Original Article

Management and prognosis comparison between incidental and nonincidental intravenous leiomyomatosis: a retrospective single-center real-life experience

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Background: Intravenous leiomyomatosis (IVL) is a rare, difficult-to-treat type of smooth muscle tumor that originates from the uterine myoma. However, its clinical characteristics, management, and prognosis are not clearly understood. Moreover, the 2 different methods used to diagnose IVL—incidental and nonincidental—result in completely different treatments.

Methods: We conducted a single-center, retrospective study. Our real-life case series included patients pathologically diagnosed with IVL between July 2011 and December 2020. All patients with IVL were divided into 2 groups: an incidental group and a nonincidental group. Medical records of patients, including clinical characteristics, primary treatment, treatment after recurrence, and prognosis, were reviewed.

Results: A total of 39 patients were included in the study, with a median patient age of 47 years. Of the 39 cases, 15 (38.5%) were incidentally diagnosed with only intrapelvic tumors. Among the 24 patients with IVL in the nonincidental group, tumor spread in the inferior vena cava, right heart, and pulmonary artery was identified in 4, 17, and 3 patients, respectively. The most common symptoms were abnormal uterine bleeding in the incidental group and chest distress and dyspnea in the nonincidental group. Among the 15 patients in the incidental group, ovary-preserving surgery was performed in 6 young women (≤40 years old), of whom 3 underwent myomectomy. All 24 patients with IVL in the nonincidental group underwent thrombectomy without uterine or ovary preservation by multidisciplinary surgical treatment. Only 1 patient in each group underwent postoperative adjuvant therapy. During the median follow-up of 36.0 months, recurrence was recorded in 5 (12.8%) cases in the incidental group, with no deaths recorded. Only 1 patient was lost to follow-up. No recurrence was noted in the cases in the nonincidental group. Among the 5 patients who experienced recurrence, 4 received secondary surgical treatment and 1 received hormone therapy. All patients were alive as of this report.

Conclusions: Patients with IVL who are diagnosed incidentally have a higher recurrence risk than those who are diagnosed nonincidentally and undergo complete tumor resection. However, patients incidentally diagnosed with IVL can still experience long disease-free survival rates following secondary surgical treatment after recurrence.

Keywords: Intravenous leiomyomatosis (IVL); incidentally diagnosed; management; prognosis

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Introduction

Intravenous leiomyomatosis (IVL) is a rare type of smooth muscle tumor which was first reported in 1896 by Birch–Hirschfeld. Although IVL can behave malignantly, it is classified as a benign disease (1). Typically, IVL originates from uterine myoma and extends along the venous system to the ovarian vein, iliac vein, inferior vena cava (IVC), right heart, and pulmonary artery, causing various clinical symptoms, including sudden death (2). To date, owing to the low morbidity of IVL, only approximately 200 cases have been reported worldwide. It has been deemed difficult to treat and has a relatively high relapse rate (2,3), which may be related to the large tumor lesions, large vein involvement, and broad ligament involvement (4,5).

Primary treatment of IVL includes surgery, with either a 1- or 2-stage approach, and adjuvant therapy. Complete resection of IVL tumor lesions can effectively reduce the recurrence risk (6,7), but the extent of surgery and surgical pattern still lack conformity (8-10). Some studies have also stressed that a precise and full-scale preoperative evaluation is crucial for surgical planning and achieving successful outcomes (11,12). Adjuvant therapy to reduce the levels of estrogen, including gonadotropin-releasing hormone agonists, letrozole, and tamoxifen, is sometimes used to delay tumor recurrence, but its efficiency remains controversial (4,5,13).

The management methods for IVL patients with different tumor extents are quite different. Most cases of early-stage IVL confined to the pelvic cavity can be easily misdiagnosed or missed before surgery due to the lack of typical symptoms and supplementary examination (14). These cases are normally incidentally discovered via intraoperative exploration or postoperative pathology and treated by gynecologists. Surgical treatment for incidentally found IVL can include myomectomy and hysterectomy with/without bilateral salpingo-oophorectomy (BSO). However, some cases of advanced-stage IVL that invade beyond the pelvic cavity and cause dyspnea, shortness of breath, double lower-limb edema, and even sudden death, can be grossly identified by preoperative imaging, such as cardiac echocardiography or computed tomography venography (CTV). These patients may primarily be diagnosed by the cardiovascular disease department and receive multidisciplinary surgical treatment.

We conducted a retrospective study that included consecutive cases of IVL. All patients were closely followed up and their clinical characteristics, treatment, and prognosis results were collected by the authors in this study. We divided all cases into 2 groups—an incidental group and nonincidental group—to show differences in management and prognosis among patients with IVL. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5376/rc).

