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The impact of laparoscopic surgical treatments on oncologic outcome of Stage I uterine leiomyosarcoma

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Summary

Background: Morcellation may worsen the outcome of occult uterine leiomyosarcoma (uLMS), while the effect of laparoscopic surgery itself, without morcellation, on the oncological outcomes of patients with early stage uLMS is also currently unknown. *Materials and Methods:* A retrospective analysis of 75 patients who underwent treatment for Stage I uLMS at Shanghai Cancer Center was performed. Kaplan–Meier and Cox proportional hazards regression models were used for analyses. *Results:* Fifty-five patients underwent primary open surgery and 20 underwent laparoscopy. Patient age was significantly lower in the laparoscopy (44 ± 9.04 years) compared with the open surgery group (50.85 ± 9.96 years) ($p < 0.007$). Laparoscopic surgery was associated with shorter overall survival (OS) according to Kaplan–Meier (KM) log-rank test ($p = 0.046$), and multivariate Cox regression ($f = 0.032$, RR = 2.423, 95% confidence interval, 1.081–5.429), but not disease-free survival (DFS) ($p = 0.682$, Kaplan–-Meier log-rank test). In stratification analysis, patients who underwent laparoscopic total hysterectomy/modified radical hysterectomy (without morcellation) had shorter DFS ($p = 0.006$) and OS ($p = 0.001$), compared with the open group. However, laparoscopic myomectomy and sub-total hysterectomy were associated with a similar DFS ($p = 0.924$) and OS ($p = 0.580$) to open total hysterectomy/modified radical hysterectomy. There was no significant difference in DFS ($p = 0.941$) or OS ($p = 0.737$) between laparoscopic surgery with and without morcellation. *Conclusions:* Laparoscopic surgery may be associated with poorer survival than open surgery in patients with early stage uLMS, even in the absence of morcellation.

Key words: Uterine leiomyosarcoma; Laparoscopy; Recurrence; Survival.

Introduction

Uterine leiomyosarcoma (uLMS) is a rare malignant disease accounting for only approximately 1% of all uterine malignancies[1-3]. Many patients are diagnosed during the early stage of the disease; however, the recurrence rate even among patients with uterine confined disease (FIGO Stage I) exceeds 50%, and the five-year survival rate is approximately 40% [1-3]. Surgical treatment remains the mainstay of the management of leiomyosarcoma [3]. Total abdominal hysterectomy and removal of extra-uterine disease are recommended for the treatment of uLMS [1, 4, 5].

Minimally invasive surgery, such as laparoscopy, has recently replaced open abdominal procedures in certain gynecologic surgery settings, because of its faster recovery time and lower perioperative complication rates. However, although morcellation is commonly used in laparoscopy to remove large benign tumors, the FDA warns against its use because of the risk of intraoperative spread of malignant tissue [6]. Several recent retrospective studies showed that morcellation of undiagnosed uterine sarcoma was associated with poorer survival outcomes [7, 8]. However, the risk of death following laparoscopic surgery without morcellation in patients with uLMS remains undefined. The purpose of this retrospective study was to investigate the impact of laparoscopic surgical treatments on oncologic outcome of in patients with Stage I uLMS.

Materials and Methods

The institutional review board at Fudan University Shanghai Cancer Center (FDUSCC) approved the study. Patients with Stage I uLMS who underwent treatment at FDUSCC between 2000 and 2016 were identified from the pathology archives and the tumor registry database. Assignment of stage was performed in accordance with the 2009 International Federation of Gynecology and Obstetrics staging criteria for sarcoma. Demographic, clinical, pathological, and treatment-related data were extracted from the patients' records. All patients underwent surgery. The period from surgery to recurrence or the last visit was defined as disease-free survival (DFS), and the period from surgery to death or the last visit was defined as overall survival (OS).

