




# Clinical analysis of uterine intravenous leiomyomatosis: A retrospective study of 260 cases

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## Abstract

**Methods:** We collected the clinical data of 260 patients admitted to the hospital from April 2003 to September 2019 with pathologically confirmed intravenous leiomyomatosis (IVL) and followed up with these patients regularly. Univariate and multivariate logistic regression analyses were carried out on the relevant recurrence factors.

**Results:** A total of 166 patients were regularly followed up, the median follow-up time was 36 (range 2–168) months, 14 (5.4%) patients eventually relapsed, and the median recurrence time was 8.5 (range 2–42) months. The univariate analysis showed that age ( $p = 0.003$ ) and surgical type ( $p < 0.001$ ) were associated with recurrence, and multivariate regression analysis demonstrated that surgical type was the only factor associated with recurrence ( $p < 0.001$ , OR 20.01).

**Conclusions:** The use of gonadotrophin releasing hormone agonist (GnRHa) cannot reduce the postsurgical recurrence rate of patients with UIVL. Compared to total hysterectomy and bilateral salpingo-oophorectomy (TH-BSO), total hysterectomy (TH) does not increase the odds of recurrence, but the chance of recurrence with tumorectomy (TE) is 20 times higher than that of TH-BSO.

**Key words:** GnRHa, intravenous leiomyomatosis, recurrence, surgery, uterine intravenous leiomyomatosis.

## Introduction

Intravenous leiomyomatosis (IVL) is a clinically rare benign smooth muscle tumor that generally originates from uterine leiomyoma or myometrium<sup>1</sup> and can spread along uterine or ovarian veins to the iliac vein,<sup>2</sup> renal vein,<sup>3</sup> inferior vena cava,<sup>4</sup> right atrium, right ventricle,<sup>5</sup> and even the pulmonary artery<sup>6</sup> and subclavian vein.<sup>7</sup> Preoperative diagnosis is difficult, and no consensus has been reached about its clinical diagnosis and treatment. Surgery is the primary treatment. Considering that IVL might be an estrogen-related tumor, total hysterectomy and bilateral adnexectomy are recommended along with complete tumor resection to

reduce recurrence,<sup>8</sup> and antiestrogen is the main adjuvant therapy for those who retained their ovaries or had incomplete resection.<sup>9–11</sup> However, recent studies have reported that resection of bilateral ovaries and postoperative antiestrogen treatment are not associated with recurrence.<sup>12,13</sup> We retrospectively summarized the clinical data of 260 patients with UIVL and identified prognostic factors for postoperative recurrence.

## Materials and Methods

### Data collection

A total of 260 patients with UIVL underwent surgery at the Obstetrics and Gynecology Hospital of Fudan

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University from April 2003 to September 2019, and the operations were performed by experienced surgeons. The data collected from the clinical database for these patients were: age, initial clinical manifestations, history of myomectomy and cesarean section, tumor size and location, parauterine metastasis, surgical types, and postoperative pathology. The tumor size was based on postoperative pathological records, and pathologic diagnosis was determined by two experienced pathologists. The clinicopathological features are shown in Figure 1.

