically appear as large masses with varying degrees of necrosis, calcifications, and heterogeneous contrast enhancement [39]. Endoscopic ultrasound (EUS) remains the most useful method of distinguishing most of the GI mesenchymal tumors [40, 41]. LMS or GISTs are suspected when the tumor disrupts normal tissue planes, has cystic spaces, or is associated with enlarged lymph nodes [42]. However, pathological confirmation of LMS is necessary, and a preoperative diagnosis remains challenging. A preoperative biopsy is generally not recommended in potentially resectable tumors. If a biopsy is undertaken, an EUS-guided biopsy is recommended to decrease the theoretical risk of tumor capsule rupture and peritoneal seeding [43]. Pathological diagnosis of LMS requires the detection of nuclear atypia, necrosis, and high mitotic counts in addition to the IHC stains showing negative CD117, negative CD 34, and positive smooth muscle cell markers in most of the cases [4, 5].

As for the risk factors for LMS, age, radiation therapy exposure, genetic predisposition, inflammatory bowel disease, and immunosuppression have all been implicated. Even though gastric LMS had a relatively young median age at diagnosis (37 years) in our case review, the general median age at diagnosis of other LMS is 55 years and above. There are several reports in the literature on the association between pelvic radiation therapy and rectal LMS development decades later [44, 45]. One of our patients (case 5) has a personal history of breast cancer, but there is no mention of the presence of a pertinent positive family history in any of the LMS cases reported to suggest a familial association. However, genetic factors including the frequent presence of the K-ras oncogene mutation in association with LMS have been reported in older LMS series that preceded the GIST era [46]. Also preceding the GIST era in 1998, a series on 11,000 patients reported a possible relationship between LMS and Crohn's disease. Six percentage of the patients with LMS also had a history of Crohn's disease [47]. Some studies report on LMS development in patients with immunosuppression, whether due to human immunodeficiency virus (HIV) infection or solid organ transplant recipients. This has been linked to Epstein-Barr virus (EBV) infection in most of these cases [48-50].

Similar to our cases, complete surgical resection with negative margins remains the gold standard of treatment. Lymph node dissection is unnecessary given the low likelihood of nodal metastasis [51]. As for adjuvant or neoadjuvant therapy, there are no randomized trials to date on GI LMS that show a benefit of hormonal therapy, chemotherapy, or radiation therapy [52]. In our case series, 2 patients, with small and large intestine LMS, received

**Table 6** Colorectal leiomyosarcoma cases, demographic, clinical, and histopathological characteristics, treatment, and outcome data