Data analyses were performed using the SPSS 20 program . Continuous variables were evaluated by the Student's *t*-test or the Wilcoxon–Mann-Whitney test, as appropriate. Categorical variables were evaluated by the χ^2 test or Fisher's exact test as appropriate for category size. Categorical variables were analyzed by Kaplan–Meier survival analysis, using the log-rank test to determine statistical significance regarding DFS and OS. Multivariate analyses were performed with the Cox proportional regression method, and significant factors were determined using the for-

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Table 1. — *Characteristics of the study population.*

Characteristics	Non- laparoscopy (n=55)	Laparoscopy (n=20)	*p* value
Median age (range)	51.00 (26-76)	43 (23-59)	0.018
differentiation			0.114
Undifferentiation	4 (7.2%)	4 (20.0%)	
Type			0.798
Myxoid	7 (12.7)	3 (15%)	
Lymphadenectomy			0.215
Yes	16 (29.1%)	3 (15.0%)	
BSO			0.290
Yes	47 (85.5%)	15 (75%)	
Adjuvant radiotherapy			0.798
Yes	7 (12.7%)	3 (15%)	
Adjuvant chemotherapy			0.311
Yes	32 (58.2%)	9 (45%)	
Primary surgical treatment of uterine myomectomy & sub-TH	15 (27.3%)	12 (60%)	0.009
Complete hysterectomy after primary or immediately reoperation			0.717
Yes	46 (83.6%)	18 (90%)	

BSO: bilateral salpingo-oophorectomy. TH: total hysterectomy. mRH: modified radical hysterectomy.

ward-stepwise method. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Seventy-five patients with Stage I uLMS who underwent surgical treatment were eligible for analyses. Of the overall cohort, 45.3% (34/75) were deceased after a median follow-up of 36.0 (range, 11.1–169.8) months. The median DFS and OS were 20 [95% confidence interval (CI)]: 11.4-28.5) and 62.8 (95%CI: 44.4-81.2) months, respectively. For the primary surgery, 55 patients underwent open surgery and 20 underwent laparoscopy. Ten, two, and eight patients who were initially treated by laparoscopy underwent myomectomy, subtotal hysterectomy, and total hysterectomy, respectively. Ten (83.3%) patients with unexpected uLMS initially treated with laparoscopic uterus-preserving surgery were immediately reoperated on for hysterectomy (8/10 myomectomy and 2/2 subtotal hysterectomy). Among the patients who underwent open surgery, nine, six, 37, and three patients underwent myomectomy, subtotal hysterectomy, total hysterectomy, and modified radical hysterectomy, respectively. Nine (60%) patients with unexpected uLMS who were initially treated with open uterus-preserving surgery were immediately reoperated for hysterectomy (6/9 myomectomy and 3/6 subtotal hysterectomy). Patient age was significantly lower in the laparoscopy group than in the open surgery group (50.85 ± 9.96, $p = 0.007$). However, there was no significant difference between the laparoscopy and open surgery groups with regards to histological type (myxoid), pathologic stage, adjuvant chemotherapy, adjuvant radiotherapy, and completion of hysterectomy after primary and/or immediate reoperation (Table 1).

The Kaplan–Meier curves and log-rank tests showed no significant difference in DFS ($p = 0.682$, Figure 1A) between patients who underwent laparoscopic surgery and those who received open surgery as the initial treatment. However, the median OS was significantly shorter among patients undergoing initial laparoscopic surgery (27.5 months, 95% CI, 22.1–32.8) compared with open surgery (63.9 months, 95% CI, 43.1–84.7) ($p = 0.046$, Figure 1B). Morcellation is considered to be important factor affecting the outcome of uLMS. Morcellation was performed in 10/12 patients who received laparoscopic myomectomy/subtotal hysterectomy, but none of the eight patients who underwent laparoscopic total hysterectomy/modified radical hysterectomy. However, there was no significant difference in DFS ($p = 0.941$) or OS ($p = 0.737$) between patients undergoing laparoscopic surgery with and without morcellation. The authors further stratified the patients in the laparoscopic and open surgery groups according to whether or not they received complete hysterectomy. Kaplan-Meier curves and log-rank tests showed no difference in DFS ($p = 0.924$) or OS ($p = 0.580$) between the laparoscopic and open surgery groups among patients undergoing myomectomy/subtotal hysterectomy (Figures 1C and D). However, both DFS and OS were shorter in patients undergoing laparoscopic compared with open surgery among patients with total hysterectomy/modified radical hysterectomy ($p = 0.006$ and $p = 0.001$ for DFS and OS, respectively, Figures 1E and F). These results suggested that laparoscopy may still be associated with poor outcomes, even without the use of morcellation.

