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ORIGINAL RESEARCH

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Systemic therapy is effective in the management of leiomyomatosis

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Abstract

Objective: Leiomyomatosis is an intermediate neoplasm of uterine origin. There is limited understanding of its natural history and response to systemic therapy. The objective of this retrospective review is to describe the management and response to systemic therapy for leiomyomatosis. **Methods**: A retrospective chart review was performed from 1 January 2000 – 1 February 2021 for patients 18 years of age or older with leiomyomatosis treated at The Royal Marsden Hospital. Descriptive statistics were performed. **Results**: Fifteen female patients with a median age of 45 years (range 34–49) were identified. Patients were ethnically diverse (Black n = 4 [26%], Asian n = 1 [7%], Caucasian n = 6 [40%], other n = 3 [20%], Unknown n = 1 [7%]). Most patients presented with advanced disease (n = 12/15, 80%); common sites being abdomen (n = 9/12, 75%), abdominal veins (n = 6/12, 50%), including the IVC 4/12 (30%). At presentation, two patients (17%) had cardiac extension from the IVC. Eleven patients (73%) underwent surgery and 4 (27%)active surveillance as first treatment. All patients undergoing surgery had residual disease (n = 9/9 for those with available data). Ten patients received systemic therapy for advanced disease (median 3 treatments, range 1–5) and most patients (n = 9/10, 90%) were treated with endocrine therapy. Response rate (RR) and clinical benefit rate (CBR) was higher for GNRH agonist (RR 43%, CBR 86%) and GNRH agonist + aromatase inhibitor (AI) (RR/CBR 100%), than AI alone (RR 0%, CBR 66%). Patients were only treated with non-endocrine systemic therapy after failure of endocrine therapy, and no responses were seen. No patients had confirmed malignant transformation; two patients had clinical suspicion of transformation but no correlative features on repeat biopsy. **Conclusions**: Leiomyomatosis is a rare, but morbid condition. The mainstay of treatment for advanced disease is endocrine therapy, the choice of initial approach requires careful consideration within a multi-disciplinary team.

Keywords

leiomyomatosis; intra-vascular leiomyomatosis; soft tissue neoplasm; systemic therapy; aromatase inhibitor

1. Introduction

Leiomyomatosis is an ultra-rare soft tissue neoplasm of uterine origin. Histopathologically these tumours are composed of smooth muscle cells with low mitotic activity and absent to mild nuclear atypia. They resemble cellular leiomyomas and express myoid markers, but the degree of atypia does not fulfill the criteria for leiomyosarcoma [1] . Leiomyomatosis peritonealis disseminata describes the finding of multiple smooth muscle nodules specifically on the peritoneal surface. Vascular involvement or intravascular leiomyomatosis, can occur whereby intravascular growth of benign-appearing smooth muscle cells are seen in small and large vessels, including the pelvic veins, superior and inferior vena cava (IVC) with or without a uterine leiomyoma. It may be that leiomyomatosis clinically represents a spectrum of uterine disease with potential for dissemination to the peritoneum and vasculature. Very rarely, patients present with both renal cell carcinoma and multiple uterine and skin leiomyomas caused by an autosomal dominant mutation in fumarate hydratase gene, known as hereditary leiomyomatosis and renal cell carcinoma (HLRCC) [1]. However, for the purposes of this series, we focus on non-HLRCC associated leiomyomatosis.

Though histologically bland, leiomyomatosis can cause morbidity through vaginal bleeding and pelvic symptoms, and rarely intra-cardiac extension has been associated with sudden death [2]. Recently, intra-vascular proliferation has been shown to be associated with a variety of molecular alterations including unbalanced translocations such as der(14)t(12;14), deletions (del(14q)) involving *RAD51B* and specific recurrent

deletions of 1p, 22q, 2q, 1q, 13q, 3q, 10q [3, 4]. These multiple chromosomal alterations distinguish leiomyomatosis from benign leiomyoma, but the specific molecular drivers of proliferation in leiomyomatosis are as yet unknown [3, 4].