Case	References	Age	Site	Gross appearance	Mitosis/50HPF	Surgery	Chemo	XRT	Primary mets	Secondary mets	LR	Outcome
1	Our case series	68	Transverse colon	Pedunculated	150	Yes	Yes	No	Yes	No	Yes	Dead
2	Our case series	75	Rectum	Ulcerated	100	Yes	No	No	No	Yes	Yes	Dead
3	Our case series	38	Cecal	Ulcerated	100	Yes	No	No	No	No	No	Alive
4	Our case series	24	Sigmoid	Pedunculated	100	Yes	No	No	Yes	No	Yes	Dead
5	Our case series	47	Rectum	Ulcerated	150	Yes	No	No	No	Yes	Yes	Dead
6	Our case series	69	Sigmoid	Pedunculated	250	Yes	No	No	Yes	Yes	Yes	Dead
7	Miettinen et al. [29]	40	Rectum	Polypoid	45	NR	NR	NR	NR	NR	NR	Alive (27 years)
8	Miettinen et al. [29]	63	Rectum	Polypoid	68	NR	NR	NR	NR	NR	NR	Alive (16 years)
9	Miettinen et al. [29]	52	Rectum	Intramural	46	NR	NR	NR	NR	NR	NR	DOC
10	Miettinen et al. [29]	67	Rectum	Plaque	>100	NR	NR	NR	No	Yes	NR	DOC
11	Miettinen et al. [29]	79	Rectum	Polypoid	26	NR	NR	NR	NR	NR	NR	DOC
12	Miettinen et al. [29]	32	Rectum	Polypoid	>100	NR	NR	NR	NR	NR	NR	Alive (3 years)
13	Miettinen et al. [29]	73	Rectum	NA	>100	NR	NR	NR	NR	NR	NR	DOD
14	Miettinen et al. [29]	24	Rectum	Polypoid	62	NR	NR	NR	NR	NR	NR	NR
15	Miettinen et al. [8]	41	Cecum	Pedunculated	100	NR	NR	NR	NR	NR	NR	NR
16	Miettinen et al. [8]	61	Ascending colon	Sessile	>100	NR	NR	NR	NR	NR	NR	Alive (12 years)
17	Miettinen et al. [8]	36	Sigmoid	Polypoid	>100	NR	NR	NR	No	Yes	NR	DOD
18	Miettinen et al. [8]	54	Descending colon	Polypoid	>100	NR	NR	NR	NR	NR	NR	DOD
19	Miettinen et al. [8]	66	Ascending colon	Polypoid	38	NR	NR	NR	No	Yes	No	DOD
20	Miettinen et al. [8]	76	Cecum	Multinodular	>100	NR	NR	NR	No	Yes	No	DOD
21	Miettinen et al. [8]	75	Ascending colon	Plaque	>100	NR	NR	NR	No	Yes	No	DOD
22	Insabato et al. [20]	65	Descending colon	Polypoid	100	NR	NR	NR	No	Yes	No	DOD
23	Michalopoulos et al. [30]	67	Transverse colon	Polypoid	NR	Yes	No	No	No	No	No	Alive (2 years)
24	Resch et al. [31]	70	Sigmoid	Intramural	100	NR	NR	NR	NR	NR	NR	DOD
25	Agaimy and Wunsch [3]	52	Sigmoid	Intramural	55–166	NR	NR	NR	NR	NR	NR	NR
26	Hamai et al. [32]	66	Sigmoid	Polypoid	100	Yes	Yes	No	Yes	Yes	No	DOD
27	Basu et al. [33]	79	Rectum	Intramural	Numerous	Yes	No	No	No	NR	NR	alive
28	Kourda et al. [34]	NR	Rectum	NR	Numerous	NR	NR	NR	No	Yes	NR	DOD
29	Kourda et al. [34]	NR	Rectum	NR	Numerous	NR	NR	NR	No	Yes	NR	NR
30	Ouh et al. [35]	52	Rectum	NR	>100	Yes	Yes	No	No	NR	NR	NR
31	Figueiredo et al. [36]	70	Rectum	Polypoid	>50	Yes	No	No	No	No	No	Alive (3 years)

NR not reported, XRT radiotherapy, LR local recurrence, DOD dead of disease, DOC dead of other causes

adjuvant chemotherapy with one of them receiving doxorubicin. However, one patient passed away, and the other patient was lost to follow-up after 2 recurrences within 3 years. Regarding the other cases of LMS reviewed, one additional patient with small intestine LMS had metastasis at diagnosis and received adjuvant chemotherapy and then passed away 9 months later. Two additional colorectal LMS patients received adjuvant chemotherapy where one had metastasis at diagnosis and passed away, while the other was lost to follow-up. No specific details on the type of chemotherapy were found. Doxorubicin and ifosfamide are the drugs commonly used in soft tissue sarcomas. However, for LMS, studies failed to show efficacy of these regimens. A retrospective study on first-line chemotherapy in unresectable or metastatic LMS showed a response rate of only 18 % [53]. As for gemcitabine and docetaxel, they have benefit in the adjuvant setting in uterine LMS [54], but this has not been proven yet in non-uterine LMS. Regarding the use of targeted therapy, PALETTE study addressed the use of the tyrosine kinase inhibitor pazopanib in advanced soft tissue sarcomas and did not demonstrate significant benefits specifically against LMS [55].

Retroperitoneal and abdominal LMS were reported to have higher recurrence rates than LMS at other sites [56]. When studying the GI LMS in particular, the relatively small number of cases in the literature limits survival analysis. In a review by Aggarwal et al. [57], it was suggested that colonic LMSs are more aggressive than those located in the small bowel or rectum. A study on primary GI LMS by Yamamoto et al. [15] found that size being equal or more than 5 cm is associated with a worse prognosis. In the same study, they did not find a significant effect of mitotic count on prognosis. The presence of K-ras mutation and the association between radiation therapy history and LMS have also been associated with worse prognosis in the literature [44, 46].

