Original Research

Cytoreduction can reduce the recurrence rate of patients with occult uterine sarcoma undergoing morcellation: a retrospective study

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Abstract

Background: Tumor morcellation happened to facilitate iatrogenic metastasis for patients with occult uterine sarcoma. The optimal completion surgery for these patients needed to be established. **Methods**: Data were retrospectively collected and analyzed from patients with occult uterine sarcoma undergoing morcellation. **Results**: 19 consecutive patients with uterine sarcomas undergoing morcellation were accessed between January 2008 and December 2018, including 12 patients with uterine leiomyosarcoma and 7 with endometrial stromal sarcoma. Compared with a simple hysterectomy and individualized surgical resection for suspicious extra-uterine lesions, cytoreduction was significantly associated with a lower recurrence rate ($p = 0.017$), and none of the seven patients undergoing cytoreduction suffered a recurrence. However, the interval between the initial operation and re-operation, transabdominal route (laparoscopic vs. open surgery), and adjuvant therapy had no such significant difference. **Conclusions**: Cytoreduction was considered as the optimal completion surgery for patients with occult uterine sarcoma undergoing morcellation.

Keywords: uterine sarcoma; tumor morcellation; cytoreduction

1. Introduction

Uterine sarcoma is a rare solid malignant tumor in the uterine, accounting for 3%–7% of all uterine malignancies [1]. The major histological types involve carcinosarcomas (accounting for 50% of cases), leiomyosarcomas (LMS, 30%), endometrial stromal sarcomas (ESS, 15%), and undifferentiated sarcomas (5%) [2]. Complete tumor resection is the most effective modality, while other modalities, such as radiation therapy, chemotherapy, and targeted therapy, are not effective [3,4]. Hormonal therapy appeared to be effective in reducing the recurrence of ESS [5]. Clinical trials have shown no definite survival benefit of adjuvant therapy [6,7].

It is challenging to distinguish occult uterine sarcoma from other benign uterine tumors because of neither specific symptoms nor reliable preoperative diagnostic modality [7,8]. A real-world study in western China showed the diagnostic sensitivity of ultrasound for uterine malignant tumors was very low (11%), and only 41.2% patients with uterine sarcoma were diagnosed correctly before operation [9]. Therefore, many patients with occult uterine sarcoma underwent laparoscopic surgery with morcellation by accident. Tumor morcellation means tumor fragmentation in the abdominal cavity during laparoscopic surgery by a power morcellator or any other modalities. A power morcellator is a surgical instrument used to divide and remove large tissues during laparoscopic surgery. In cases of myomectomy or supracervical hysterectomy, the tissue has to be morcellated before extraction. Some studies showed that

the tumor morcellation utilized in uterine sarcoma increased pelvic recurrence rate, facilitated abdominal dissemination, or induced poor prognosis [10–20]. Raine-Bennett T *et al*. [16] showed the incidence of occult uterine sarcomas identified during hysterectomies performed for leiomyomas was 1/278 or 3.60 (95% confidence interval [CI] 2.97–4.23) per 1000 hysterectomies. The incidence was similar in open abdominal surgery and laparoscopy (3/743 vs. 1/1216; $p = 0.16$) [21]. In 2014 FDA stated that tumor morcellation used for laparoscopic myomectomy or hysterectomy is associated with increased risk for spreading cancer and restricts the usage of tumor morcellation [22]. In 2019, the American College of Obstetricians and Gynecologists (ACOG) stated that morcellation of a malignancy is contraindicated [23], and the Society of Obstetricians and Gynaecologists of Canada/Gynecologic Oncologists of Canada (SOGC/GOC) clinical practice guideline contraindicated morcellation of any type in women with pre-cancerous lesions or suspected cancer [24]. However, some studies found the prevalence of occult leiomyosarcoma at surgery for presumed uterine fibroids were 1/8300 [25], 1/10,000–13/10,000 [26] or 12.9/10,000 [27]. A meta-analysis showed the estimated rate of leiomyosarcoma was 0.51/1000 procedures (95% credible interval (CrI) 0.16–0.98) [28]. These prevalences were all lower than the prevalence evaluated by U.S. Food and Drug Administration (FDA) (1/498).

However, which type of completion surgery should be taken to benefit these patients remained unclear. A previous

study indicated that patients who underwent cytoreduction and were not upstaged appeared to have a good prognosis [29]. Two questions were tried to answer in this research.