The present authors also investigated the recurrence patterns in the two groups. Peritoneal dissemination is the major type of tumor recurrence in patients with uLMS. Forty-two (76.3%) patients in open surgery group and 12 patients (65%) in laparoscopic group developed recurrence with peritoneal dissemination (pelvic and/or abdominal) during follow-up. Eight patients (14.5%) in the open surgery group (14.5%) and 2 (10%) in the laparoscopic group developed lung metastases ($p = 0.721$ *vs*. open group), and one patient in the laparoscopic group developed ovarian metastasis. Among patients with peritoneal dissemination, the mean number of recurrent peritoneal carcinomatoses was slightly higher in the laparoscopic group (4.3 per patient) compared with the open surgery group (2.3 per patient), but the difference was not significant ($p = 0.150$). Trocar-site metastasis occurred in five (25%) patients who underwent laparoscopic surgery, and abdominal wall metastasis occurred in five patients (9.1%) who underwent open surgery ($p = 0.119$).

Multivariate analysis using Cox regression and including all the factors showed that tumor differentiation ($p < 0.001$, RR = 7.4, 95% CI 3.2–17.1) was the only independent fac-

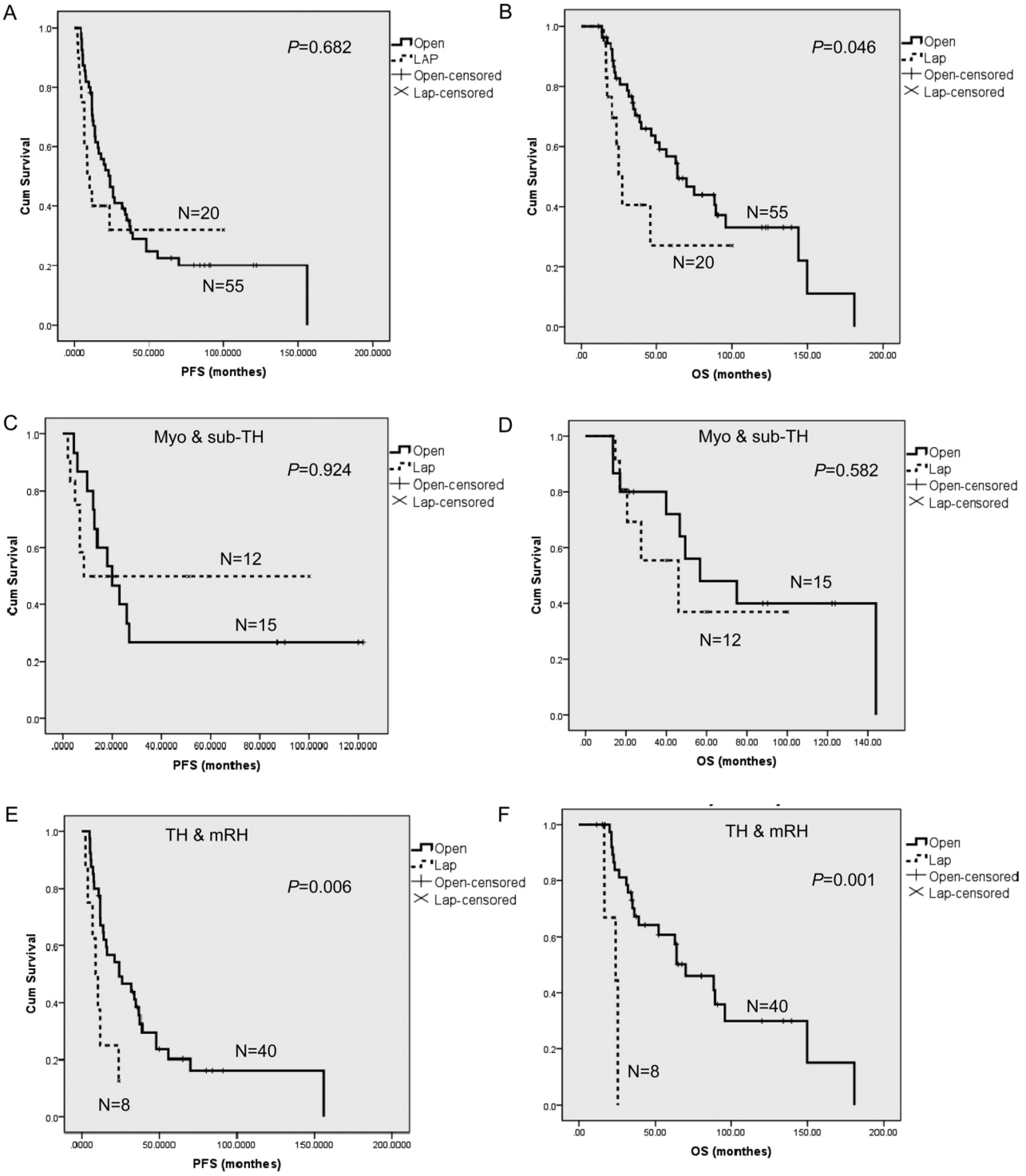

Figure 1. — Kaplan–Meier survival curves of matched cohorts. Disease-free (A) and overall (B) survival curves for patients undergoing laparoscopic *vs*. open surgery. (C) Disease-free survival of patients undergoing myomectomy/sub-total hysterectomy via laparoscopic *vs.* open surgery as the initial surgical treatment. (D) Overall survival of patients undergoing myomectomy/sub-total hysterectomy performed by laparoscopic *vs.* open surgery as the initial surgical treatment. (E) Disease-free survival of patients undergoing total hysterectomy/modified radical hysterectomy performed by laparoscopic *vs.