ELSEVIER

CrossMark

JMIG The Journal of Minimally Invasive Gynecology

Original Article

Risk Factors for Occult Uterine Sarcoma Among Women Undergoing Minimally Invasive Gynecologic Surgery

Titilope Oduyebo, MD, Emily Hinchcliff, MD, Emily E. Meserve, MD, MPH, Michael A. Seidman, MD, PhD, Bradley J. Quade, MD, PhD, J. Alejandro Rauh-Hain, MD, Suzanne George, MD, Marisa R. Nucci, MD, Marcela G. del Carmen, MD, MPH, and Michael G. Muto, MD*

From the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, MA (Drs. Oduyebo, Hinchcliff, and Muto), Division of Gynecologic Oncology, Vincent Obstetrics and Gynecology, Massachusetts General Hospital, Boston, MA (Drs. Oduyebo, Hinchcliff, Rauh-Hain, and del Carmen), Division of Women's and Perinatal Pathology, Department of Pathology, Brigham and Women's Hospital, Boston, MA (Drs. Meserve, Seidman, Quade, and Nucci), Harvard School of Medicine, Boston, MA (Drs. Oduyebo, Hinchcliff, Meserve, Seidman, Quade, Rauh-Hain, George, Nucci, del Carmen, and Muto), and Dana-Farber Cancer Institute, Boston, MA (Dr. George).

ABSTRACT **Study Objective:** To determine factors that can identify a population at increased risk for uterine leiomyosarcoma.
Design: Retrospective case-control study (Canadian Task Force classification II-2).
Setting: University teaching hospitals.
Patients: Seventy-two women who underwent minimally invasive gynecologic surgery for presumed leiomyoma. Patients diagnosed with leiomyosarcoma (cases) were matched with up to 4 controls on age, year of surgery, and surgeon specialty.
Intervention: Cases were identified through the pathology database, and the diagnosis of leiomyosarcoma or leiomyoma was confirmed by gynecologic pathologists. The cumulative risk of leiomyosarcoma was calculated, and factors predictive of elevated risk for leiomyosarcoma were investigated using conditional logistic regression.
Measurements and Main Results: Fifteen patients with the diagnosis of inadvertently morcellated leiomyosarcoma were identified and matched with 57 controls. The cumulative risk of diagnosing uterine leiomyosarcoma on pathology after performing minimally invasive gynecologic surgery with morcellation was 0.19% (95% confidence interval [CI], 0.06%–0.56%). The presence of a hematocrit value $< 30\%$ (adjusted odds ratio [aOR], 20; 95% CI, 1.08–100; $p = .05$) was independently associated with the diagnosis of uterine leiomyosarcoma on multivariate analysis. Increased myoma size (aOR, 9.73; 95% CI, 0.75–1.26; $p = .08$) and presence of a solitary myoma (aOR, 3.85; 95% CI, 0.65–25; $p = .14$) were associated with a greater risk of uterine leiomyosarcoma; however, the difference was not statistically significant.
Conclusion: Anemia and myoma size >7 cm may be associated with occult leiomyosarcoma; however, these criteria are not sufficiently discriminatory to allow for preoperative identification of patients with uterine sarcoma. Future large multicenter studies are needed to further investigate these findings and the discovery of innovative ways to detect uterine leiomyosarcoma are urgently needed. Journal of Minimally Invasive Gynecology (2016) 23, 34–39 © 2016 AAGL. All rights reserved.

Keywords: Laparoscopy; Morcellation; Myoma; Sarcoma; Uterine leiomyosarcoma

DISCUSS You can discuss this article with its authors and with other AAGL members at **http://www.AAGL.org/jmig-22-6-JMIG-D-15-00290**.

Use your Smartphone to scan this QR code and connect to the discussion forum for this article now*

* Download a free QR Code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Present address for Dr. Oduyebo: Centers for Disease Control, Atlanta, GA.
Present address for Dr. Seidman University of British Columbia, Vancouver, BC, Canada.
Dr. Muto was supported by an internal grant from the Brigham and Women's Hospital Obstetrics and Gynecology Department called Expanding Boundaries, which paid for data collection and analysis assistance.
Disclosures: None declared.
An abstract of this manuscript was presented at the Connective Tissue Oncology Society's 18th annual meeting, New York, NY, October 2013.

Corresponding Author: Dr. Michael G. Muto, MD, Department of Gynecologic Oncology, Brigham and Women's Hospital, 75 Francis St, ASBI 3rd Floor, Boston, MA 02115.
E-mail: mmuto@partners.org

Submitted May 13, 2015. Accepted for publication July 24, 2015.
Available at www.sciencedirect.com and www.jmig.org

http://dx.doi.org/10.1016/j.jmig.2015.07.017

The increasing use of minimally invasive surgical approaches to gynecologic surgery has prompted a rise in the number of patients undergoing minimally invasive gynecologic surgery (MIGS) [1,2]. Initially, the role of MIGS was limited by the inability to remove these often large tumors through laparoscopic ports; however, the advent of electromechanical morcellation has allowed MIGS surgeons to extend the benefits of minimally invasive techniques to a much wider group.

