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Morcellation worsens survival outcomes in patients with undiagnosed uterine leiomyosarcomas: A retrospective MITO group study

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HIGHLIGHTS

- Morcellation worsens survival of patients affected by uterine leiomyosarcomas.
- Effects of morcellation on STUMP and ESS need to be further evaluated.
- The role of morcellation of apparent benign fibroids deserves further investigations.

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ABSTRACT

Objective. To investigate the impact of morcellation on survival outcomes of patients affected by undiagnosed uterine sarcoma.

Methods. This is a retrospective study performed in 8 referral centers of MITO group. Data of women undergoing morcellation for apparent benign uterine myomas who were ultimately diagnosed with stage I uterine sarcoma on final pathology were compared with data of women who did not undergo morcellation. Uterine sarcoma included: leiomyosarcomas (LMS), smooth muscle tumors of uncertain malignant potential (STUMP), low-grade endometrial stromal sarcomas (LG-ESS) and undifferentiated uterine sarcomas (UUS). Two-year survival outcomes were evaluated using Kaplan-Meir and Cox models.

Results. Overall 125 patients were identified: 31(24.8%), 21(16.8%) and 73(58.4%) patients had power morcellation during laparoscopy, non power morcellation during open surgery and non morcellation during open procedures, respectively. Considering patients affected by LMS, morcellation did not correlated with disease-free survival. However, patients undergoing either morcellation or power morcellation experienced a 3-fold increase risk of death in comparison to patients who had not morcellation ($p = 0.02$). A trend towards an increase of recurrence was observed for patients undergoing morcellation for STUMP (HR 7.7, $p = 0.09$); while no differences in survival outcomes were observed for patients with LG-ESS and UUS.

Conclusions. Our data suggest that morcellation increase the risk of death in patients affected by undiagnosed LMS. Further prospective studies are warranted in order to assess the risk to benefit ratio of power morcellator utilization in patients with apparent benign uterine myomas.

1. Introduction

Uterine leiomyosarcoma represents a rare entity, constituting about 1.5% of all uterine malignancies, with an estimated annual incidence of

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0.64/100,000 women [1]. Excluding carcinosarcomas which are actually classified as undifferentiated carcinomas, leiomyosarcomas (LMSs) and stromal sarcomas account for about 70% and 30% of all uterine sarcomas, respectively [2].

The survival of patients with LMS is strongly associated with the FIGO stage of disease at diagnosis: Stage I tumors have a 5-year survival rate of 84.3%, that decreases dramatically in stage II (43.6%), III (38.8%), and IV (19.8%) respectively [2]. Unfortunately, preoperatively it may be difficult to discriminate between benign uterine fibroids and uterine sarcomas. The true prevalence of uterine sarcomas in presumed fibroids is not exactly known, given the wide range (0.45–0.014%) reported in meta-analyses mainly based on retrospective data [3,4]. Moreover, although some patients' characteristics (including older age and the presence of symptoms) and morphological features of the uterine lesions at imaging may be suggestive for the presence of uterine sarcoma, a reliable differential diagnosis is still difficult [5].

In November 2014, the U.S. Food and Drug Administration (FDA) issued a safety communication against power morcellation; morcellation was "discouraged" due to its detrimental potential effects in patients with undiagnosed uterine sarcoma [6]. In fact, if a presumed fibroid reveals to be a sarcoma (or other malignancy), any method of morcellation disrupts the integrity of the tumor, thus possibly upstaging the disease and affecting survival. In case of power morcellation, the centripetal forces of the cylindrical knife may add to the phenomenon of 'seeding' of tumor cells on the peritoneum [7].

Thereafter, representatives of many scientific societies published their opinions on this issue concluding about the lack of solid scientific evidence to reach strong recommendations on the use of power morcellation [8]. In this retrospective study we sought to determine the oncologic outcome of undiagnosed uterine sarcoma in a large group of women who underwent morcellation in comparison to a group of patients treated without morcellation at 8 referral institutions of MITO (Multicentre Italian Trialists in Ovarian Cancer and Gynecologic Malignancies) group.

2. Materials and methods

This is a retrospective study performed in eight high volume centers hospitals of MITO group. The medical records of consecutive women who underwent surgical treatment for apparent benign uterine myomas that revealed to be sarcomas at final diagnosis from January 1, 2004, to December 31, 2014 were reviewed and Institutional review board (IRB) was obtained for the study. All patients included in the study gave written consent to data collection and to the use of personal records for health research.

Inclusion criteria were: (1) patients undergoing surgery for apparent benign uterine disease (2) final histological diagnosis of stage I uterine sarcoma and (3) patients aged 18 years or older. Exclusion criteria were: consent refusal and diagnosis of other solid malignancies within 5 years.

The primary endpoint of the study was to assess progression free and overall survival of uterine sarcomas patients treated with morcellation in comparison to patients treated without morcellation.