* open surgery as the initial surgical treatment. (F) Overall survival of patients undergoing total hysterectomy/modified radical hysterectomy performed by laparoscopic *vs.* open surgery as the initial surgical treatment. TH: total hysterectomy; mRH: modified radical hysterectomy; Myo, myomectomy; Lap: laparoscopy.

Table 2. — *Factors predicting for overall survival in patients affected by uterine leiomyosarcomas.*

Characteristics	Univariate analysis HR (95%CI)	*p* value	Multivariate analysis HR (95%CI)	*p* value
Age, years	0.992 (0.950-1.036)	0.72	-	
Grade				
I &II	Reference			
III	**5.063 (2.002-12.808)**	**<0.001**	**4.385 (1.672–11.500)**	**0.003**
Type				
Myxoid	Reference			
Non-myxoid	1.210 (0.501-2.923)	0.671		
Lap surgery				
No	Reference			
Yes	2.155 (0.997-4.662)	0.051	**2.423 (1.081–5.429)**	**0.032**
Lymphadenectomy				
No	Reference			
Yes	1.392 (0.702-2.760)	0.344	-	
BSO				
No	Reference			
Yes	0.581 (0.281-1.198)	0.141	-	
Adjuvant radiotherapy				
No	Reference			
Yes	0.921 (0.359-02.362)	0.864	-	
Adjuvant chemotherapy				
No	Reference			
Yes	**0.447 (0.237-0.843)**	**.013**	**0.469 (0.244–0.902)**	**0.023**
Primary surgical treatment of uterine				
TH	Reference			
Myomectomy & sub-TH	0.916 (0.476-1.764)	0.793	-	
Morcellation				
No	Reference			
Yes	1.726 (0.668-4.463)	0.260		

BSO: bilateral salpingo-oophorectomy. TH: total hysterectomy. mRH: modified radical hysterectomy. Lap: laparoscopy.

tor associated with DFS. However, tumor differentiation (p = 0.003, RR = 4.385, 95% CI 1.672–11.5), adjuvant chemotherapy (p = 0.023, RR = 0.469, 95% CI 0.244–0.902), and laparoscopic surgery (p = 0.032, RR = 2.423, 95% CI 1.081–5.429) were the independent factors associated with OS (Table 2).