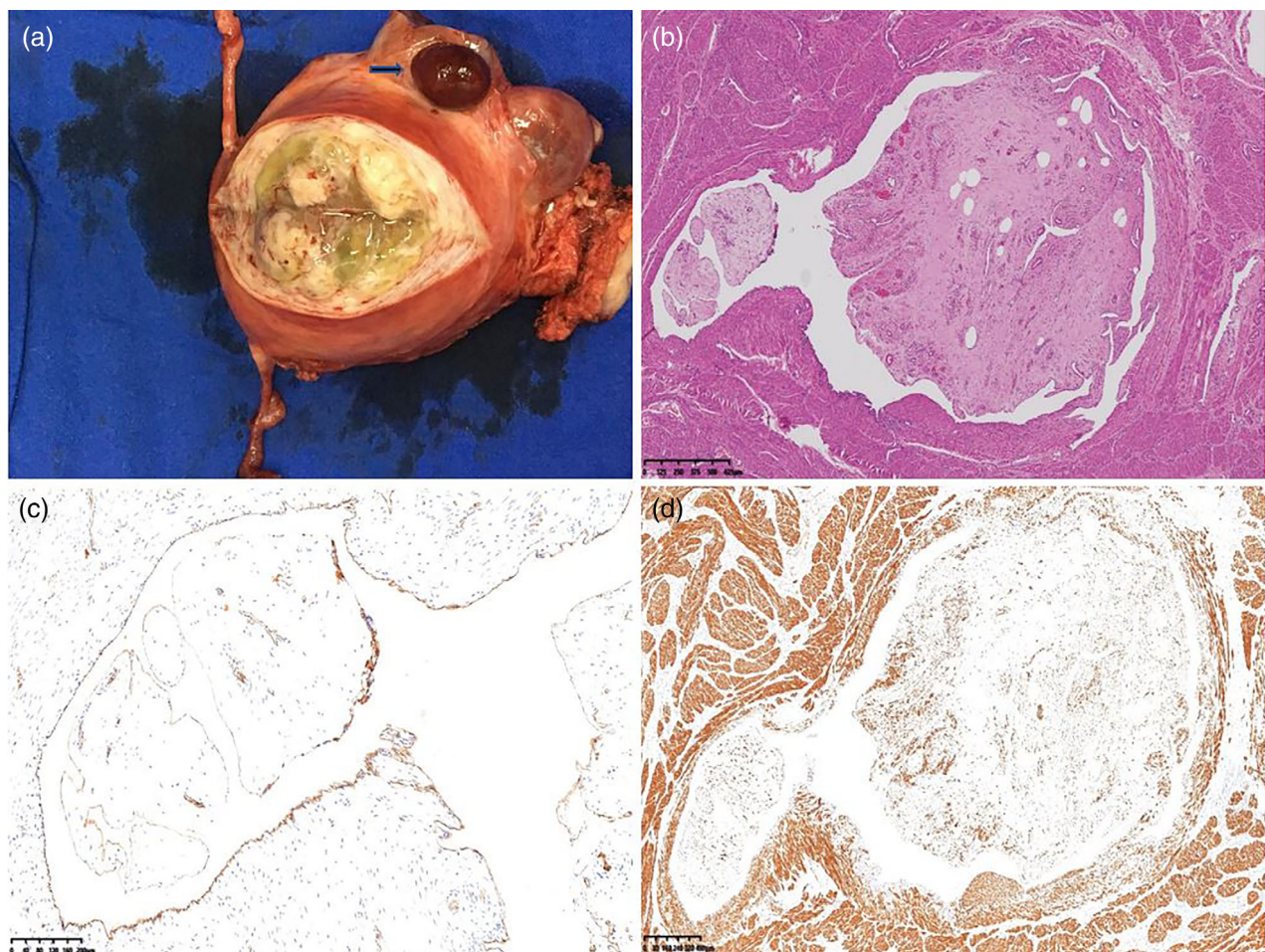
### Follow-up

Among the 260 patients, only 166 underwent regular follow-up (every 3–6 months) and were enrolled in

our recurrence study; the others (36.2%) were excluded. At each follow-up visit, pelvic physical examinations and imaging tests, including pelvic ultrasound or computed tomography (CT), and echocardiography if necessary, were performed. Detection of a mass with a diameter larger than 1 cm at the same location during two consecutive imaging examinations was defined as a recurrence, and the follow-up time was from the surgery to the last follow-up.