Which kind of surgery can be taken as an effective completion surgery? According to the 2020 updated National Comprehensive Cancer Network (NCCN) clinical practice guideline on uterine neoplasms, if disease was limited to uterus, simple hysterectomy $\pm$ oophorectomy was often enough for uterine sarcoma, and additional surgical resection for intraoperative discovery of extrauterine disease was individualized. However, was it also sufficient for the patients undergoing morcellation? Some surgeons thought cytoreduction was excessive for these patients with no visible lesions after morcellation, and treated these patients as early staging uterine sarcoma without regard to morcellation. Moreover, can adjuvant therapy (chemotherapy or anti-hormone therapy) be helpful for these patients?

Our study tried to find an optimal option of remedial therapies for these patients.

2. Materials and methods

2.1 Study group

The data of consecutive patients with uterine sarcoma undergoing power morcellation in a single center were retrieved retrospectively from January 2008 to December 2018 through the digital medical record system. The diagnosis and recurrence of every patient should be confirmed by a research team include gynecologists, sonographers, radiologists and pathologists. All previous imaging findings were confirmed by gynecologists, sonographers and radiologists. Pathologic slides were all reviewed by two experienced pathologists. Follow-up data were obtained from our material database. Every patient was able to follow up. There was a total of 19 uterine sarcoma patients undergoing morcellation for our study. Table 1 displays the baseline characteristics of these patients.

The data included patient age, menopausal status, and body mass index; clinicopathologic data including International Federation of Obstetrics and Gynecology (FIGO) staging, the interval between the initial surgery and reoperation, types of re-operation, and adjuvant therapy; and follow-up data including tumor recurrence, location of recurrent tumor, and death. FIGO staging mentioned in our study was based on 2021 updated FIGO staging. We analyzed the data of all patients undergoing morcellation to determine which type of completion surgery could improve the prognosis.

2.2 Surgical procedure

The completion surgery after morcellation was performed by three gynecological oncology surgeons, in which there was at least one surgeon with over 10-year experience of gynecological oncology surgery. Because of no available guidelines or research, which kind of completion surgery should be performed depends on the judgment of the chief surgeon. On entering the abdomen, all peritoneal surface should be visualized and explored. All patients in our study did not have visible lesions after initial surgery with morcellation. Afterwards, there were two different procedures, cytoreduction, and simple hysterectomy $\pm$ oophorectomy. Cytoreduction involved total hysterectomy $\pm$ oophorectomy, omentectomy, and additional surgical resection for the intraoperative discovery of the extrauterine disease. The term "cytoreduction" we used suggested that the subclinical lesion should be attached importance to. Some chief surgeons hypothesized that morcellation could cause iatrogenic subclinical extrauterine lesions and applied cytoreduction on these patients as a completion surgery performed on ovarian cancer. All completion surgeries in our study resulted in complete cytoreduction.

2.3 Statistical analysis

Data analysis was performed using SPSS software for Windows (version 21.0; SPSS Inc., Chicago, IL, USA). The patient sample size in our study cannot but be tiny, so analyses of factors (such as cox regression) were not suitable for this study. As instead, recurrence rates were compared using chi-squared and Fisher's exact tests. Disease-free survival (DFS) was calculated as the number of months from the surgery to either recurrence date or date censored. Two-sided p-values less than 0.05 were considered statistically significant.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This research was approved by the ethics committee of Zhejiang Cancer Hospital. The reference number was IRB-2019-199 (IRB, Institutional Review Board).

3. Results

Nineteen patients with uterine sarcoma were treated and followed at Zhejiang Cancer Hospital, including 12 with LMS and 7 with ESS. The median follow-up times were 18 months (range from 5–66 months) for all patients. The characteristics of patients are present in Table 1.

78.9% of patients underwent the laparoscopic myomectomy as an initial operation, and 21.1% experienced the laparoscopic supracervical hysterectomy. All patients were preoperatively diagnosed with uterine leiomyoma and used tumor morcellation by accident.

According to Table 2, there were no significant differences between groups in age, menopausal status, and FIGO stage. In addition, the median of the interval between the initial operation and re-operation was 23 days, ranging from 0 to 93 days. Twelve patients underwent simply hysterectomy $\pm$ oophorectomy as a re-operation, while 7 underwent cytoreduction. After re-operations, ten patients received adjuvant therapies, while nine received none. Adjuvant therapy involved in our study contained chemotherapy,

Table 1. Characteristics of patients with uterine sarcoma (n = 19).