Unfortunately, several studies have shown that electromechanical and manual morcellation may disseminate unsuspected uterine sarcomas, resulting in a potential decline in the 5-year disease-free interval and 5-year survival rate compared with patients whose lesions were removed intact [3]. Although, this studies are limited due to their small sample size.

Uterine leiomyosarcoma (ULMS) is rare, and differentiating it from benign leiomyoma (LM) preoperatively is very difficult [1,4–13]. The difficulty arises from similarities in clinical presentation and the inability of existing imaging modalities to clearly distinguish the 2 entities [4]. Thus, organizations including the American Congress of Obstetricians and Gynecologists have provided guidance to clinicians regarding possible clinical factors, such as the presence of a large uterine size, menopausal status, and rapid uterine growth, which should increase the concern for occult uterine sarcoma in patients with presumed uterine myomas [14].

However, none of these factors have been examined in a comparison group research study [1,8,11]. Thus, we undertook this case-control study to identify characteristic features of ULMS to identify women at increased risk for these occult neoplasms.

Materials and Methods

The Institutional Review Boards at the participating institutions approved the study and waived the requirement to obtain informed consent. Case and control patients were identified through a search of the archives of the Department of Pathology at Brigham and Women's Hospital and Dana-Farber Cancer Institute. The database included all of the pathology reports of all surgeries performed for presumed ULMS at Brigham and Women's Hospital and cases with a final diagnosis of ULMS referred to Dana-Farber Cancer Institute between January 2005 and August 2012.

Cases were defined as subjects who had undergone myomectomy or hysterectomy using either robotic or conventional laparoscopy, with either electromechanical or manual morcellation, for a preoperative diagnosis of presumed uterine LM and a final diagnosis of ULMS. Some of the clinical data for these patients have been previously published by Oduyebo et al [12]. This cohort of cases was chosen because they represented patients eligible for MIGS with morcellation and thus at risk for the complications of inadvertently morcellated ULMS [3].

Controls were defined as subjects who underwent myomectomy or hysterectomy for a preoperative diagnosis of presumed uterine LM by laparoscopy, either robotic or conventional, with either electromechanical or manual morcellation and had a final diagnosis of LM. We confirmed that the procedures for both cases and controls were performed for a preoperative diagnosis of presumed uterine LM by examining their clinical charts and operative reports.

For each case, up to 4 controls were selected and matched on age ($\pm$5 years), date of procedure ($\pm$2 years), and surgeon (specialist vs generalist). Four controls per case were chosen because studies have indicated that little statistical power is gained by increasing this ratio further [15,16]. A specialist surgeon was defined as either an MIGS surgeon or a reproductive endocrinologist infertility specialist who had completed postgraduate training in those subspecialties. For surgeons that did not practice at the participating hospitals, this determination was made by phone calls to their offices to obtain their practice and/or specialty information.

Gynecological pathologists confirmed the diagnosis of ULMS and LM of the selected cases and controls. At least 1 representative diagnostic hematoxylin and eosin–stained slide from each case (from surgical procedures performed at initial and reoperation) and any available immunohistochemical-stained slides were rereviewed by study pathologists. No discrepancies were discovered.

Once the cases and controls were identified, their medical records were reviewed, and information pertaining to demographic data, clinicopathological data, and surgical procedure performed for presumed myomas and complications were collected.

The cumulative risk of ULMS over an 8-year period was calculated using only the subjects that underwent MIGS with morcellation for presumed uterine LM at Brigham and Women's Hospital. This was calculated by dividing the number of ULMS cases first discovered at Brigham and Women's Hospital (excluding referral cases) over the 8-year period by the total number of patients who underwent MIGS with morcellation for presumed uterine LM over the 8-year period at Brigham and Women's Hospital.

Descriptive statistics were tabulated by patient group. Continuous variables were summarized by means and standard deviations. The Student t test and Fisher's exact test were used to compare the means and proportions between the cases and controls. Continuous variables, such as myoma size and uterine size, were also examined as categorical variables. The number of presumed myomas preoperatively was dichotomized into the presence of a single myoma vs multiple myomas based on the literature showing an association between single myoma and ULMS [8,11]. Given that clinicians use the absolute change as well as specific thresholds, myoma size, uterine size, and hematocrit were evaluated as both continuous and categorical variables. Myoma size was classified as $<$5 cm, 5 to 7 cm, and $\geq$7 cm based on the literature [8] and the natural separation points in the observed distribution. Uterine size was