### Study design

Our study was approved by the institutional review board of the Obstetrics and Gynecology Hospital of Fudan University. One hundred and forty-six regularly followed up patients were included in our study



**FIGURE 1** The clinicopathological features of uterine intravenous leiomyomatosis. (a) Hysterectomy and bilateral salpingectomy specimen with wormlike tumor into the right parauterine vein (black arrow). (b) Intravascular tumor almost completely fills the lumen of an expanded vein with hematoxylin and eosin (H&E) staining. (c) Immunohistochemical (IHC) staining for CD31 marker, confirming that the tumor mass grows within endothelial vascular walls. (d) IHC staining for Desmin marker, confirming the component of smooth muscle in UIVL

**TABLE 1** The clinical data of 260 uterine intravenous leiomyomatosis

Clinical data	Number of patients(%)
Menopause ( <i>n</i> = 260)	24 (9.2)
Initial manifestation ( <i>n</i> = 260)	
Pelvic pain	16 (6.2)
Abdominal mass	142 (54.6)
Hypermenorrhea	30 (11.5)
Menostaxis	16 (6.2)
None	56 (21.5)
History of myomectomy ( <i>n</i> = 260)	39 (15.0)
History of cesarean ( <i>n</i> = 260)	
Surgery ( <i>n</i> = 260)	82 (31.5)
Ovariohysterectomy	139 (53.5)
Hysterectomy	74 (28.5)
Lesionectomy	47 (18.0)
Tumor location ( <i>n</i> = 260)	
Intramural	227 (87.3)
Cervix	4 (1.5)
Submucosa	9 (3.5)
Subserosum	7 (2.7)
Broad ligament	12 (4.6)
Rectouterine pouch	1 (0.4)
Parauterine involvement ( <i>n</i> = 210)	111 (52.9)

and were divided into recurrence and nonrecurrence groups. The differences in the clinical medical records between the two groups were compared to analyze the recurrence-related factors of IVL. We evaluated the impact of different types of surgery and postoperative adjuvant treatment on recurrence.

### Statistical analysis

Statistical analysis was performed with SPSS 22.0. Continuous data with a normal distribution are presented as the mean and standard deviation ( $\bar{x} \pm s$ ), and a skewed distribution is presented as the median with a 25th–75th percentile range ( $M_{P25 \sim P75}$ ). Continuous variables were analyzed with the Z-test or Mann–Whitney test, and categorical variables were analyzed with the chi-square test. We chose statistically significant or clinically relevant variables in the univariate analysis for multivariate logistic regression analysis, and the odds ratio (OR) and 95% confidence interval (CI) were calculated. Kaplan–Meier survival analysis was performed to evaluate the associations between recurrence and the related factors. A *p*-value <0.05 was considered statistically significant.

**TABLE 2** The follow-up information after surgery of 166 patients

Clinical data	Number of patients (%)
Surgery	
Ovariohysterectomy	86 (51.8)
Hysterectomy	46 (27.7)
Lesionectomy	34 (20.5)
GnRHa after surgery	24 (9.2)
Recurrence	14 (5.4)
Recurrence location	
Uterus	9
Parauterine tissue	2
Rectouterine pouch	1
Iliac vein	1
Inferior vena cava	1

### Results

The clinical data of the 260 UIVL patients are summarized in Table 1. The mean age of the patients was  $45.3 \pm 7.4$  (ranging from 23 to 66) years old (Figure S1), among which 24 (9.2%) had natural menopause. The clinical manifestations were diverse when they first visited a doctor. The primary manifestations were abdominal masses (54.6%), followed by asymptomatic masses (21.5%); others included hypermenorrhea (11.5%), menostaxis (6.2%), and pelvic pain (6.2%). When asked about their surgery history, 39 (15.0%) of them had undergone myomectomy, and 82 (31.5%) had a cesarean section.

For treatment, all patients underwent surgery; a total of 139 (53.3%) patients underwent TH-BSO, 74 (28.5%) underwent TH, and 47 (17.0%) underwent lesionectomy due to fertility concerns and personal reasons. Obviously, the most common location of IVL was intramural (87.3%), and according to the postoperative pathology, the median tumor size was 6.0 (4.5–8.0) cm (Figure S2), which ranged from 2 to 27 cm. Parauterine involvement was observed in 111 (52.9%) out of 210 patients.