Patients are predominantly pre-menopausal with median age of 42–45.5 years [3, 5]; however, the reported age range in the literature varies between 28–82 years [3, 5]. Patients can present with uterine, abdominal and pelvic, as well as distant disease, including lung and vascular involvement [2]. There is little published information on the ethnicity or clinical characteristics of women who present with leiomyomatosis [6, 7].

There is no international consensus for the management of leiomyomatosis. Often, initial treatment choice is made due to the clinical suspicion of a common diagnosis, namely uterine fibroids [8]. The majority of the literature focuses on surgical management of both pelvic/uterine [9] and vascular disease [2, 10]. There are few case reports of women with advanced disease being treated with aromatase inhibitors [11, 12], GnRH agonists [12, 13] or antagonists [14], Vitamin D/sun exposure [12] and chemotherapy (doxorubicin-dacarbazine and liposomal doxorubicin) [15]. There are published case reports and case series describing the use of adjuvant endocrine therapy [2, 16]; however, there are challenges with interpretation given the small number of patients, age, hormonal status and presence/absence of ovaries.

Here, we describe the management and outcomes of fifteen women with leiomyomatosis treated at a single institution to understand the natural history, outcome with surgery and benefit of systemic therapy. An understanding of such outcomes is key to inform a multi-disciplinary approach to care for patients with this unusual soft tissue neoplasm.

2. Methods

Institutional approval was obtained (SE1027) prior to commencing this study. Patients 18 years of age or older with a diagnosis of leiomyomatosis on expert pathology review were identified from the prospectively maintained Royal Marsden Sarcoma Unit database. All patients with those clinical features where histology showed any atypical features or was doubtful (ie not conclusive between benign and malignant) were all excluded A retrospective chart review was performed for patients diagnosed between 1 January 2000 – 1 December 2021. All new patients were reviewed at a multi-disciplinary tumour board team (MDT) meeting. There is no institutional standard surveillance for patients with leiomyomatosis. Our standard surveillance strategy for patients with high-grade completely resected gynaecological soft tissue sarcomas is a Computed Tomography (CT) chest, abdomen, pelvis or chest imaging + Magnetic Resonance Imaging (MRI) abdo/pelvis every 3 months for the first 2 years, every 6 months until 5 years, followed by annual surveillance until 10 years. This protocol was often followed. For those treated with systemic therapy, re-staging CT or MRI scans were generally performed every 2–3 months. Response assessment was performed using Response Evaluation in Solid Tumours (RECIST) 1.1 [17].

The electronic patient record was used to extract baseline demographic, treatment, toxicity and follow-up data. Descriptive statistics were applied.

Residual disease was defined based on review of operative notes at the time of surgery indicating tumour remaining at the end of surgery, or disease present on pre-operative CT scan not amenable to surgery (i.e., lung nodules or vascular disease not removed at time of surgery) or first post-operative CT scan (within 3 months) consistent with residual disease. Time to systemic therapy was defined as time from surgery or date of diagnosis (if no surgery was performed) to start of systemic treatment. Data cut-off date was 1 February 2021.

3. Results

Fifteen patients were identified, with available baseline demographic information shown in Table 1. Median follow-up was 60 (range 0–180) months. All women were pre-menopausal at diagnosis and their ethnicity was diverse. Over half were nulliparous (n = 6/11, 55%); no woman became pregnant after their diagnosis. One woman had a history of ductal carcinoma in situ, but no others had a history of invasive cancer. Two thirds of women had a history of uterine fibroids, and one third (n = 5/15) had their diagnosis made after a surgery for presumed uterine fibroids. For those who had information available, all women presented with symptoms; most commonly abnormal vaginal bleeding or abdominal pain. One woman each presented with symptoms of IVC obstruction and non-fatal pulmonary embolism. One quarter of women with baseline staging data had venous involvement at presentation (Table 2), with 2 of these women having cardiac involvement. Of women who had vascular involvement, all were treated with therapeutic anticoagulation. Tumours were nearly universally hormone receptor positive (Estrogen Receptor (ER) Positive n = 14/15, 93%; Progesterone Receptor Positive n = 14/15, 93%).