Methods

Participants

A single-center retrospective study on patients with IVL was conducted in Fudan University Zhongshan Hospital from July 2011 to December 2020. The diagnosis of IVL was pathologically confirmed in all cases. The medical records of patients were reviewed, and an attempt was made to follow-up each individual case by our multidisciplinary team.

Study protocol

Medical records, including the demographic information (age at diagnosis, menstrual history, and obstetric history), clinical information (operation history and chief complaint), auxiliary examination findings (imaging data including the site and size of lesions), and pathological findings [immunohistochemistry (IHC) data], were carefully reviewed. All cases received surgical treatment, and the extent of the lesion was recorded in detail by the surgeons interoperatively. Surgical records (site and size of tumor lesions and residual tumor lesions) were reviewed. All cases were followed up every 3 months for the first year, every 6 months for the next 3 years, and every 1 year thereafter according to our center's standardized practice. At each follow-up, physical examinations, imaging tests (magnetic resonance venography/CTV and echocardiography), postoperative therapy, and clinical symptoms were reviewed to monitor disease recurrence.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study

Table 1 Patient characteristics

Patients' characteristics	Incidental group (n=15)	Nonincidential group (n=24)	Total (n=39)
Age, median [range], years	47 [20–59]	46.5 [30–62]	47 [20–62]
Menopausal status, n (%)			
Pre-menopause	12 (80.0)	17 (70.8)	29 (74.4)
Natural menopause	2 (13.3)	4 (16.7)	6 (15.4)
Artificial menopause	1 (6.7)	3 (12.5)	4 (10.3)
Parous status, n (%)			
Yes	13 (86.7)	22 (91.7)	35 (89.7)
Never	2 (13.3)	2 (8.3)	4 (10.3)
Previous surgery history			
Myomectomy	1 (6.7)	5 (20.8)	6 (15.4)
Hysterectomy	0	4 (16.7)	4 (10.3)
None	14 (93.3)	15 (62.5)	29 (74.4)
Maximal myomas size, n (%)			
<50 mm	2 (13.3)	8 (33.3)	10 (25.6)
50–100 mm	7 (46.7)	7 (29.2)	14 (35.9)
>100 mm	2 (13.3)	2 (8.3)	4 (10.3)
NA	4 (26.7)	1 (4.2)	5 (12.8)
No myomas	0	6 (25.0)	6* (15.4)
Number of myomas (%)			
Solitary	3 (20.0)	2 (8.3)	5 (12.8)
Multiple	8 (53.3)	15 (62.5)	23 (59.0)
NA	4 (26.7)	1 (4.2)	5 (12.8)
No myomas	0	6 (25.0)	6 (15.4)
Extent of disease, n (%)			
Uterus and parauterine tissue	15 (100.0)	0	15 (38.5)
Iliac vein	0	0	0
Inferior vena cava	0	4 (16.7)	4 (10.3)
Right atrium/ventricle	0	17 (70.8)	17# (43.6)
Pulmonary artery	0	3 (12.5)	3 (7.7)

*, 4 patients underwent hysterectomy and 2 patients underwent myomectomy before first diagnosis; #, 3 patients shown right ventricle metastasis.

was approved by the Medical Ethics Committee of Fudan University Zhongshan Hospital (No. B2021-488R), and individual consent for this retrospective analysis was waived. The last follow-up month was June 2021.

Definition

The incidental group included patients who were diagnosed during surgery with visible intravenous tumor lesions and those unexpectedly diagnosed with IVL according to postoperative pathological examination. The nonincidental group included patients who had been diagnosed according to their clinical symptoms, results of preoperative imaging examination, such as echocardiography, computed tomography (CT), or CTV, and pathological findings. Tumor recurrence was defined as the appearance of a new tumor lesion or the enlargement of a residual tumor based on postoperative imaging examination. Disease-free survival (DFS) was defined as the time from surgery to tumor recurrence.

Statistical analysis

The software SPSS 19.0 (IBM Corp., Chicago, IL, USA) was used for statistical analysis. The disease characteristics, treatment, pathological findings, and prognosis were summarized and expressed as numbers and percentages.