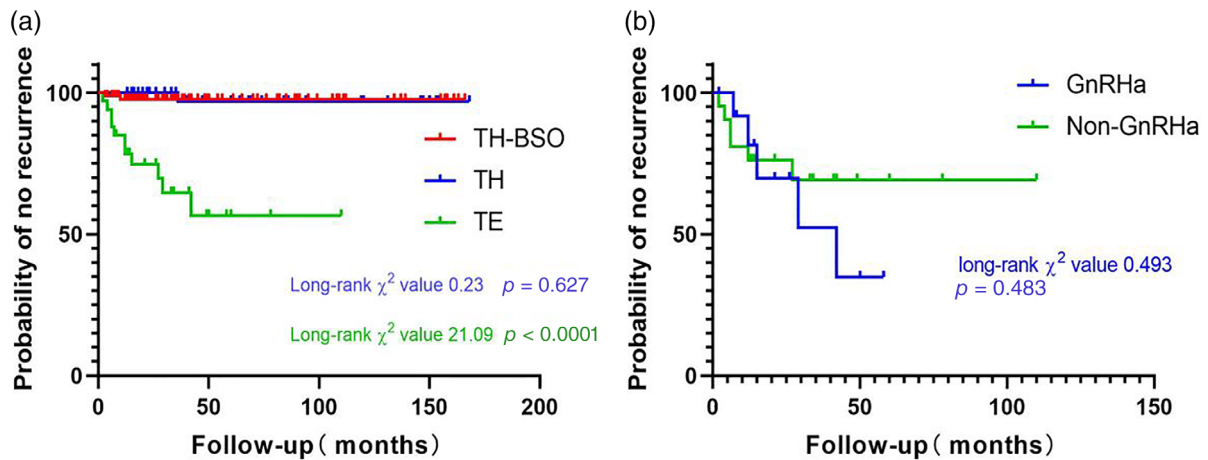
A total of 166 patients were regularly followed up after surgery (Table 2), and the median follow-up time was 36 months (range 2–168 months). Among them, 86 (51.8%) underwent TH-BSO, 46 (27.7%) received TH, and 34 (20.5%) had TE. Twenty-four patients were treated with gonadotrophin releasing hormone agonist (GnRHa) after surgery, and the treatment time ranged from 3 to 12 months. Eventually, 14 patients relapsed with a recurrence rate of 5.4% (95% CI 3.1–9.1), the median recurrence time was 8.5 (4.0–18.0) months. The clinical data of the 14 patients are shown in Table S1. Nine patients

**TABLE 3** Univariate analysis of recurrence factors in 166 follow-up patients

		Recurrence ( <i>n</i> = 14)	Non-recurrence ( <i>n</i> = 152)	$\chi^2/Z$	<i>p</i> -value
Age ( $\bar{x} \pm s$ )		37.4 $\pm$ 9.7	45.5 $\pm$ 6.8	-2.970	0.003
Tumor size ( $M_{P25} \sim P_{75}$ )		6.5 (6.0 ~ 10.0)	6.0 (5.0 ~ 8.0)	-1.129	0.259
Menopause	Yes	0 (0)	15 (9.9)	0.555	0.456
	No	14 (100)	137 (90.1)		
History of myomectomy	Yes	4 (28.6)	22 (14.5)	1.009	0.315
	No	10 (71.4)	130 (85.5)		
History of cesarean	Yes	4 (28.6)	52 (34.2)	0.017	0.895
	No	10 (71.4)	100 (65.8)		
Parauterine involvement	Yes	2 (66.7)	67 (52.8)	0.233	0.546
	No	1 (33.3%)	48 (47.2)		
Surgical type					
Ovariohysterectomy		2 (14.3)	84 (55.3)	22.3	<0.001
Hysterectomy		1 (7.1)	45 (29.6)		
Lesionectomy		11 (78.6)	23 (15.1)		
GnRHa after surgery	Yes	6 (42.9)	18 (11.8)	2.330	0.127
	No	8 (57.1)	134 (88.2)		

**TABLE 4** Multivariate regression analysis of recurrence factors in 166 follow-up patients

	<i>p</i> -value	OR	95% CI
Age	0.09	0.91	0.82–1.02
Tumor size	0.73	0.96	0.75–1.22
Surgery type			
Ovariohysterectomy		1.00	
Hysterectomy	0.96	0.96	0.08–10.58
Lesionectomy	<0.01	20.09	4.16–97.10
GnRHa after surgery	0.86	1.15	0.26–5.14