None of the women died from leiomyomatosis or another cause during follow up.

Most women (n = 11/15, 73%) underwent upfront surgery (Table 3). Five of these women had surgery at another centre for management of presumed fibroids. Women underwent a variety of surgical procedures as primary treatment; most women (n = 8/11,73%) underwent at least a total abdominal hysterectomy (TAH), and over half of women also had either one or both ovaries removed (n = 6/11, 55%). Both women who underwent cardiac and abdominal surgery had both performed in one operation.

3.1 Systemic therapy

3.1.1 Post-surgery

Eleven women underwent surgery. None of the eight (n = 8/11, 73%) patients with adequate follow-up information were treated with adjuvant systemic therapy, and all underwent active surveillance after surgery. For the eight women with sufficient data, the median time to systemic therapy after surgery was 22.45 months (range 7– NR months). For these women, systemic therapy was started for radiological progression alone (n = 3/8, 38%), symptoms and radiological progression (n = 2/8, 25%) or symptoms alone (n = 1/8, 13%). The remaining two women (1 of these women had underwent

TABLE 1. Baseline characteristics of patients with leiomyomatosis.

Baseline characteristic		N = 15
Median age at diagnosis (range)		45 years (34–49)
Ethnicity	Black	4
	Asian	1
	White	6
	Other	3
	Unknown	1
Parity	P0	6
	P1	1
	P2	3
	P3 or greater	1
	Unknown	4
History of infertility		2
History of uterine fibroids		10
Presenting symptoms (n = 10)	Abnormal Vaginal Bleeding	4
	Abdominal/Pelvic Pain	5
	Thrombosis	1
	IVC compression	1
	Abnormal Vaginal Bleeding and Abdominal/Pelvic Pain	3
	Unknown	4

TABLE 2. Sites of involvement at presentation for patients with baseline staging imaging.

Large veins (IVC or SVC)	4/12
Pelvic veins	2/12
Heart	2/12
Uterus	12/12
Abdomen	11/12
Hydronephrosis	2/12
Umbilical nodule	1/12
Paraaortic lymphadenopathy	1/12
Lung nodules	5/12

a BSO) remain on active surveillance (120 and 140 months of follow up) at the time of data cut off.

3.1.2 Active surveillance

Median time to systemic therapy was not reached (range 5 months – NR) for the 4 women who underwent active surveillance as first treatment. One woman each started for radiological progression of vascular involvement, and both symptoms and radiological progression. Two women remain on active surveillance at a median follow-up of 4 months.

3.2 Outcomes

Ten women were treated with a median of 3 systemic therapies (range 1–5) (Table 4). All women were treated with at least 1 endocrine therapy. There were no radiological complete responses. Partial responses by RECIST 1.1 were seen for gonadatrophin releasing hormone (GNRH) agonist (n = 3/3, 100%), GNRH agonist + aromatase inhibitor (AI) (n = 3/7, 43%), but not for AI alone (n = 0/3, 0%). Duration of treatment was variable, with patients ultimately stopping for either progression or side effects. For patients treated with endocrine therapy, most stopped due to progressive disease (n = 9/14; 64%), but a significant number stopped due to treatment related side effects (n = 5/14; 36%). One patient with a radiological partial response who stopped due to side effects was changed from GNRH agonist + AI to a GNRH agonist alone. She required breaks from the GNRH agonist due to side effects, but had two sequential partial responses. This patient was subsequently unable to tolerate further endocrine therapy re-challenge and was transitioned to low dose oral cyclophosphamide for 5 months, stopping due to side effects. The best radiological response to cyclophosphamide was stable disease which has been maintained on active surveillance for 13 months. This has also coincided with her becoming menopausal. One woman had a break of 28 months off GNRH agonist + AI due to side effects after a partial response. She then re-started the same regimen with a further partial response. This patient stopped once again at 26 months due to side effects and remains on active surveillance with stable disease.