## Conclusion

Our review of 76 GI LMS cases includes, to our knowledge, the largest number of combined GI LMS cases reported. It sheds light on the common presentations, variable gross appearances, microscopic appearance characterized by atypia, high mitotic count, and necrosis, and IHC pathological diagnosis. It shows that the age range is variable and the presentation is non-specific, making pathological diagnosis essential. In addition to that, the review highlights surgery as the mainstay of treatment with negative margins attained most of the times. Adjuvant chemotherapy is used in around 7–27 % of the cases mainly small intestinal and colorectal LMS. However, LMS has a high risk of recurrence reaching 39–80 % and

secondary metastasis reaching 55–71 % in small intestinal and colorectal cases. The relatively small number of patients is a limitation on outcome analysis. Nevertheless, it seems that small intestinal LMS patients have a bad prognosis with only 17.9 % alive at a median follow-up of 4.7 years. CRC LMS have a better survival outcome with 30 % alive at 7.5 years. As for the esophageal and gastric LMS, with small sample sizes, gastric LMS appears to have the highest percentage of patients alive, but with the shortest follow-up period (0.5 years) and without enough power to conclude accurate survival outcome data.

It is important to note that the retrospective nature of all the included studies limits the completeness of the data collected. Further prospective studies with better follow-up are required for more appropriate survival analysis. Also, in light of the high frequency of recurrence and metastasis, enrolling patients in clinical randomized trials to investigate the role of chemotherapy, radiation therapy, and targeted therapy is required for better control of this rare aggressive GI tumor. Two clinical trials that include small intestinal LMS are registered on [clinicaltrials.gov](http://clinicaltrials.gov). One is on the use of erlotinib and cetuximab in patients with advanced GI or head and neck Cancer (NCT00397384), and the other is on the use of vismodegib and NOTCH inhibitors in patients with advanced or metastatic sarcomas (NCT01154452). However, those two trials include a wide variety of other malignancies and only advanced stage cancers. New trials that address GI LMS more specifically and earlier stages of the disease are needed.

## Compliance with ethical standards

**Conflict of interest** None.

## References

1. Kumar V, Abbas AK, Fausto NMR. Robbins basic pathology, vol. 8. Philadelphia: Elsevier; 2007.
2. Evans HL, Chawla SP, Simpson C, Finn KP. Smooth muscle neoplasms of the uterus other than ordinary leiomyoma. A study of 46 cases, with emphasis on diagnostic criteria and prognostic factors. *Cancer*. 1988;62:2239–47.
3. Agaimy A, Wunsch PH. True smooth muscle neoplasms of the gastrointestinal tract: morphological spectrum and classification in a series of 85 cases from a single institute. *Langenbecks Arch Surg*. 2007;392:75–81.
4. Greenson JK. Gastrointestinal stromal tumors and other mesenchymal lesions of the gut. *Mod Pathol Off J U S Can Acad Pathol Inc*. 2003;16:366–75.
5. Yamaguchi U, Hasegawa T, Masuda T, et al. Differential diagnosis of gastrointestinal stromal tumor and other spindle cell tumors in the gastrointestinal tract based on immunohistochemical analysis. *Virchows Arch*. 2004;445:142–50.
6. Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with