**FIGURE 2** Kaplan–Meier curve about effects of different surgical approaches (a) and the use of GnRHa (b) on recurrence of UIVL. (a) we compared total hysterectomy (TH, *n* = 46) and tumorectomy (TE, *n* = 34) with total hysterectomy and bilateral salpingo-oophorectomy (TH-BSO, *n* = 86), the patients with TE had a significantly earlier recurrence time (*p* < 0.0001), no difference was showed between TH and TH-BSO (*p* = 0.627). (b) Recurrence between GnRHa and non-GnRHa was analyzed in the 34 patients who received TE, and no significant difference was observed (*p* = 0.483)

relapsed in the uterus, two relapsed in parauterine tissue, and one each relapsed in the inferior vena cava, iliac vein and rectouterine pouch.

To uncover the possible causes of recurrence, univariate analysis of the variables associated with recurrence was performed for the 166 follow-up patients

(Table 3). We found that younger people were more likely to relapse; the mean age of the recurrence group was  $37.4 \pm 9.7$  years old, and that of the non-recurrence group was  $45.5 \pm 6.8$  ( $p = 0.003$ ). There was no significant difference in tumor size (6.5 cm in the recurrence group, 6.0 cm in the nonrecurrence group,  $p = 0.259$ ), menopause ( $p = 0.456$ ), history of myomectomy ( $p = 0.315$ ), history of cesarean section ( $p = 0.895$ ), parauterine involvement ( $p = 0.546$ ), or the use of GnRHa ( $p = 0.127$ ). The different surgical types ( $p < 0.001$ ) were, however, associated with recurrence.

The variables age and different surgical types were included in the logistic regression model for the multivariate analysis (Table 4), and considering its clinical relevance, the use of GnRHa was also included. According to the level of  $\alpha = 0.15$ , the results demonstrated that TE was the only factor associated with recurrence ( $p < 0.001$ ). We compared TH and TE with TH-BSO. The recurrence rate of TE was 20 times higher than that of TH-BSO (95% CI 4.16–97.10), and no difference in recurrence was found between patients with TH and TH-BSO ( $p = 0.96$ ). The same results were confirmed by Kaplan–Meier curves (Figure 2a). There was no difference in age ( $p = 0.09$ ) or GnRHa use after surgery ( $p = 0.86$ ). Given the influence of the surgical approaches, recurrence rates between GnRHa and non-GnRHa were analyzed by Kaplan–Meier curve analysis in the 34 patients who underwent TE (Figure 2b), and no significant difference was observed.

## Discussion

To our knowledge, this is the largest series of patients with UIVL. In our study, we summarized the clinical features of 260 patients and analyzed the relevant prognostic factors in 166 regularly followed up patients, among whom 14 experienced a recurrence at a median follow-up time of 36 months. The univariate analysis revealed that age and surgical type were associated with recurrence (Table 3). However, the logistic regression model for the multivariate analysis demonstrated that the surgical approach was the only factor associated with recurrence, and the patients with TE had a much higher recurrence rate than those with TH and TH-BSO (Table 4). Bilateral ovary resection and postoperative GnRHa treatment were not associated with recurrence.

IVL is a peculiar and rare tumor that is histologically benign but has malignant biological behavior. It is generally believed that IVL originates from uterine leiomyoma or myometrium,<sup>1</sup> and it can maliciously invade surrounding vessels and extend to a distance.<sup>7</sup> Ordulu et al. believed that IVL was an unusual intermediate between benign and malignant uterine smooth muscle tumors,<sup>14</sup> but none have been reported to be malignant.