All four patients treated with chemotherapy had stable disease, with no radiological responses documented. Chemotherapy was given after progression on at least one line of endocrine therapy. One woman received chemotherapy as second, third, fourth and fifth line respectively. No patients stopped therapy due to progressive disease, rather due to patient choice (n = 2/3; 66%) or side effects (n = 1/3; 33%). One

TABLE 3. Details of first treatment.

Treatment		N = 15
Surgery		11
	Type of Surgery	
	TAH	2
	TAH + Unilateral SO	2
	TAH + BSO	2
	TAH + Pelvic resection of disease	1
	TAH + Vascular resection of disease	1
	Unilateral SO + Vascular resection of disease	1
	BSO + Pelvic resection of disease	1
	Pelvic resection of disease only	1
	Residual Disease Post Operatively	
	Yes	9
	No	0
	Unknown	3
Active surveillance		4

patient was treated with first-line nintedanib as part of a clinical trial, and was subsequently lost to follow up.

3.3 Cardiac involvement

Two women who presented with cardiac involvement underwent upfront surgery. Both women had a single operation for removal of the intra-cardiac, IVC tumour and pelvic tumour deposits. One subsequently developed progression in the pelvis and IVC within 3 months of surgery, but was subsequently lost to follow-up. The other had recurrent disease in the pelvis, IVC and right atrium 3 years after her initial surgery. This was treated with endocrine therapy, with a partial response. This patient has not undergone subsequent surgery and has had no deleterious effects on cardiac function.

One woman initially presented with SVC/IVC involvement, subsequently developed cardiac involvement on active surveillance and was started on a GNRH agonist with a partial response on their first interval imaging after 2 months (Fig. 1).

3.4 Hydronephrosis

Two women presented with hydronephrosis. One woman has unilateral hydronephrosis with normal renal function and continues on active surveillance. One woman had stenting for bilateral hydronephrosis, however, even with stenting one kidney became atrophic and her baseline renal function remains impaired (creatinine 120–160). She underwent a pelvic exenteration with ileal conduit formation, however developed recurrent disease 12 months after surgery.

3.5 Women treated with unilateral salpingo-oophorectomy (SO) or bilateral salopingo-oopherectomy (BSO)

Three women had SO (n = 3/11, 27%), 1 of whom was lost to follow-up. Both women with available data treated with SO started systemic therapy for progressive disease at 11.7 and 42.6 months respectively. Three women had a BSO as part of initial treatment, 1 was lost to follow up. One remains on active surveillance at 140 months post-surgery, 1 was treated with letrozole 7 months after surgery due to radiological progressive disease. Letrozole was stopped due to side effects and she has since remained stable on active surveillance for over 6 years.

3.6 Treatment at cut off by age

More women greater than or equal to 50 years of age were on active surveillance at data cut off compared to the younger age group (Table 5).

3.7 Transformation

Two women had imaging features concerning for transformation. Image-guided biopsies did not confirm evidence of transformation to high-grade malignancy, showing smooth muscle neoplasms with bland histologic features and no evidence of histologically atypical features (cellular atypia, mitotic activity or coagulative-type necrosis).

4. Discussion

To our knowledge, this represents the largest published cohort of women with leiomyomatosis treated with systemic therapy for advanced disease. As with other published series, women in our cohort were all pre-menopausal [3, 5], ethnically diverse [6, 7] and their upfront treatment was surgery [2, 18], most commonly a hysterectomy. As expected given the young age of our cohort, a smaller proportion underwent ovarian removal. This finding likely reflects consideration of fertility preservation and wish to avoid long-term complications of premature menopause for young women. The diagnosis was often incidental. We acknowledge that a significant number of women with leiomyomatosis will be referred after surgery elsewhere for presumed benign disease. At our institution, our approach is to offer these women radiological follow up. Adjuvant therapy is not recommended given the lack of evidence and assumption that many patients will have residual disease, as seen in our cohort. Our practice over time has

TABLE 4. Outcomes of systemic therapy.