Results

In total, 39 patients were included in this study, with a median age of 47 years. As shown in *Table 1*, 29 (74.4%) cases were premenopausal and 6 (15.4%) were naturally menopausal. A total of 4 (10.3%) cases who had undergone hysterectomy had experienced induced menopause. In addition, 6 cases had undergone myomectomy before their diagnosis of IVL. According to preoperative imaging, 25.6%, 35.9%, and 10.3% of the cases showed myomas with maximal sizes of <50, 50–100, and >100 mm, respectively. There were 6 patients who did not have myomas, of whom 4 underwent hysterectomy and 2 myomectomy before the diagnosis of IVL. Of the 39 patients with IVL, 15 (38.5%) were incidentally diagnosed and had tumors confined to the uterus and parauterine tissue. The nonincidental group included 24 (61.5%) patients, all of whom had IVL that had been grossly identified preoperatively via imaging. Of these 24 patients, the IVC, right atrium/ventricle, and pulmonary artery were

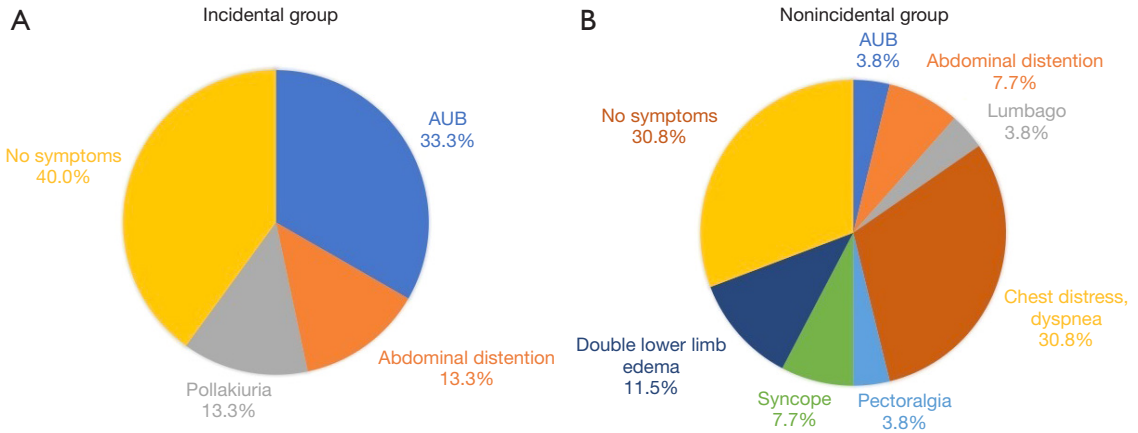

Figure 1 The clinical symptoms of IVL patients. AUB, abnormal uterine bleeding; IVL, intravenous leiomyomatosis.

Table 2 Treatment and recurrence in the incidental and nonincidental groups

Treatment	Number (%)
Incidental group (n=15)	
Laparotomic surgery	9 (60.0)
Laparoscopic surgery	6 (40.0)
Myomectomy	3 (20.0)
TH	3 (20.0)
TH + BSO	8 (53.3)
TH + BSO + adjuvant therapy	1* (6.7)
Nonincidental group (n=24)	
One-stage surgery	22 (91.7)
Two-stage surgery	2 (8.3)
Complete resection of tumor	22 (91.7)
Postoperative adjuvant therapy	1# (4.2)

*, one patient underwent letrozole therapy; #, one patient received 6 cycles of GnRH-a therapy. TH, total hysterectomy; BSO, bilateral salpingo-oophorectomy.

involved in 4, 17, and 3 cases, respectively. The clinical characteristics of each group are described in *Table 1*.

Patient symptoms are shown in *Figure 1*. In the incidental group, all cases had concomitant uterine fibroids. Furthermore, 40% of the patients had no symptoms. Patients with symptoms presented abnormal uterine bleeding (33.3%), abdominal distention (13.3%), and pollakiuria (13.3%). In the nonincidental group, 33.3% of the patients had no symptoms. However, 8 (30.8%) and 2 (7.7%) patients complained of chest distress/dyspnea and syncope, respectively. There were 3 (11.5%) patients who experienced double lower-limb edema, 2 of whom experienced consistent chest distress (*Figure 1*).

As shown in *Table 2*, of the 15 patients in the incidental group, 9 (60%) and 6 (40%) underwent laparotomic and laparoscopic surgeries, respectively. Myomectomy, total hysterectomy (TH), and TH + BSO were performed in 3 (20%), 3 (20%), and 9 (60%) patients, respectively. Only 1 patient received postoperative adjuvant therapy. Among the 24 patients with non-incidentally identified tumors, 1- and 2-stage surgeries were performed in 22 (91.7%) and 2 (8.3%) patients, respectively. Complete resection of the IVL tumor was performed in 22 patients, and 1 patient received postoperative adjuvant therapy (*Table 2*).