- esophageal leiomyomas and leiomyosarcomas. *Am J Surg Pathol*. 2000;24:211–22.
7. Miettinen M, Kopczynski J, Makhlof HR, et al. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum. *Am J Surg Pathol*. 2003;27:625–41.
  8. Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Gastrointestinal stromal tumors and leiomyosarcomas in the colon: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases. *Am J Surg Pathol*. 2000;24:1339–52.
  9. Kubota T. Gastrointestinal stromal tumor (GIST) and imatinib. *Int J Clin Oncol*. 2006;11:184–9.
  10. Lux ML, Rubin BP, Biase TL, et al. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. *Am J Pathol*. 2000;156:791–5.
  11. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science*. 2003;299:708–10.
  12. Emile J, Théou N, Tabone S, et al. Clinicopathologic, phenotypic, and genotypic characteristics of gastrointestinal mesenchymal tumors. *Clin Gastroenterol Hepatol*. 2004;2:597–605.
  13. Pantaleo MA, Astolfi A, Indio V, et al.: SDHA Loss-of-Function Mutations in KIT-PDGFR Wild-Type Gastrointestinal Stromal Tumors Identified by Massively Parallel Sequencing. *J Natl Cancer Inst*. 2011.
  14. Katz SC, DeMatteo RP. Gastrointestinal stromal tumors and leiomyosarcomas. *J Surg Oncol*. 2008;97:350–9.
  15. Yamamoto H, Handa M, Tobo T, et al. Clinicopathological features of primary leiomyosarcoma of the gastrointestinal tract following recognition of gastrointestinal stromal tumours. *Histopathology*. 2013;63:194–207.
  16. Stelow EB, Jones DR, Shami VM. Esophageal leiomyosarcoma diagnosed by endoscopic ultrasound-guided fine-needle aspiration. *Diagn Cytopathol*. 2007;35:167–70.
  17. Lindenmann J, Matzi V, Maier A, Smolle-Juettner FM. Transthoracic esophagectomy and lobectomy performed in a patient with synchronous lung cancer and combined esophageal cancer and esophageal leiomyosarcoma. *Eur J Cardio Thorac Surg*. 2007;31:322–4.
  18. Zhu X, Zhang XQ, Li BM, Xu P, Zhang KH, Chen J. Esophageal mesenchymal tumors: endoscopy, pathology and immunohistochemistry. *World J Gastroenterol*. 2007;13:768–73.
  19. Pramesh CS, Pantvaitya GH, Moonim MT, Jambhekar NA, Sharma S, Deshpande RK. Leiomyosarcoma of the esophagus. *Dis Esophagus*. 2003;16:142–4.
  20. Insubato L, Di Vizio D, Ciancia G, Pettinato G, Tornillo L, Terracciano L. Malignant gastrointestinal leiomyosarcoma and gastrointestinal stromal tumor with prominent osteoclast-like giant cells. *Arch Pathol Lab Med*. 2004;128:440–3.
  21. Soufi M, Errougani A, Chekkof RM. Primary gastric leiomyosarcoma in young revealed by a massive hematemesis. *J Gastrointest Cancer*. 2009;40:69–72.
  22. Pauser U, Grimm H. Intramucosal leiomyosarcoma of the stomach following hereditary retinoblastoma in childhood—a case report and review of the literature. *World J Surg Oncol*. 2008;6:131.
  23. Masuzawa N, Kishimoto M, Nishimura A, et al. Gastric leiomyosarcoma manifesting peculiar findings: radiological-pathological correlation. *Pathol Int*. 2009;59:306–11.
  24. Insubato L, Masone S, Campione S, et al. Coexistence of primary gastric giant cell-rich leiomyosarcoma and gastrointestinal stromal tumor: report of a very rare combination and review of the literature. *Int J Surg Pathol*. 2012;20:74–8.
  25. Miettinen M, Sobin LH, Lasota J. True smooth muscle tumors of the small intestine: a clinicopathologic, immunohistochemical, and molecular genetic study of 25 cases. *Am J Surg Pathol*. 2009;33:430–6.
  26. Kefalas CH, Altrabulsi B, Milvenan JS, Goldschmiedt M. Endoscopic electrosurgical snare resection of leiomyosarcoma of main duodenal papilla. *Gastrointest Endosc*. 2004;59:743–5.
  27. Pahwa M, Girotra M, Rautela A, et al. Periapillary leiomyosarcoma presenting with cutaneous metastases: a rare entity. *South Med J*. 2010;103:1190–1.
  28. Jabr FI, Skeik N. A leiomyosarcoma of the small bowels causing obscure gastrointestinal bleeding diagnosed by capsule endoscopy. *J Med Liban*. 2010;58:238–40.
  29. Miettinen M, Furlong M, Sarlomo-Rikala M, et al. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases. *Am J Surg Pathol*. 2001;25:1121–33.
  30. Michalopoulos A, Papadopoulos VN, Basdanis G, et al. Colorectal gastrointestinal mesenchymal tumours. Report of a stromal case of the rectum (GIST) and a leiomyosarcoma of the transverse colon. *Tech Coloproctol*. 2004;8:155–7.
  31. Resch T, Oberhuber R, Zitt M, et al. Leiomyosarcoma of the colon: unresolved issues of a rare but highly aggressive malignancy. *Am Surg*. 2011;77:E62–4.
  32. Hamai Y, Hihara J, Emi M, et al. Leiomyosarcoma of the sigmoid colon with multiple liver metastases and gastric cancer: a case report. *BMC Gastroenterol*. 2012;12:1.
  33. Basu I, Lemonas P. Leiomyosarcoma of the rectum following pelvic irradiation: a difficult histological diagnosis. *Ann Roy Coll Surg*. 2012;94:44–5.
  34. Kourda N, Kourda J, Aouam J, et al. Rectal leiomyosarcoma: report on two cases and a practical approach to differential diagnosis. *Pathologica*. 2010;102:417–9.
  35. Ouh YT, Hong JH, Min KJ, et al. Leiomyosarcoma of the rectum mimicking primary ovarian carcinoma: a case report. *J Ovarian Res*. 2013;6:2–5.
  36. Figueiredo JA, Andrade AFZBD, Carneiro BGMCE, et al. Rectal leiomyosarcoma, three-year follow-up. *J Coloproctol (Rio Janeiro)*. 2012;32:72–4.
  37. Conlon KC, Casper ES, Brennan MF. Primary gastrointestinal sarcomas: analysis of prognostic variables. *Ann Surg Oncol*. 1995;2:26–31.
  38. Kurugoglu S, Ogut G, Mihmanli I, et al. Abdominal leiomyosarcomas: radiologic appearances at various locations. *Eur Radiol*. 2002;12:2933–42.
  39. Lee SH, Ha HK, Byun JY, et al. Radiological features of leiomyomatous tumors of the colon and rectum. *J Comput Assist Tomogr*. 2000;24:407–12.
  40. Yasuda K, Cho E, Nakajima M, Kawai K. Diagnosis of submucosal lesions of the upper gastrointestinal tract by endoscopic ultrasonography. *Gastrointest Endosc*. 1990;36:S17–20.
  41. Boyce GA, Sivak MV, Rösch T, et al. Evaluation of submucosal upper gastrointestinal tract lesions by endoscopic ultrasound. *Gastrointest Endosc*. 1991;37:449–54.
  42. Palazzo L, Landi B, Cellier C, Cuillierier E, et al. Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours. *Gut*. 2000;46:88–92.
  43. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: colon cancer. V 32012. [https://www.nccn.org/professionals/physician\\_gls/PDF/colon.pdf](https://www.nccn.org/professionals/physician_gls/PDF/colon.pdf). Accessed Oct 2015, p. 27.
  44. Futuri S, Donohoe K, Spaccavento C, Yudelman I. Rectal leiomyosarcoma: a rare and long-term complication of radiation therapy. *BMJ Case Rep*. 2014;2014:bcr2014205240.
  45. Oruc M, Mayır B, Bilecik T, et al. Rectal leiomyosarcoma, late complication of pelvic radiotherapy. *Int J Colorectal Dis*. 2015;30:571–2.
  46. Hill MA, Gong C, Casey TJ, et al. Detection of K-ras mutations in resected primary leiomyosarcoma. *Cancer Epidemiol Biomark Prev*. 1997;6:1095–100.