Characteristics of patients		Value
Age	Mean ± SD	44.9 ± 7.3
Menopause, n (%)	No	16 (84.2)
	Yes	3 (15.8)
Body mass index	Mean ± SD	22.1 ± 2.2
Initial symptoms, n (%)	Asymptomatic	11 (57.9)
	Palpable mass	4 (21.1)
	Vaginal bleeding	3 (15.8)*
	Abdominal pain	2 (10.5)*
Preoperative presumptive diagnosis, n (%)	Uterine sarcoma	0 (0)
	Uterine leiomyoma	19 (100)
Initial operation, n (%)	Myomectomy	15 (78.9)
	Supracervical hysterectomy	3 (15.8)
	Hysterectomy	1 (5.3)
Pathological type, n (%)	LMS	12 (63.2)
	ESS	7 (36.8)
FIGO stage, n (%)	I	17 (89.5)
	II and III	2 (10.5)

Values are presented as the number of patients (%) or average ± standard deviation.

SD, standard deviation; FIGO, International Federation of Obstetrics and Gynecology; LMS, Uterine leiomyosarcoma; ESS, Endometrial stromal sarcoma; *, one patient complained about vaginal bleeding and abdominal pain.

and hormone therapy.

We found that cytoreduction could reduce the recurrence rate compared with the simple hysterectomy group (0% vs. 58.3%, $p = 0.017$) (Table 2). The median follow-up time of cytoreduction group was 19 months (16–30 months). As a result, cytoreduction as completion surgery was very important for those patients to reduce recurrence rate. None of the seven patients undergoing cytoreduction, including 3 LMS and 4 ESS, suffered a recurrence. However, the interval between the initial operation and re-operation (42.9% vs. 20.0%, $p = 0.603$), chemotherapy on LMS ($p = 0.080$) and anti-hormonal therapy on ESS ($p = 0.375$) did not impact the recurrence rate. Whether to take Laparoscopic surgery or abdominal surgery also seem no significant difference between each other (40.0% vs. 33.3%, $p = 1.000$). As a hypothesis, cytoreduction after the initial morcellation may eliminate all suspicious iatrogenic implantation metastasis caused by morcellation.

All seven patients undergoing cytoreduction had no tumor manifestation on entering the abdomen. However, post-operative pathological examination found subclinical metastatic lesions on both the omentum and rectal serosa in one patient, and the rectal serosa in another patient.

Our study summarized the data of every recurrence of patients in Table 3. About 36.8% of patients experienced the first recurrence at 16 months (range from 4–56 months) after the initial surgery. The disease-free inter-

vals before the second recurrence were reduced to 4 months (range from 3–31 months). 3 in 15 stage I patients suffered a recurrence, 1 in 2 stage II patients recurred, and all of 2 stage III recurred. Most recurrence (23.5%) occurred in the pelvic peritoneum without rectum and lymph nodes. Rectal and small intestinal implantation was the second most common form of cancer metastasis (14.7%), while pelvic and para-aortic lymph metastasis was rare. Iatrogenic implant metastasis was the most common form of metastasis in patients with uterine sarcoma undergoing morcellation. As a result, cytoreduction might be a better completion surgery than simple hysterectomy.

4. Discussion

Morice et al. [11] found pelvic recurrence rate three months after surgery was higher in the morcellation group than in the non-morcellation group, but the difference was not statistically significant (8.8% vs. 3.6%, $p = 0.25$). Jeong-Yeol Park et al. [12] confirmed that tumor morcellation facilitated recurrence in the peritoneal cavity and adversely affected DFS (Odds ratio (OR), 2.59; 95% CI, 1.03–6.50; $p = 0.043$) and overall survival (OS) (OR, 3.07; 95% CI, 1.05–8.93; $p = 0.040$) in patients with uterine LMS. One of the 25 morcellated cases were performed by power morcellation, and the rest were manually tumor fragmentation. They also found tumor morcellation was associated with a significantly higher rate of abdominopelvic recur-

Table 2. Re-operation and adjuvant therapy associated with disease-free survival of patients undergoing tumor morcellation (n = 19).

		Total, n	Recur†, n (%)	p-value
Age	≤47 years	9	1 (11.1)	0.057
	>47 years	10	6 (60.0)	
FIGO stage	I	17	6 (35.3)	1
	II and III	2	1 (50.0)	
Histological types	LMS	11	6 (54.5)	0.147
	ESS	8	1 (12.5)	
The interval between the initial operation and re-operation	<30 days	14	6 (42.9)	0.603
	≥30 days	5	1 (20.0)	
Types of completion surgery	Simply hysterectomy ± oophorectomy	12	7 (58.3)	0.017*
	Cytoreduction	7	0 (0)	
Transabdominal route	Laparoscopic	10	4 (40.0)	1
	Open	9	3 (33.3)	
Adjuvant therapy	Chemotherapy on LMS — No	6	5 (83.3)	0.080
	Chemotherapy on LMS — Yes	5	1 (20.0)	
	Anti-hormonal therapy on ESS — No	3	1 (33.3)	0.375
	Anti-hormonal therapy on ESS — Yes	5	0 (0)	

Values are presented as the number of patients (%).