We next reviewed the pathological findings of all 39 cases, among whom IHC was performed for 25 patients. Grossly, the IVL tumor was a yellowish-white or gray, elastic, elongated, mobile, serpent-like polypoid mass found in the vessels. The typical histopathological features of IVL included benign smooth muscle cells within venous vascular spaces. Variable degrees of vascularity and hyalinization were present in some lesions. The lesion lacked nuclear division, mitoses, atypia, and coagulation necrosis. The hematoxylin and eosin (HE) staining picture of IVL is shown in *Figure 2*. As shown in *Table 3*, although all cases showed positive Ki-67 staining, the median percentage of Ki-67 staining was 2% (1–30%), indicating that the proliferation of IVL was relatively slow. All cases showed positive staining of alpha-smooth muscle actin (alpha-SMA), desmin, progesterone receptor (PR), caldesmon, and vimentin, followed by estrogen receptor

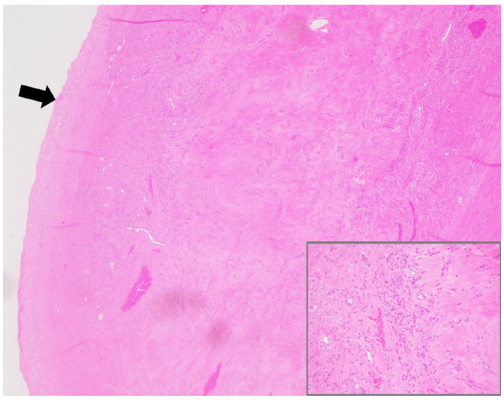

Figure 2 The hematoxylin and eosin staining of IVL (×40/×200). Benign smooth muscle cells present within venous vascular spaces. The black arrow shows the venous wall. IVL, intravenous leiomyomatosis.

Table 3 Immunohistochemistry information of IVL

Marker	Available cases	Positive cases (%)
Ki-67	25	25 (100.0)*
SMA	24	24 (100.0)
Desmin	24	24 (100.0)
CD34	23	19 (82.6)
PR	19	19 (100.0)
ER	18	17 (94.4)
Caldesmon	13	13 (100.0)
CD10	17	12 (70.6)
Vimentin	8	8 (100.0)
CD31	8	6 (75.0)
D2-40	8	4 (50.0)
Inhibin	5	4 (80.0)
p53	4	3 (75.0)

*, the median percentage of Ki-67 staining was 2% (range, 1–30%). IVL, intravenous leiomyomatosis; SMA, smooth muscle actin; ER, estrogen receptor; PR, progestogen receptor.

(ER) (94.4%), CD34 (82.6%), inhibin (80.0%), CD31 (75.0%), p53 (75.0%), CD10 (70.6%), and D2-40 (50.0%) (*Table 3*). The IHC staining of each marker is shown in *Figure 3*.

The median follow-up of all 39 IVL patients was 36.0 (1.4–121.5) months, and only 1 patient was lost to follow-up. In total, 5 patients were diagnosed with recurrence, and no deaths were recorded. Notably, all 5 patients with recurrence belonged to the incidental group, and no cases of recurrence were reported in the nonincidental group.

Figure 4 shows the prognosis of 15 patients with incidentally diagnosed IVL, of whom 5 showed recurrence. Patient 2 had the shortest DFS, with the disease recurring in the pelvis (a 66 mm tumor lesion) 1.4 months after TH + BSO. The patient received letrozole therapy and was living with the disease at the last time of follow-up. Patient 6 (34 years old) was diagnosed with IVL and underwent myomectomy. A new lesion was observed at the iliac vein, IVC, and heart after 10.5 months, and the patient underwent complete resection surgery, including TH, BSO, and thrombectomy; at present, the patient is alive and disease-free. Patients 11 and 13 underwent TH and BSO when first diagnosed with IVL. These 2 cases showed recurrence 10.7 and 51.5 months later, respectively, with extensive tumors in the pelvis, iliac vein, IVC, heart, and pulmonary artery. At the time of writing, both patients are alive and disease-free after complete resection and thrombectomy. Patient 15 was 35 years old when diagnosed with IVL, and TH was performed with the preservation of both ovaries. In this patient, pulmonary recurrence was identified 11.9 months later, and lung tumor resection was performed. After 17.2 months, she had another recurrence at the pelvic cavity and underwent pelvic resection again. At 88.9 months since IVL diagnosis, the patient was alive and disease-free (*Figure 4*).

A total of 24 patients with IVL were included in the nonincidental group. All the patients in this group were diagnosed with grossly identified tumors according to preoperative imaging findings, and their diagnosis was confirmed based on pathological findings. All these patients had tumors outside the pelvic cavity, with involvement of the IVC (4 cases), right atrium/ventricle (17 cases), and pulmonary artery (3 cases). There were 5 patients with previous surgical history, including myomectomy, TH + BSO, and TH in 5, 1, and 3 patients, respectively. All patients underwent thrombectomy with or without TH/BSO and multidisciplinary care, with the involvement of the departments of gynecology, general surgery, vascular surgery, and cardiac surgery. In total, 22 (91.7%) of the 24 patients underwent complete debulking, and the remaining 2 had residual disease. A patient with residual disease in the pelvic cavity received adjuvant therapy postoperatively. After a median follow-up of approximately 4 years, only 1 patient was lost to follow-up, and all patients were alive with no tumor recurrence (*Table 4*).