Treatments	Duration of treatment (months)	Best response by RECIST 1.1					Reason for discontinuation		
(Median 3, range 1–5)		PR	SD	PD	UNK	PD	Side Effects	Patient Choice~	On Treatmment
Hormonal Therapy									
GNRH Agonist (n = 3)	1.5–47	3	0	0	0	1	1	0	1
GNRH Agonist + AI (n = 7)	1.5–28	3	3	1*	0	5	2	0	0
AI (n = 3)	4–13	0	2	0	1	1	2	0	0
Exemestane + Sirolimus (n = 1)	6	0	1	0	0	1	0	0	0
Ulipristal (n = 1)	3	0	0	1	0	1	0	0	0
Chemotherapy									
Doxorubicin (n = 1)	1	0	0	0	1	0	0	0	1
Cyclophosphamide (n = 2)	5–40.8	0	2	0	0	0	1	1	0
Gemcitabine-Dacarbazine (n = 1)	5	0	1	0	0	0	0	1	0
Other									
Nintedanib (n = 1)	11.7	0	1	0	0	1	0	0	0

** Patient treated for 1.5 months. ~ Not related to side effects.*

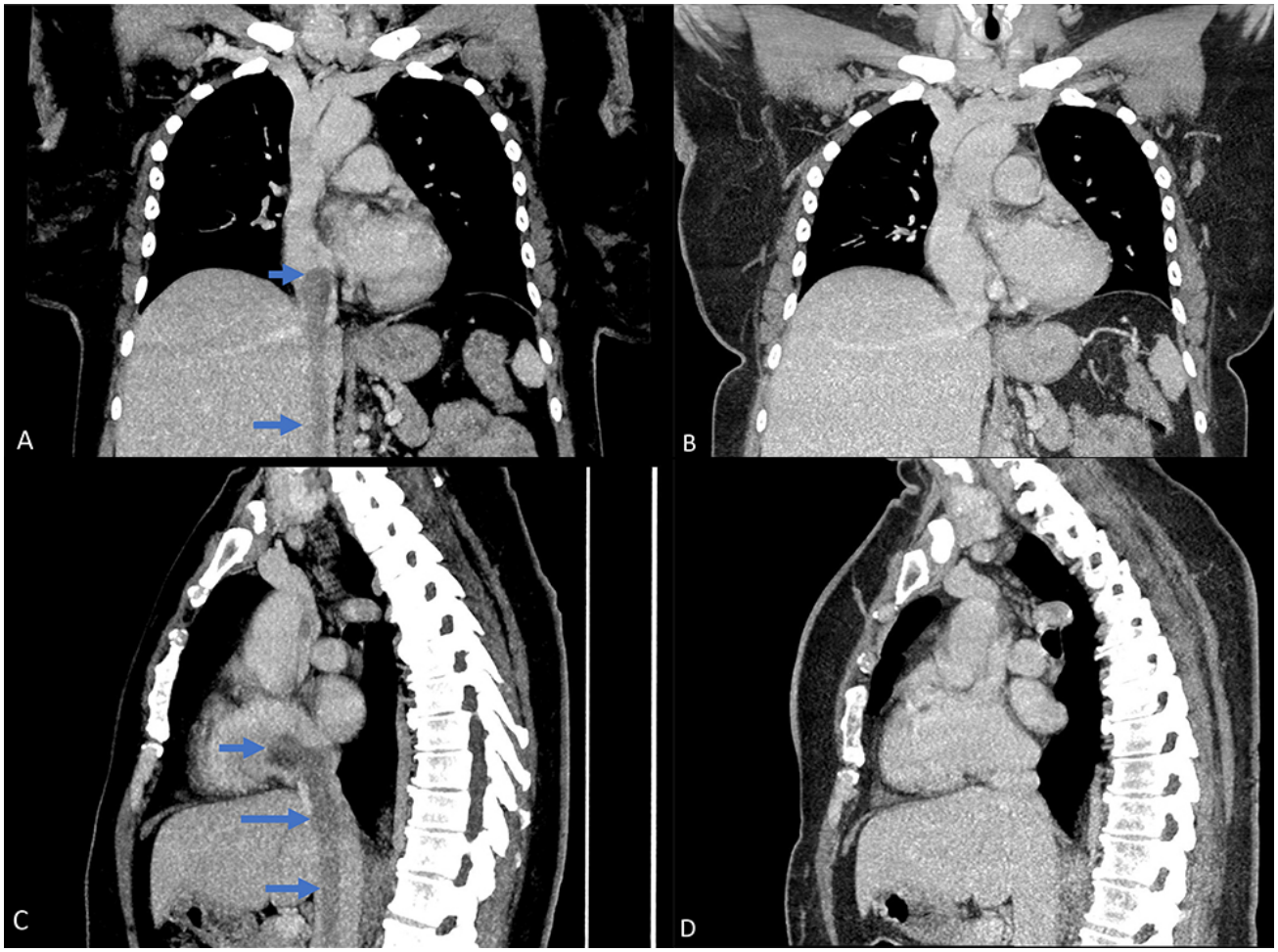

FIGURE 1. Partial response to GNRH agonist for woman presenting with venous involvement. CT thorax (Single portovenous phase post contrast) demonstrates tumour related thrombus extends through entire IVC into heart on pre-treatment images and resolution of IVC thrombus after 2 months of GNRH agonist. She had persisting disease in the low IVC and right common iliac vein (not shown). Coronal Images: (A) Pre-treatment scan. (B) Post treatment. Sagittal Images: (C) Pre Treatment. (D) Post treatment.

TABLE 5. Treatment stratified by age at data cut off (1 February 2021).

Treatment		Age <50 years	Age ≥50 years or BSO
Systemic treatment		1	1
	Hormone Therapy	0	1
	Chemotherapy	1	0
Surveillance		3	7
Unknown/Lost to follow up		1	2

shifted to also offering active surveillance for newly diagnosed patients with advanced disease. For women with a high body mass index, counselling and resources are offered to encourage weight loss given that adipose tissue manufactures estrogen [19, 20]. Within this framework, multi-disciplinary care is key.