Discussion

This retrospective study confirmed the impact of laparoscopic surgery on oncologic outcomes of patients with Stage I uterine leiomyosarcoma. The results suggested that laparoscopic surgery, even without morcellation, was associated with shorter OS.

The FDA reported on the prognostic impact of morcellation of unexpected sarcomas, based on a pooled analysis of retrospective studies [9, 10]. This pooled analysis suggested that morcellation increased the risks of overall and intra-abdominal recurrence, and the risk of death, compared with surgery without morcellation. Morcellation is more frequently used during laparoscopic myomectomy and subtotal hysterectomy. A recent study showed no correlation between morcellation and DFS in patients with LMS, but morcellation or power morcellation was associated with a three-fold increase in the risk of death, compared with patients who did not undergo morcellation [7]. However, the current results suggested that the poor prognostic effect of laparoscopic surgery may not only be attributed to morcellation. First, patients who underwent laparoscopic surgery with morcellation had similar DFS and OS to those without morcellation. Second, both DFS and OS were shorter in the laparoscopy (no morcellation) compared with the open surgery group among patients who received total hysterectomy/modified radical hysterectomy. Finally, the present study identified laparoscopic surgery as an independent predictor of poor OS according to multivariate analysis.

The high degree of heterogeneity among the treatment procedures in each group made it difficult to draw firm conclusions from the present data. However, the authors attempted to balance the factors potentially influencing the results by statistical analyses. The percentages of patients receiving adjuvant radiotherapy and chemotherapy were similar in the laparoscopic and open surgery groups, and immediate reoperation for total hysterectomy resulted in similar high completion rates for uterine dissection in both groups. It is therefore likely that the poor outcome of patients with uLMS may have been at least partially due to the laparoscopy procedure itself, as indicated by multivariate analysis.

The reasons for the adverse impact of laparoscopic

surgery are unknown. Tumor spread due to pneumoperitoneum has been suggested as a possible explanation, and experimental data suggested that the risk of tumor dissemination in the non-traumatized peritoneum may be greater after pneumoperitoneum than after laparotomy [11]. The incidence of cancer cell invasion into the muscle layers of the abdominal wall was shown to be significantly higher in mice undergoing laparotomy with high intraperitoneal pressure compared with control mice and mice with low intraperitoneal pressure [12]. However, this theory does not apply to most types of gynecologic cancers, and laparoscopic treatment is well-established for endometrial and cervical cancers, and for ovarian cancer staging [13, 14]. LMS appears to be more aggressive and prone to peritoneal dissemination when the tumor is disturbed, e.g., by high intraperitoneal pressure or uterine manipulation. The recurrence rate of early stage uLMS (up to 40%) is also higher than that of endometrial cancer. The current results showed that the trocar site was a relatively common site of recurrence (5/20 patients), with a higher incidence compared with other studies of endometrial cancer [15]. The number of intra-abdominal recurrent tumors also tended to be higher in the laparoscopic compared with the open surgery group in the present study, though the difference was not significant. The poorer outcomes associated with laparoscopic surgery may therefore be attributed to the aggressive behavior of uLMS and the greater disturbance caused by laparoscopic surgery.

This study had several limitations. Firstly, it was a retrospective observational study with a limited number of patients from one center, and it could therefore carry all the inherent limitations and biases associated with such studies. However, it is difficult to perform a prospective or randomized trial in uLMS because of its low incidence and difficult preoperative diagnosis. Other limitations included the heterogeneity of follow-up, surgical approach, as well as differences in the treatments following recurrence.

In conclusion, the present results indicate that laparoscopic surgery increases the risk of death in patients affected by early stage uLMS, even without morcellation. The authors suggest that laparoscopic surgery should thus be performed carefully in patients with suspected uLMS. However, further studies are needed to confirm these results.

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