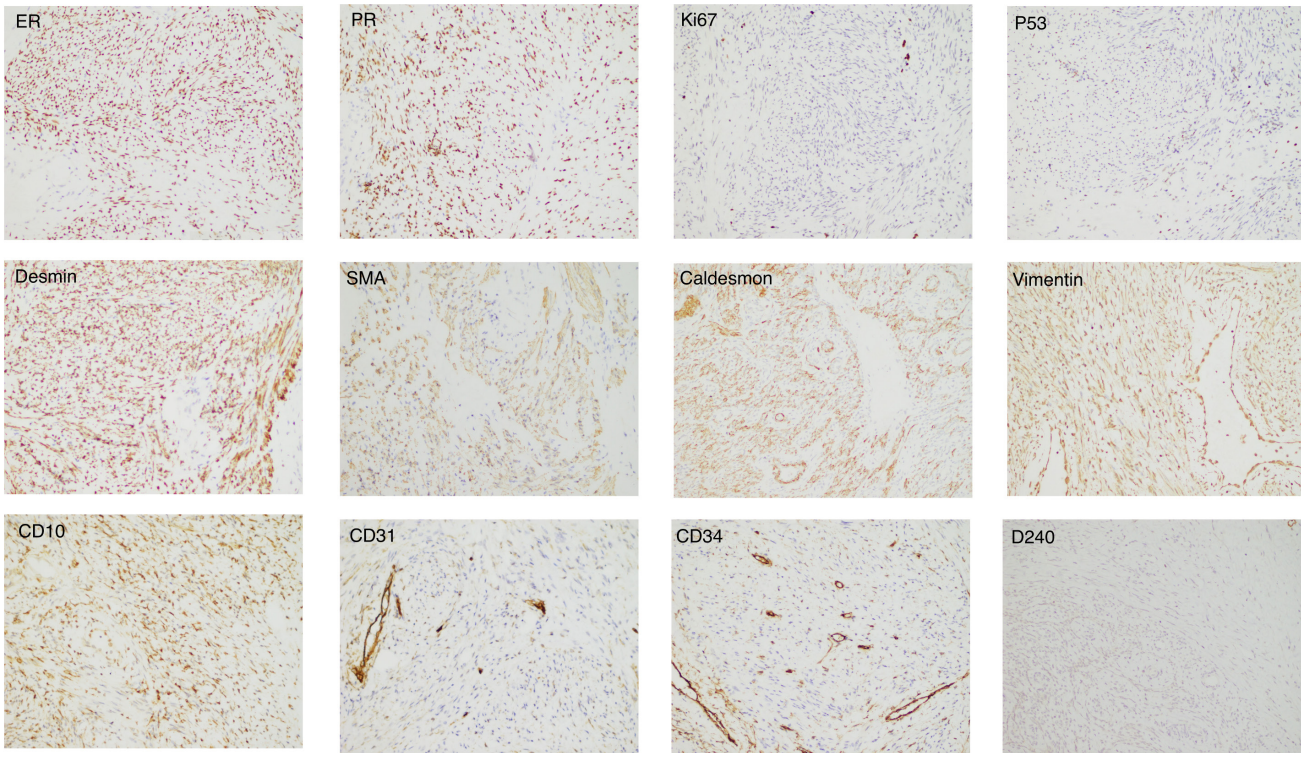

Figure 3 Representative Immunohistochemical images of typical markers in IVL lesions (×200). IVL, intravenous leiomyomatosis; ER, estrogen receptor; PR, progesterone receptor; SMA, smooth muscle actin.