The age of onset in patients with UIVL reportedly ranges from 21 to 80 years, but the vast majority occur before menopause, and the mean age at onset is 47 years old.<sup>15</sup> Most patients have a uterine surgical history,<sup>8,13,16</sup> such as cesarean section, myomectomy, and hysterectomy. Na et al. retrospectively analyzed 69 patients with IVL and revealed that nearly 64% of them had previously undergone hysterectomy,<sup>17</sup> and Li et al. reported 53.6% of 194 IVL patients had undergone hysterectomy.<sup>18</sup> In our patients, the average age at onset was  $45.3 \pm 7.4$  years old, and 91% of them were premenopausal, among whom 46.5% had a uterine surgical history. Therefore, we consider that vascular damage due to a uterine operation may create conditions for the formation of IVL in the future, but further studies are needed to verify this hypothesis.

The clinical manifestations of IVL are usually diverse and nonspecific, and depend on its location and extension. In the early stage, the tumor is confined to the pelvic cavity. When confined to the uterus, the symptoms are similar to uterine myoma. Most patients are usually asymptomatic,<sup>17</sup> and 90% of patients have symptoms suggestive of a pelvic mass, such as irregular vaginal bleeding, hypermenorrhea, menostaxis, abdominal swelling, or unexplained pelvic pain<sup>19</sup>; when it compresses the ureter, it can lead to urinary tract obstruction.<sup>20</sup> In the middle stage, it extends out of the pelvic cavity to the renal vein or inferior vena cava and can gradually lead to edema and heaviness of the lower extremities.<sup>21</sup> In the late stage, it reaches the right atrium or the pulmonary artery, and chest discomfort, dyspnea and syncope develop,<sup>22</sup> and as the condition worsens, congestive heart failure occurs,<sup>23</sup> even pulmonary embolism<sup>24</sup> and sudden death.<sup>25</sup> All 260 of our patients were in the early stages, 55% had abdominal masses and 22% were asymptomatic. Other symptoms included hypermenorrhea, menostaxis, and pelvic pain, and most were misdiagnosed with uterine leiomyoma due to the nonspecific manifestations and imaging when they first visited the doctor.

Early-stage IVL is difficult to detect by current imaging examination because the tumor extension remains inside the myometrial small vessels.<sup>17</sup> Contrast-enhanced CT<sup>26,27</sup> and MRI<sup>28</sup> might be helpful for preoperative diagnosis, but a definite diagnosis mainly depends on intraoperative findings and postoperative pathology. When a worm-like mass is found in the broad ligament during surgery, the diagnosis should be considered and confirmed by rapid pathological examination.<sup>29</sup> Liu et al. revealed that 77% of IVL patients with pelvic masses involved the broad ligament.<sup>17</sup> All 260 of our patients were in the early stages and underwent surgery. Apparently, the majority (87.3%) of the tumors were intramural, and 52.9% of the patients had parauterine involvement of the broad ligament among 210 patients with parauterine records according to postsurgical pathology. We have reason to believe that this tumor is derived from the myometrium and that parauterine metastasis is the first step toward extrapelvic involvement.

Surgery is the primary treatment for IVL, but the selection of surgical approaches has always been controversial. There is little dispute that the mass should be removed as completely as possible to reduce future recurrence, and a previous study reported that partial resection had a higher recurrence rate.<sup>18</sup> Considering that IVL is a hormone-dependent tumor owing to its positive expression of estrogen and progesterone receptors,<sup>15</sup> hysterectomy and bilateral salpingo-oophorectomy have previously been recommended as the primary surgical approach,<sup>8,29,30</sup> but given fertility concerns and the side effects of estrogen deficiency, this is generally only recommended for those who are 40 years of age or older,<sup>10</sup> and TH or TE is performed for younger patients combined with postoperative adjuvant therapy. However, recent studies revealed that TH was sufficient, and bilateral oophorectomy was not associated with recurrence.<sup>11,13,31</sup>

To determine the influence of different surgical types on recurrence, we analyzed our 166 regularly followed up patients. Fourteen eventually relapsed after a median follow-up of 36 months, and their detailed information is shown in Table S1. All 14 relapsed patients were premenopausal, two underwent TH-BSO, one received TH, and 11 underwent TE. Multivariate analysis demonstrated that preservation of bilateral ovaries did not increase the postoperative recurrence rate, and the only relevant factor was TE; its recurrence rate was 20 times higher than that of TH-BSO. The importance of complete resection of the tumor has been proven. Tumorectomy is most likely just partial resection of the tumor, leaving

behind lesions in the small vessels that can result in future recurrence. Therefore, hysterectomy should always be recommended if fertility is not a factor.