FIGO, International Federation of Obstetrics and Gynecology; LMS, uterine leiomyosarcoma; ESS, endometrial stromal sarcoma; *, $p < 0.050$, Fisher's exact test; †, the median follow-up times were 18 months (5–66 months).

Table 3. Anatomical location of recurrent disease at every recurrence (n = 19).

Recur		1st recur	2nd recur	3rd recur	Total, n (%)
n (%)		7 (36.8)	5 (26.3)	2 (10.5)	
Death, n		1	0	1	
The disease-free interval (month)	Median (range)	16 (9–56)	4 (3–31)	9 (7–11)	
Pathological type	LMS	6	4	1	
	ESS	1	1	1	
Anatomical location of recurrence	Pelvic peritoneum (without rectum and lymph nodes)	3	4	1	8 (23.5)
	Rectum	2	3	0	5 (14.7)
	Small intestine	2	3	0	5 (14.7)
	Colon (without rectum)	2	2	0	4 (11.8)
	Peritoneum (not in the pelvis)	1	2	1	4 (11.8)
	Lung	1	1	1	3 (8.8)
	Abdominal wound	1	1	0	2 (5.9)
	Omentum	0	1	0	1 (2.9)
	Pancreas	0	1	0	1 (2.9)
	Liver	0	0	1	1 (2.9)
	Pelvic lymph nodes	0	0	0	0 (0)

Values are presented as the number of patients (%) or median (range).

LMS, uterine leiomyosarcoma; ESS, endometrial stromal sarcoma.

rence and significantly poorer DFS (OR, 4.03; 95% CI, 1.06–15.30; $p = 0.040$) in patients with ESS, but OS was not significantly compromised [13]. Raine-Bennett *et al.* [16] found decreased early survival of women undergoing power morcellation with occult leiomyosarcomas, but failed to conclude associations between power morcellation and 3-year survival as a result of small sample. Xu *et al.* [17] analyzed the data in New York and concluded that uncontained power morcellation was associated with higher disease-specific mortality risk in patients with occult uterine sarcoma (adjusted hazard ratio [aHR], 2.66; 95% CI, 1.11–6.37), especially in those with occult leiomyosarcoma (aHR, 3.64; 95% CI, 1.50–8.86). Francesco Raspagliesi *et al.* [18] identified 125 patients and found that morcellation induced a 3-fold increase risk of death in comparison to no morcellation group ($p = 0.02$). Silvana Pedra Nobre *et al.* [19] enrolled 152 patients, and concluded that morcellation was associated with significantly higher risk of recurrence and a nearly 4-fold increase in peritoneal recurrence. A meta-analysis, screening sixty manuscripts, showed that morcellation increased the overall (62% vs. 39%; OR, 3.16 (95% CI, 1.38–7.26)) and intra-abdominal (39% vs. 9%; OR, 4.11 (95% CI, 1.92–8.81)) recurrence rates as well as death rate (48% vs. 29%; OR, 2.42 (95% CI, 1.19–4.92)) [20]. The U.S. FDA stated that tumor morcellation promoted an adverse effect on the prognosis of patients with LMS [22]. The ACOG committee and the SOGC/GOC guideline all stated that an unexpected uterine malignancy may be spread through morcellation, leading to a potentially worsened prognosis [23,24]. Most reviews supported morcellation not only upstaged uterine sarcoma, but may also be responsible for reduced survival rate, and concluded that intra-abdominal morcellation should be banned [30–32].

Our study found that one of 7 patients undergoing cytoreduction as a completion surgery had subclinical metastatic lesions on the omentum, and two had metastatic lesions on the rectal serosa, according to the postoperative pathological examinations. Without cytoreduction, 58.3% of patients suffered from sarcoma recurring. Erika L. Mowers *et al.* [33] demonstrated their similar experience in the University of Michigan Hospital. Seven patients in their study undergoing power morcellation had a secondary surgery 6–19.2 weeks after their initial procedure. One of 7 patients had widespread malignant implants. It was much frequent that the recurrence occurred in the pelvis where the former primary lesion was located. The peritoneal and gastrointestinal implantation in the upper abdomen were also prevalent. As a result, cytoreduction seemed to be a better completion surgery than simply hysterectomy.