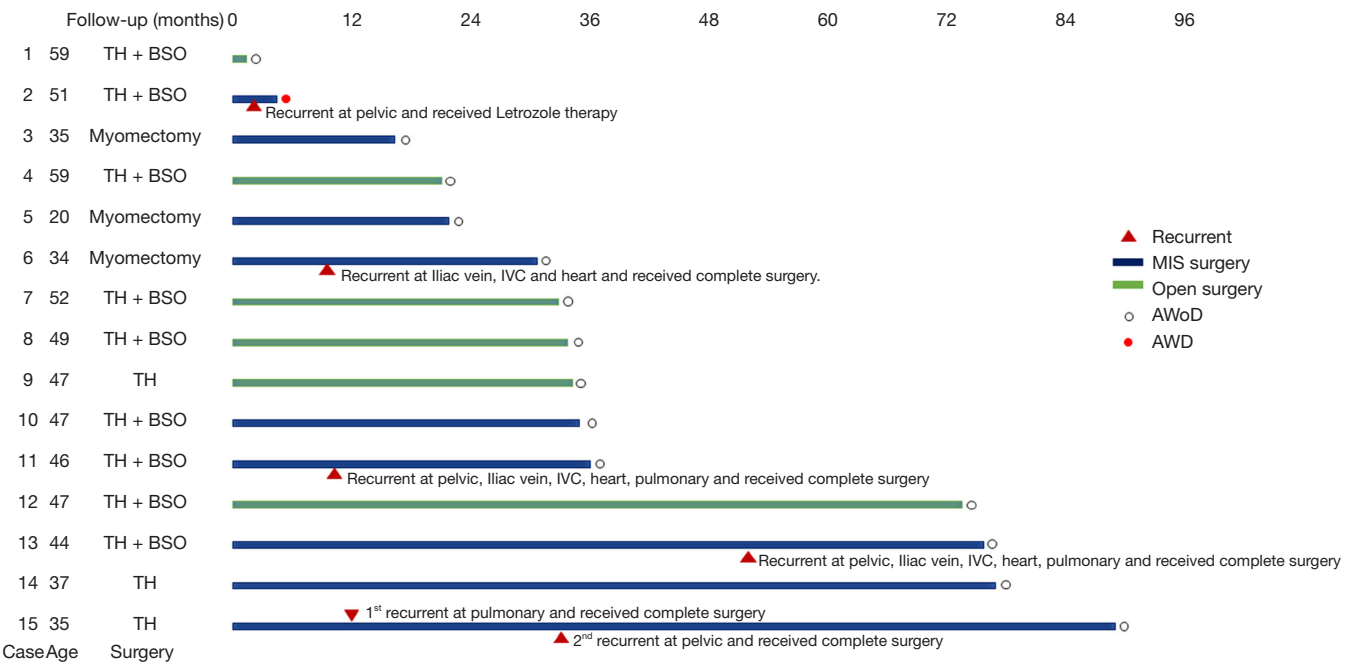

Figure 4 Management and prognosis in the incidental group. TH, total hysterectomy; TH + BSO, total hysterectomy with bilateral salpingo-oophorectomy; MIS, minimally invasive surgery; AWoD, alive without disease; AWD, alive with disease; IVC, inferior veno cava.

Table 4 Characteristics, treatment, and follow-up of 24 IVL patients in the nonincidental group

No	Age	Previous surgery history	Extent of disease	Surgical procedure	Residual disease	Adjuvant therapy	Follow-up (months)
16	37	None	IVC	TH + BSO + thrombectomy	No	No	68.3
17	42	TH + BSO	IVC	Thrombectomy	No	No	85.8
18	44	None	IVC	TH + BSO + thrombectomy	No	No	48.9
19	48	None	IVC	TH + BSO + thrombectomy	No	No	3.3
20	50	TH	RA	BSO + thrombectomy	No	No	68.6
21	62	None	RA	TH + BSO + thrombectomy	No	No	26.6*
22	47	Myomectomy	RA	TH + BSO + thrombectomy	No	No	56.5
23	50	None	RA	TH + BSO + thrombectomy	No	No	52.1
24	59	None	RV	TH + BSO + thrombectomy	No	No	43.9
25	42	None	RA	TH + BSO + thrombectomy	No	No	43.8
26	45	TH	RV	BSO + thrombectomy	No	No	33.3
27	43	Myomectomy	RA	TH + BSO + thrombectomy	No	No	29.6
28	55	None	RA	TH + BSO + thrombectomy	Yes	Yes#	11.6
29	38	Myomectomy	RV	TH + BSO + thrombectomy	No	No	121.5
30	34	None	RA	TH + BSO + thrombectomy	No	No	119.2
31	49	TH	RA	BSO + thrombectomy	No	No	88.5
32	48	None	RV	TH + BSO + thrombectomy	No	No	84.2
33	46	None	RA	TH + BSO + thrombectomy	No	No	7.1
34	47	Myomectomy	RA	TH + BSO + thrombectomy	No	No	6.4
35	51	None	RA	TH + BSO + thrombectomy	No	No	71.2
36	30	None	RA	TH + BSO + thrombectomy	No	No	56.3
37	47	None	PA	TH + BSO + thrombectomy	No	No	42.2
38	45	None	PA	TH + BSO + thrombectomy	No	No	31.6
39	39	Myomectomy	PA	TH + BSO + thrombectomy	Yes	No	19.3

*, the patient was lost to follow-up; #, the patient received 6 cycles of GnRH-a therapy. IVL, intravenous leiomyomatosis; RA, right atrium; RV, right ventricle; PA, pulmonary artery; IVC, inferior vena cava; TH, total hysterectomy; BSO, bilateral salpingo-oophorectomy.