Postoperative hormonal treatment for IVL patients is also controversial. Carr et al. revealed that IVL is always estrogen and progesterone receptor-positive by immunohistochemical analysis of 14 cases,<sup>15</sup> and because of its estrogen dependence, antiestrogenic therapy has been recommended as a potential approach in reducing recurrence of the tumor.<sup>32</sup> Tamoxifen<sup>10</sup> and aromatase inhibitors<sup>33,34</sup> have been proven effective in several case reports, but GnRHa is more commonly reported in the literature. GnRHa was previously recommended as a postoperative approach to reducing the risk of recurrence if complete tumor resection was not possible or bilateral ovaries were preserved,<sup>9,11</sup> but a recent retrospective study of 58 patients with IVL revealed that postoperative treatment with GnRHa was not associated with recurrence.<sup>13</sup> Even a comprehensive analysis of 194 cases showed that postoperative antiestrogen therapy could not prevent recurrence.<sup>18</sup> In our 166 follow-up patients, 24 received GnRHa for at least 3 months after surgery, and six received GnRHa among the 14 relapsed patients. Our multivariate analysis showed that using GnRHa was not associated with recurrence, and this was also confirmed by Kaplan–Meier survival analysis in the 34 patients who received TE (Figure 2b). We believe based on the current evidence that antiestrogenic therapy is not a useful treatment.

Long-term follow-up is necessary for monitoring the recurrence of tumors after surgery. The recurrence rate has been reported to range from 14% to 31%,<sup>13,15,35</sup> and the recurrence sites are mainly confined to the pelvic cavity and iliac veins and are rarely found in the inferior vena cava and heart.<sup>11</sup> After the initial surgery, recurrence might occur within months to years.<sup>15</sup> However, consistent conclusions about factors that cause recurrence cannot be obtained thus far, and all possible factors, including age, tumor size, incomplete resection, ovarian preservation, and postoperative antiestrogenic therapy, were differently reported in different articles. The recurrence rate in our 166 regular follow-up patients was 5.4% (95% CI 3.1–9.1), which is lower than that reported in the literature. The median recurrence time was 8.5 months, and more than 75% of patients relapsed within 18 months. The recurrence location was mainly concentrated in the pelvic cavity (12/14), and only one extended to the inferior vena cava. We included factors such as age, tumor size, surgical history,

para-uterine involvement, surgical type, and the use of GnRHa in the analytical model. Univariate and multivariate analyses showed that the application of TE was the only factor associated with recurrence. Given the lack of effective therapy in preventing the recurrence of IVL at present, surgery is still the primary treatment when a relapse occurs, and long-term follow-up appears to be particularly important.

## Limitations

Our study is a single-center retrospective study, and information and selective bias are inevitable during data collection. Only 14 patients relapsed among all of the follow-up patients, and the limited number of recurrence events may affect the reliability of the results. Additional prospective cohort and multicenter research is necessary to confirm these research conclusions.

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## Author Contribution

Jing Peng Methodology, Formal analysis and Data Curation. Jing Peng, Fangfang Zhong and Yuemeng Zhu Writing – original draft preparation. Jing Peng, Mingxing Zhang, Meng Zhang, Chong Lu, Yumeng Wang, Xingling Qi and Congwen Wang Investigation. Guiling Li Conceptualization, Supervision and Writing – reviewing and editing.

## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Data Availability Statement

Data available on request due to privacy/ethical restrictions.

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## Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Figure S1** Age distribution of 260 patients at the diagnosis of UIVL. The mean age was  $45.3 \pm 7.4$  (ranged from 23 to 66) years old.

**Figure S2** Tumor size distribution of 260 UIVL patients. The tumor size ranged from 2 to 27 cm and the median was 6.0 cm.

**Table S1** Clinical data of 14 patients with recurrence.