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Review

Impact of morcellation on survival outcomes of patients with unexpected uterine leiomyosarcoma: A systematic review and meta-analysis

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HIGHLIGHTS

- Intra-abdominal morcellation of unexpected leiomyosarcoma is related to a 4-fold increase in intra-abdominal recurrence rate.
- Owing to the limited evidence about the effects of morcellation on patients with undiagnosed leiomyosarcoma, further studies are warranted.

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ABSTRACT

Objective. To review the current evidence on the effects of intra-abdominal morcellation on survival outcomes of patients affected by unexpected uterine leiomyosarcoma (ULMS) and to estimate the risk of recurrence in those patients.

Methods. PubMed (MEDLINE), Scopus, Embase, Web of Science databases as well as ClinicalTrails.gov, were searched for data evaluating the effects of intra-abdominal morcellation on survival outcomes of patients with undiagnosed ULMS. Studies were evaluated per the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) and the American College of Obstetricians and Gynecologists (ACOG) guidelines.

Results. Sixty manuscripts were screened, 11 (18%) were selected and four (7%) were included. Overall, 202 patients were included: 75 (37%) patients had morcellation of ULMS, while 127 (63%) patients had not. A meta-analysis of these studies 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)). No between-group difference in cumulative extra-abdominal recurrence (OR: 0.34 (95% CI: 0.07, 1.59)) rate was observed.

Conclusions. Our data support a significant correlation between uterine morcellation and an increased risk of intra-abdominal recurrence in patients affected by unexpected ULMS. However, the limited data on this issue and the absence of high level of evidence suggest the need of further studies designed to estimate the risk to benefit ratio of morcellation in patients with uterine fibroids and undiagnosed ULMS.

Contents

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Introduction

In the last two decades, the widespread diffusion of minimally invasive surgery has modified gynecological practice dramatically. The introduction of laparoscopic and robotic-assisted technology allowed a decrease in the rate of surgical procedures performed via open surgery, thus improving short-term patients' outcomes and the overall burden for the health care system [1–3].

One of the crucial steps in minimally invasive procedures is specimen retrieval through smaller port incision. Power morcellators have allowed the removal of solid masses (i.e., myoma, uterine corpus) [4]. However, accumulating evidence suggested that, in case of undiagnosed uterine malignancies (in particular, uterine leiomyosarcoma), intra-abdominal specimen morcellation correlated to an increase risk of dispersion of occult cancerous tissues within the abdominal cavity (e.g. tumor spread beyond the uterus), thus impacting negatively on the prognosis of patients affected by undiagnosed uterine malignancies [5–8]. Additionally, the increased intra-abdominal pressure and the airborne circulation, due to pneumoperitoneum, have been suggested to promote the exfoliation and growth of malignant cells into the abdominal cavity [9].

Recently, a safety communication, advising against the use of power morcellators, by the Food and Drugs Administration (FDA) and the consequent suspension of power morcellator sales from Johnson & Johnson, are increasing concerns on the embrace of minimally invasive route for myomectomy and hysterectomy (especially in case of large uteri or supracervical hysterectomy) [10–12]. However, only a few series exist which describe the impact of intra-abdominal morcellation on survival outcomes of patients with undiagnosed uterine malignancies [5–8]. Therefore, in the present paper we aimed to review and analyze the current evidence on the effect of intra-abdominal morcellation of undiagnosed uterine leiomyosarcomas, thus estimating the impact of intra-abdominal morcellation on survival outcomes of these patients.

Materials and methods

PubMed (MEDLINE), Scopus, Web of Science, and Embase databases as well as ClinicalTrails.gov (www.clincaltrials.gov) were systematically searched for records from January 1990 to August 2014, using the terms "sarcoma", "leiomyosarcoma" or "uterine sarcoma" in combination with "morcellation" or "morcellator". We aimed to identify all English-language original reports comparing outcomes of patients affected by uterine leiomyosarcoma who had intra-abdominal uterine morcellation versus patients who had not. References, of pertinent papers, were hand searched to identify other potential relevant studies. Single arm studies were excluded since they can not be included in the meta-analysis process. In each report, we sought to extrapolate: (1) pathological characteristics; (2) surgery-related outcomes and (3) survival outcomes (disease-free (DFS) and overall (OS) survivals).