Discussion

Principal findings and results

The IVL is a rare disease that originates from a uterine myoma. No specific clinical symptoms are observed in most cases until the tumor invades the IVC or the right atrium/ventricle or pulmonary artery. Occasionally, IVL is diagnosed during hysterectomy or myomectomy and/or confirmed by pathology. As the morbidity of IVL is low and the tumor is rarely described and investigated, no clinical guidelines have been established for its treatment.

Several previous studies (shown in *Table 5*) have focused on the recurrence rate of IVL and attempted to analyze the prognostic factors associated with tumor recurrence; however, the results have shown extreme variation (2,4,5,13,15-18). Yu *et al.* (4) conducted a retrospective study of 58 patients with IVL, of whom 31 (53.4%) had tumors spreading into the IVC and heart. In their study, the recurrence rate was 31.0% during a median follow-up of 11.5 months. They concluded that large vein involvement was associated with an increased risk of recurrence, whereas neither resection of bilateral ovaries nor postoperative

Table 5 Review of retrospective literatures about clinical features and prognosis of IVL in recent 5 years

Literature	Number of Pts.	Tumor lesion extension	Management	Median follow-up [range]	Recurrence	Conclusion
Ma G, 2016 (15)	76	Pelvic cavity; IVC; RA; RV; PA	Different surgical strategies based on the staging	54 months [12–156]	4 cases	Removal of both ovaries is necessary to inhibit tumor growth and avoid recurrence
Low HY, 2017 (13)	9	Pelvic cavity	TAH and BSO; TAH; Subtotal hysterectomy and BSO; myomectomy; recurrent patients: secondary surgery + GnRH-a.	60 months	2 cases	If complete surgical resection is not possible, partial resection followed by hormone therapy using gonadotropin-releasing hormone agonists is recommended
Yu X, 2016 (4)	58	Pelvic cavity; IVC; RA; RV; PA	One-stage surgery: 45 (77.6%); two-stage surgery: 13 (22.4%)	11.5 months	18 cases	Large vein involvement was associated with an increased risk of recurrence. Neither resection of bilateral ovaries nor postoperative hormone therapy was associated with recurrence
Zhang G, 2017 (2)	38	IVC; RA; RV; PA	One-stage surgery: 23 (60.5%); two-stage surgery: 15 (39.5%); postoperative hormone therapy: 18 (72%)	12 months	15 cases	The postoperative recurrence rate is high, and postoperative antiestrogen hormone therapy is not significantly correlated with recurrence
Yu HY, 2018 (16)	8	Pelvic cavity; IVC; IVC and RA; PA	One-stage surgery: 7; two-stage surgery: 1	38.5 months [3–120]	2 cases	One-stage operation to completely remove IVL is feasible and correlated with good long-term outcomes
Su Q, 2020 (17)	14	Pelvic cavity; IVC; RA; PA	One-stage surgery: 13; one case was misdiagnosed and treated by staging surgery	57.5 months [27–120]	1 case	The disease is at high risk of thrombosis, and perioperative routine anticoagulation is required
Yu X, 2021 (5)	25	Broad ligament; Ovarian vein	Surgery with complete resection; three received GnRH-a after surgery.	36 months [5–80]	3 cases	Patients with large lesions (≥7 cm) and lesions extending to the broad ligament may have an increased risk of recurrence
Lian C, 2021 (18)	10	Right cardiac chambers; IVC	One-stage surgery: 7; two-stage surgery: 3; antiestrogen therapy: patients with ovary preserved	57.5 months [27–120]	0	Two-stage surgery is more beneficial for patient recovery if the lesion exhibits intracardiac involvement

IVL, intravenous leiomyomatosis.

hormone therapy was associated with recurrence. Ma *et al.* (15) retrospectively reviewed 76 patients with IVL, of whom 35 (46.1%) were diagnosed with stage I (pelvic cavity) and 41 (54.9%) had extrapelvic tumors. They reported that 4 (5.3%) out of 76 patients showed recurrence, all 4 of whom had stage I disease and opted for surgery with preservation of the ovaries and uterus.

In our study, the recurrence rate was 12.8% (5 out of 39 patients) in the whole cohort. We found that patients with incidentally diagnosed IVL (with intrapelvic disease) had a higher recurrence rate than those with non-incidentally diagnosed IVL (with extrapelvic disease) (5/15 *vs.* 0/24, respectively). The results were relatively consistent with those of Ma *et al.* (15), which may not be surprising considering the following reasons. First, the preoperative imaging evaluation of the incidentally diagnosed patients was inadequate. Although patients with IVL were diagnosed postoperatively by gynecological pathologists, some of them did not undergo further imaging examination, such as echocardiography or CTV; therefore, some tumor lesions that might have existed before surgery were ignored. Such patients may exhibit distant tumor recurrence several months after the primary surgery. Second, the extent of surgery in these patients may have been insufficient.