In our cohort, the decision to start systemic therapy was more often prompted by radiological rather than both radiological and symptomatic progression. Radiological progression alone may warrant treatment for patients on active surveillance, particularly those with progressive vascular involvement or involvement near other critical organs (i.e., kidney). However, in the absence of progression near or at critical sites, the decision to start systemic therapy in the absence of progressive symptoms must be carefully considered as a significant proportion of patients stopped hormonal treatment due to side effects and there were no deaths from leiomyomatosis seen in our cohort.

Ultimately, most women in our cohort were treated with systemic therapy for recurrent or progressive disease. Radiological responses were only seen in woman treated with endocrine therapy. Benefit was documented with a range of endocrine agents. Given the small sample size, the benefit of GNRH agonist + AI versus GNRH agonist alone cannot be determined. However, given responses were seen in both groups, to reduce side effects, clinicians may wish to start with GNRH agonist alone, and assess response. If there is stabilisation of symptoms or radiological response on the first treatment scan, continuing on GNRH agonist alone is reasonable. Addition of an aromatase inhibitor can be considered for patients without stabilisation or response, or progression in a previously responding patient on GNRH agonist alone. It is important to note that patients were able to stop, re-start and derive benefit from further endocrine treatment at a later date. In order to mitigate treatment related toxicity clinicians may wish to set expectations for patients starting endocrine treatment and specialist nurse support is key. This may include a specific period of treatment, such as 1 year, followed by a break depending on tolerance and response. This approach is supported by our group of patients with a partial response who stopped due to side effects and restarted with benefit from re-challenge.