Though forbidden in myomectomy or hysterectomy for treatment of fibroids by U.S. Food and Drug Administration in 2014, the morcellation was still utilized widely outside U.S., especially in many developing countries. As a result, the situations that uterine sarcoma undergoing morcellation still exist recently. A proper completion surgery

should be considered. However, before our research, no clinical study has investigated the completion surgery for these exceptional cases.

Transabdominal route (laparoscopic or open) and adjuvant therapy seemed not to impact the recurrence rate. Satisfactory cytoreduction appeared to be the only way to achieve a good prognosis. A previous retrospective study showed that 2 of 13 patients with uterine malignancy underwent paracervical hysterectomy during the initial surgery was upstaged by re-exploration; both had LMS initially resected with morcellation. Patients who underwent completion surgery with restaging appeared to have a good prognosis [29].

Moreover, re-operation long after the initial surgery ($\geq$30 days) with morcellation can still be valuable. Cao H *et al.* [34] also confirmed that the time interval between initial treatment and definitive secondary surgery was not shown to impact prognosis. The maximum time interval time was 93 days (3 months). The first recurrence happened after 16 months (9–56 months) when the initial treatment was over. We think it would be not safe when the interval was more than 3 months.

Though a real-world research in western China in 2020 indicated the diagnostic sensitivity of ultrasound for uterine sarcoma was low (11%) [9], some novel ultrasound techniques can diagnose the occult uterine sarcoma before surgery. A retrospective multicenter study showed some vital ultrasound characteristics of uterine sarcoma, such as solid masses with inhomogeneous echogenicity and very good vascularization [35]. Diffusion-tensor imaging can be used to differentiate uterine sarcoma from uterine fibrosis, and the sensitivity and specificity can reach 96.7%/92.9% [36]. We believe that the novel and proper ultrasound technique can avoid uterine sarcoma undergoing morcellation.

Annalisa *et al.* [37] showed LMS relative with the inactivation of TP53, with 61% of the patients having at least one pathogenic mutation. OS of TP53mut/RB1wt patients was significantly lower than that of TP53mut/RB1mut (67.1 vs. 89.9 months). This study indicates that genetic testing would be helpful for the prediction of the prognosis of occult sarcoma undergoing morcellation.

Techniques for avoiding iatrogenic metastases, using insufflated isolation bags (in-bag morcellation) or transvaginal specimen extraction via endoscopic bags, are now in progress and may lead to a safe use of morcellation in a laparoscopic approach [5,38]. Zapardiel *et al.* [39] developed three ways of in-bag morcellation to avoid tumor spread. They fragmented the tumor in a unique bag and made sure that the bag was not broken and the tumor debris was not left in the abdominal cavity. Further survival data was of lack. However, the SOGC/GOC guideline said that the benefits of in-bag morcellation have not been established [24]. More research is needed in the future.

The limitation of our study included the retrospective design and the relatively small number of patients.

The situation that uterine sarcoma undergoing morcellation was very rare, much rarer than occult leiomyosarcoma at surgery for presumed uterine fibroids (1/10,000–13/10,000 [26]). So, the patient sample size in our study cannot avoid being minimal, and analyses of factors (such as cox regression) were not suitable for this study. As instead, recurrence rates were compared using chi-square and Fisher's exact tests, and the testing power was low.

5. Conclusions

Cytoreduction was considered as the optimal completion surgery for patients with occult uterine sarcoma undergoing morcellation.

Abbreviations

SD, standard deviation; FIGO, International Federation of Obstetrics and Gynecology; LMS, Uterine leiomyosarcoma; ESS, Endometrial stromal sarcoma; ACOG, American College of Obstetricians and Gynecologists; SOGC/GOC, Society of Obstetricians and Gynaecologists of Canada/Gynecologic Oncologists of Canada; OR, odds ratio; OS, overall survival; DFS, disease-free survival.

Author contributions

CD and JQZ conceived and designed the study; CD collected and analyzed the data; CD wrote the initial draft of the paper; JQZ provided critical revision and final approval. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This research was approved by the ethics committee of Zhejiang Cancer Hospital. The reference number was IRB-2019-199. Because it is a retrospective study in which many patients have been discharged for long time, lost to follow-up, or died, and there is no intervention and no personal real-name information, the ethics committee exempted informed consent.

Conflict of interest

The authors declare no conflict of interest.

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