Owing to the inadequate preoperative evaluation, the surgeries of most patients with incidentally diagnosed IVL were performed by gynecologists only, which led to residual disease and tumor recurrence. On the contrary, the treatment of patients with non-incidentally diagnosed IVL with extrapelvic tumors was more complicated and difficult, which might have drawn sufficient attention for multidisciplinary surgical treatment. Following complete tumor removal, the prognoses of these patients appeared more favorable.

Research implications

Several issues relating to IVL have not been resolved. First, should hysterectomy or BSO be performed as primary treatment in young women (≤40 years old) diagnosed with IVL? In this study, 3 young women underwent myomectomy alone as primary treatment, and IVL was diagnosed by postoperative pathological examination. None of them received further treatment after the diagnosis of IVL. However, recurrence was observed in 1 case (patient 6) 10.5 months later, with tumors at the iliac vein, IVC, and right atrium/ventricle. The patient underwent secondary surgery including TH, BSO, and thrombectomy and was alive and disease-free as of this report. The other 2 cases (patients 3 and 5) were disease-free with DFS of 16.3 and 21.8 months, respectively. Similarly, 3 cases (patients 9, 14, and 15) underwent hysterectomy with ovary preservation; 2 (patients 9 and 14) of them were alive with DFS of 34.2 and 76.8 months, respectively, whereas 1 case (patient 15) experienced recurrence twice, with the first recurrence in the pulmonary artery and the second in the pelvic cavity. This patient underwent BSO as the third surgical procedure; as of this study, she was alive and disease-free at a follow-up of 88.9 months since the first diagnosis. These results indicate that neither hysterectomy nor BSO is essential for young patients with incidentally diagnosed IVL. Therefore, extrapelvic imaging should be performed, and young patients should be closely followed up.

Second, what kind of treatment should be provided to patients with IVL that show tumor recurrence? In this study, 4 (80.0%) out of 5 patients received secondary surgical treatment for recurrence, and their long-term survival was not expected. Only patient 2 received hormone treatment after recurrence because the DFS was quite short. The tumor recurred at the pelvic cavity only 1.4 months after TH + BSO with no residual disease, and hormone therapy appeared effective (stable disease) for this patient. Therefore, although patients experienced recurrence with relatively extensive tumor involvement, the results suggest that secondary surgery with a professional multidisciplinary team should be considered.

Benign metastasizing leiomyoma (BML) comprises benign-appearing smooth muscle cells in the uterus and metastatic sites; it has benign morphology and an indolent process, but also invasive behavior. Although the biological features of BML are similar to those of IVL, the histopathological characteristics are different. It has been reported that BML lesions stain positive for only desmin and PR (weak). Other markers, including tyrosinase, ER, CD34, CD31, and D2-40 are negative (19). Our study of IVL showed that staining of PR was 100% positive, followed by ER (94.4%), CD 34 (82.6%), CD31 (75.0%), and D2-40 (50.0%), which is different from BML. Markers of endothelial cells, such as CD31, are applied for evaluating the vessel density of tumor lesions and the staining of tumor cells (20,21). We found that CD31 was positive in the majority of cases, indicating strong angiogenic activity in IVL lesions. Considering that most of the cases in this study did not receive postoperative adjuvant therapy and that ER and PR staining were positive in 94.4% and 100% of cases, respectively, further investigation on the relationship between estrogen and IVL is warranted in the future.

Moreover, although the prognosis after multidisciplinary surgical treatment was good, gynecologists might desire more effective biological agents that can circumvent surgical trauma and pain to the patients.

Strengths and limitations

Although the data were retrospectively collected and analyzed, the relatively sufficient sample size and long follow-up period render our results reliable, considering the rarity of IVL. Furthermore, to the best of our knowledge, this was the first study to compare the management and prognosis of IVL according to whether it was diagnosed incidentally or non-incidentally.

Conclusions

Patients with IVL who are incidentally diagnosed appear to have a higher recurrence risk than those who are non-incidentally diagnosed and undergo complete tumor resection. Long-term DFS can be achieved after secondary surgery in incidentally diagnosed patients with recurrent IVL. Refinement of IVL treatment and prognosis would

significantly benefit from large-scale retrospective and prospective studies.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-5376/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5376/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Fudan University Zhongshan Hospital (No. B2021-488R), and individual consent for this retrospective analysis was waived.

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