47. Hill MA, Mera R, Levine EA, et al. Leiomyosarcoma: a 45-year review at Charity Hospital, New Orleans/Discussion. *Am Surg.* 1998;64:53.
48. Chaves NJ, Kotsimbos TC, Warren MA, et al. Cranial leiomyosarcoma in an Epstein–Barr virus (EBV)-mismatched lung transplant recipient. *J Hear lung Transpl.* 2007;26:753–5.
49. Tahri A, Noel G, Figuerella-Branger D, et al. Epstein–Barr virus associated central nervous system leiomyosarcoma occurring after renal transplantation: case report and review of the literature. *Cancer Radiother J la Soc Fr Radiother Oncol.* 2003;7:308–13.
50. Tetzlaff MT, Nosek C, Kovarik CL. Epstein–Barr virus-associated leiomyosarcoma with cutaneous involvement in an African child with human immunodeficiency virus: a case report and review of the literature. *J Cutan Pathol.* 2011;38:731–9.
51. Sakurai S, Fukasawa T, Chong J, et al. C-kit gene abnormalities in gastrointestinal stromal tumors (tumors of interstitial cells of cajal). *Jpn J Cancer Res.* 1999;90:1321–8.
52. Martin-Liberal J. Leiomyosarcoma: principles of management. *Intractable Rare Dis Res.* 2013;2:127–9.
53. Oosten AW, Seynaeve C, Schmitz PIM, et al. Outcomes of first-line chemotherapy in patients with advanced or metastatic leiomyosarcoma of uterine and non-uterine origin. *Sarcoma.* 2009;2009:1–6.
54. Hensley ML, Ishill N, Soslow R, et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I–IV high grade uterine leiomyosarcoma: results of a prospective study. *Gynecol Oncol.* 2009;112:563–7.
55. Van der Graaf WTA, Blay J-Y, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2012;379:1879–86.
56. Gladdy RA, Qin L-X, Moraco N, et al. Predictors of survival and recurrence in primary leiomyosarcoma. *Ann Surg Oncol.* 2013;20:1851–7.
57. Aggarwal G, Sharma S, Zheng M, et al. Primary leiomyosarcomas of the gastrointestinal tract in the post-gastrointestinal stromal tumor era. *Ann Diagn Pathol.* 2012;16:532–40.
58. Lee KH, Fiedler P, Passarelli J, Bobrow S. Autoimmune hemolytic anemia associated with postirradiation malignant stromal tumor (leiomyosarcoma) of the jejunum. *Ann Diagn Pathol.* 2000;4:367–9.