Data of consecutive women undergoing hysterectomy or myomectomy using morcellation for apparent benign fibroids (which revealed to be unexpected uterine sarcomas) were evaluated and compared with data of women with the same clinical characteristics treated without morcellation. Uterine sarcomas were considered unexpected if the surgeon did not report any preoperative or intraoperative suspicion for malignancy in the preoperative clinic notes, admitting history, and physical or operative reports. After identification, data were abstracted from the medical records; women's demographic information, operative reports, and final pathology reports were reviewed. Other information collected included surgical indication, preoperative work up details, adjuvant therapy after final diagnosis, time and site of relapse and date of death. Stage of disease and histological classification were assessed using the International Federation of Obstetrics and Gynecologists (FIGO) [9] and World Health Organization (WHO) [10] systems, respectively. Uterine sarcoma included: LMS, smooth muscle tumors of uncertain malignant potential (STUMP), low grade endometrial stromal sarcomas (LG-ESS) and undifferentiated uterine sarcomas (UUS). Follow-up evaluations, with pelvic inspection and ultrasound examination, were planned every 3 months for the first 2 years, then every 6 months for the following 3 years and annually thereafter. Intra-abdominal recurrences were considered as any recurrence involving the peritoneal surface, while hepatic and/or splenic and/or lung parenchymal metastases were considered as distant recurrences.

2.1. Statistical analysis

Statistical analyses were performed using GraphPad Prism version 6.0 for Mac (GraphPad Software, San Diego CA) and IBM-Microsoft SPSS version 20.0 for Mac. Data are summarized using basic descriptive statistics.

Normality testing (D'Agostino and Pearson test) was performed to determine whether data were sampled from a Gaussian distribution. One-way analysis of variance (ANOVA) and Kruskal–Wallis test were performed to compare three groups of continuous parametric and non-parametric variables, respectively. Chi-square test was used to analyze proportions. Incidence of events between two groups was analyzed for statistical significance by using the Fisher exact test. Odds ratio (OR) and 95% confidence intervals (CI) were calculated for each comparison. Survival outcomes were evaluated with both Kaplan-Meier and Cox models. Hazard ratio (HR) and 95%CI were calculated for each comparison. Univariate and multivariate analysis were performed when appropriate. All covariates with a p value <0.20, based on

Table 1
Characteristics of the study population.

	Power morcellation (N = 31)	Non-power morcellation (N = 21)	No morcellation (N = 73)	P value
Age, years	43.6 (10.4)	45.3 (10.3)	52.6 (11.1)	<0.001
BMI, Kg, mq	24.1 (4.0)	26.2 (5.3)	22.6 (3.4)	0.003
Menopausal status	5 (16.1%)	8 (38%)	39 (53.4%)	0.001
HRT use	1 (3.2%)	1 (4.7%)	6 (8.2%)	0.60
Performance status ≥ 1	6 (19.3%)	6 (28.5%)	21 (28.7%)	0.59
Preoperative evaluation:				
Ultrasound	24 (77.4%)	10 (47.6%)	49 (67.1%)	0.09
Hysteroscopy	1 (3.2%)	4 (19%)	4 (5.4%)	
CT scan/MRI	0	1 (4.7%)	7 (9.5%)	
Size of the mass, cm	6.7 (2.8)	5.1 (2.2)	9.4 (5.4)	0.001
Surgical route				<0.001
Laparoscopy	31 (100%)	0	0	
Open surgery	0	21 (100%)	73 (100%)	
Type of surgical procedures				<0.001
Myomectomy	24 (77.4%)	3 (14.2%)	0	
Hysterectomy	7 (22.5%)	18 (85.7%)	73 (100%)	
Open abdominal completion surgery after sarcoma diagnosis	15 (48.3%)	3 (14.2%)	2 (2.7%)	<0.001
Lymph node dissection	10 (32.2%)	4 (19%)	21 (28.7%)	0.56
BSO in premenopausal patients	4 (12.9%)	5 (23.8%)	16 (2.9%)	0.51
Histology				0.24
LMS	21 (67.7%)	13 (61.9%)	57 (78%)	
STUMP	4 (12.9%)	2 (9.5%)	5 (6.8%)	
LG-ESS	5 (16.1%)	4 (19%)	5 (6.8%)	
USS	1 (3.2%)	4 (19%)	6 (8.2%)	
Adjuvant therapy	16 (51.6%)	14 (66.6%)	49 (67.1%)	0.30
Adjuvant therapy				0.84
Chemotherapy	14 (45.1%)	13 (61.9%)	47 (64.3%)	
Radiotherapy	2 (6.4%)	2 (9.5%)	10 (13.6%)	
Follow-up, months	35.1 (28.5)	35.4 (31.2)	49.6 (42.9)	0.27

Data are expressed as number (%) or mean (SD).
Abbreviation: BMI, body mass index; HRT, hormonal replacement therapy; BSO, bilateral salpingo-oophorectomy.

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