Responses to hormonal blockade in our cohort reinforce existing evidence that leiomyomatosis is hormonally driven [21, 22]. Acknowledging the very small sample size, the two women in our cohort post BSO have had relatively long-term stability on active surveillance. While interesting, this requires both longer follow up and outcomes from more women. However, this provides another clue that leiomyomatosis is hormonally driven. The role of inducing premature menopause as definitive treatment for women, particularly for those nearing natural menopause, warrants future consideration. In cases of women treated with hysterectomy alone, multi-disciplinary discussion regarding bilateral salpingo-oopherectomy for surgical menopause could be considered in women who are nearing natural menopause and completed their family to avoid the avoid need for future systemic therapy. Alternatively, a discussion can be had regarding starting hormone suppression for 1–2 years to induce early menopause.

The impact of chemotherapy for women in our cohort is less certain; while patients did have disease stabilization, we postulate that this benefit may have been mainly driven by the ovarian suppression induced by chemotherapy rather than direct anti-tumour effect, as suggested in pre-menopausal women with breast cancer [23]. More women over 50 years old were on active surveillance at the time of data cut off compared to those less than 50. Further work is required to understand this difference, but this suggests that a post-menopausal state may slow or stop growth of leiomyomatosis.

Importantly, there were no catastrophic vascular events or cardiac sequelae in patients in our cohort. In large case series, women with cardiac involvement are at risk of sudden death due to outflow tract obstruction [2]. Patients with vascular involvement were all treated with long term anti-coagulation. The thrombosis/haematology team plays an important role in the care of these patients. For example, patients with progressive vascular involvement while on anti-coagulation pose a therapeutic challenge for clinicians as one must explore whether plain thrombus is driving progression or if it is tumour-related. In our limited series, radiological partial responses were seen with endocrine therapy in patients with cardiac involvement. This highlights that multi-disciplinary care may enable patients with extensive vascular involvement to have a period of systemic therapy with close surveillance which may enable less extensive surgery or avoid high risk surgery all together. We acknowledge that this view differs from published cohorts reporting upfront, extensive surgery, however, given the responses seen with endocrine therapy in this disease, longer follow-up and international collaboration may further clarify such an approach, particularly for patients with cardiac involvement.

There are limitations to our retrospective study. Data were not available for the long-term impacts of hormone suppression on pre-menopausal women, as at our centre such screening and management is performed primarily by the patient's family physician. The effect of hormone suppression in pre-menopausal women is well documented [24], and women with

leiomyomatosis undergoing hormone suppression should have regular bone mineral density testing, counselling on exercise, vitamin D and calcium supplementation. While some patients had been pregnant prior to diagnosis, none of our patients became pregnant post diagnosis. However, given the age group that this affects, fertility discussion is an important consideration. There is no evidence to guide counselling, however, given the responses and stability with hormone suppression, this may suggest that the hormone surge of pregnancy may lead to worsening of leiomyomatosis. Women would need to have close, multi-disciplinary follow-up during pregnancy or fertility treatments.

5. Conclusions

Leiomyomatosis is a rare neoplasm of uterine origin. While the existing literature focuses on surgical management, our retrospective cohort illustrates the role of systemic therapy in long-term management of this disease. The majority of women develop recurrence after surgery, and response/stabilisation with endocrine treatments was seen in the majority of women, even with cardiac involvement. Side effects were an important reason for discontinuation, however, responses were seen with re-challenge allowing treatment breaks to be incorporated. The routine role of chemotherapy in this disease is less well defined. Future international collaboration is required to establish larger cohorts of women to better understand the timing and role of surgery, and optimal management of perimenopausal women.

AUTHOR CONTRIBUTIONS

AS, AO, RLJ, CB designed the research study. AS, AO, SY extracted data. SY provided images. AS performed statistical analysis. AS, CB wrote the manuscript. ABM, KT, CF, DB, AL, IJ and PHH contributed to data analysis and final manuscript review. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Institutional ethical approval from the Royal Marsden NHS Foundation Trust was obtained (SE1027) prior to commencing this study. Given the retrospective nature of this study, informed consent of participants was not required per institutional ethical approval.

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CONFLICT OF INTEREST

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