Two independent reviewers (GB and GA) evaluated all studies to verify the inclusion and exclusion criteria. Differences of opinion were resolved by consensus after consultation between the two reviewers. The quality of the included studies was graded per the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [13]. GRADE Working Group classified studies' quality in high quality (further research is very unlikely to change our confidence in the estimate of effect), moderate quality (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) and very low quality (we are very uncertain about the estimate) [13].

Grades of guideline recommendations were rated according to the American College of Obstetricians and Gynecologists guidelines [14]. ACOG categorize quality and quantity of evidence, underlying recommendations, in three levels: level A (good and consistent evidence), level B (limited or inconsistent evidence) and level C (consensus and opinion) [14]. Judgments about each risk of bias item are reported according to the Cochrane Collaboration method [15].

The meta-analysis was performed using the Cochrane Review software (Review Manager version 5.2 for Mac). A chi-square test for heterogeneity among proportions was used to determine the presence of statistical heterogeneity between studies in term of surgical related complications and success rate. Both random- and fixed-effect models were presented. Forest plots were created for each comparison. P values less than 0.05 were considered statistically significant.

Results

Overall, 60 papers were identified. After the exclusion of duplicate publications, non-English language papers, single arm papers, letters, case reports and reviews not reporting original data, and 11 (18%) articles remained for the review. Only four (7%) papers were included in the meta-analysis process. Fig. 1 shows the PRISMA flow-chart for evidence acquisition. Appendix A reports the main characteristics of the four studies, including their quality, grade of guideline recommendations and levels of evidence [5–8]. Fig. 2 shows judgments about each risk of bias item.

All the included studies compared outcomes of patients affected by uterine leiomyosarcoma who had uterine morcellation versus patients who had not [5–8]. Overall, 202 patients were included: 75 (37%) undergoing morcellation and 127 (63%) who had not. The morcellation group included patients undergoing morcellation via open abdominal, vaginal, laparoscopic and hysteroscopic surgery; while all patients included in the non-morcellation group had open abdominal surgical procedure. Details of included studies are described in Table 1.

Patients undergoing uterine morcellation are more likely to preserve the adnexa in comparison to patients in the non-morcellation group (75% vs. 31%; OR: 0.15 (95% CI: 0.06, 0.35); $p < 0.001$). Re-operation rate was higher among patients who had morcellation than patients who had not (38% vs. 3%; OR: 31.4 (95% CI: 3.8, 250.5); $p < 0.001$); however, it was not possible to estimate how many patients had hysterectomy (during primary or secondary surgery) versus patients who had not. A pooled analysis focusing on stage comparison between groups was not feasible due to the absence of data in the studies included. Considering studies with available data [6–8], the adjuvant therapy administration rate did not differ between groups (45% in the morcellation group and 48% in the non-morcellation group; OR: 1.45 (95% CI: 0.74, 2.84); $p = 0.30$). Additionally, pooled results showed no difference between different adjuvant strategies: chemotherapy (41% in the morcellation group vs. 40% in the morcellation group; OR: 0.96 (95% CI: 0.44, 2.07); $p = 1.00$), radiotherapy (0% in the morcellation group vs. 7% in the morcellation group; OR: 7.47 (95% CI: 0.40, 138.7); $p = 0.15$) and chemo-radiation (2% in the morcellation group vs. 7% in the morcellation group; OR: 2.6 (95% CI: 0.28, 24.12); $p = 0.64$) administration rate did not differ between groups.

Overall, three studies suggested that morcellation worsened survival outcomes [6–8]; while the remaining investigation reported no between group difference between morcellation and non-morcellation [5]. Table 2 reports survival outcomes of patients included. A pooled analysis of available data showed that morcellation increased the overall recurrence rate (62% in morcellation vs. 39% in non-morcellation group; OR: 3.16 (95% CI: 1.38, 7.26); $p = 0.007$ in a random-effect model and OR: 3.15 (95% CI: 1.37, 7.23); $p = 0.007$ in a fixed-effect model) and intra-abdominal recurrence rate (39% vs. 9%; OR: 4.11 (95% CI: 1.92, 8.81); $p < 0.001$ in a fixed-effect model and OR: 3.63 (95% CI: 0.82, 16.11); $p = 0.09$ in a random-effect model) in comparison to no morcellation; while no between group difference in cumulative extra-abdominal recurrence rate was observed (9% in morcellation vs. 27% in non-morcellation group; OR: 0.34 (95% CI: 0.07, 1.59); $p = 0.17$ in a random-effect model and OR: 0.30 (95% CI: 0.09, 0.97); $p = 0.04$ in a fixed-effect model). Fig. 3 displays forest plots about the risk of