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Prognostic implications of increasing uterine weight at the time of hysterectomy for endometrial cancer

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Summary

Objectives: Research on endometrial cancer (EC) has demonstrated an association between increasing tumor size and poor outcomes, including increase in nodal disease and advanced stage at diagnosis. However, the implications of overall uterine weight (UW) at the time of hysterectomy for EC are unknown. The aim of this study is to investigate if increasing UW is associated with poor prognosis, specifically regarding lymph node metastasis (LNM), lymphovascular space invasion (LVSI), and stage. *Materials and Methods:* This is a retrospective cohort study of patients undergoing robotic-assisted surgical management of EC at two institutions. Patients with a preoperative diagnosis of complex atypical hyperplasia (CAH) or EC were included. All patients underwent surgical staging including hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and when feasible, para-aortic lymphadenectomy. Patients were categorized based on UW on final pathology report, into one of six groups: < 50 grams, 51-100 grams, 101-150 grams, 151-200 grams, 201-250 grams, and > 250 grams. The rate of lymph node involvement, LVSI, and stage were then analyzed for each group. Chi-Square and *t*-test were used for statistical analysis. *Results:* From 2013-2017, 161 patients were identified. Twenty-seven patients were excluded due to final pathology diagnosis other than EC. Of the remaining 134 patients, 103 had LVSI, 96 had LNM and 116 had stage reported. There were 120 (89.6%) endometrioid, four (2.9%) papillary serous, three (2.2%) clear cell, three (2.2%) carcinosarcoma, three (2.2%) undifferentiated, and one (0.7%) endometrial stromal sarcoma histologies. Among the entire cohort, the incidence of LNM was 19.8% and LVSI was 12.6%. Increasing UW was associated with increase in LVSI ($p = 0.003$), LN metastasis ($p = 0.000$), and stage ($p = 0.010$). On further analysis, the cohort was examined as two separate groups, UW < 200 *vs.* > 200 grams. UW > 200 grams is associated with significant increase in LVSI ($p = 0.045$) and LNM ($p = 0.0005$). There were no LNM in patients with UW < 100 grams. *Conclusions:* Increasing UW at the time of hysterectomy for EC is associated with increase in LVSI, LN metastasis, and stage.

Key words: Endometrial cancer; Nodal disease; Uterine weight; Hysterectomy; Lymph node metastasis.

Introduction

The mainstay in the treatment of endometrial cancer (EC) is surgery. Controversy exists regarding which patients should undergo comprehensive surgical staging, in addition to hysterectomy with bilateral salpingo-oophorectomy. EC has demonstrated an association between increasing tumor size and poor outcomes, including increase in nodal disease and advanced stage at diagnosis. However, the implications of overall uterine weight (UW) at the time of hysterectomy for EC are unknown. The aim of this study is to investigate if increasing UW is associated with poor prognosis, specifically regarding lymph node metastasis (LNM), lymphovascular space invasion (LVSI), and stage at diagnosis.

Materials and Methods

This is a retrospective cohort study of patients undergoing robotic-assisted surgical management of EC at two institutions, Good Samaritan Hospital Medical Center (West Islip, NY) and the State University of Buffalo, University Hospital (Buffalo, NY). This study was approved by the Institutional Review Board of both institutions. Eligibility criteria included a pre-operative pathologic diagnosis of complex atypical hyperplasia (CAH) or EC based on preoperative endometrial biopsy or dilatation and curettage. All patients underwent comprehensive surgical staging including robotic-assisted laparoscopic hysterectomy, bilaterally salpingo-oophorectomy, pelvic lymphadenectomy, and when feasible, para-aortic lymphadenectomy. Patients were categorized based on UW on final pathology report, into one of six groups: < 50 grams, 51-100 grams, 101-150 grams, 151-200 grams, 201-250 grams, and > 250 grams. The rate of lymph node involvement, LVSI, and stage were then analyzed for each group. Chi-Square and *t*-test were used for statistical analysis.

Results

From 2013-2017, 161 patients were identified. Twenty-seven patients were excluded due to final pathology diagnosis other than EC. Of the remaining 134 patients, 103 had

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Table 1. — *Histologic cell type*

Histology	Percentage (%) of patients
Endometriod	120 (74.5%)
CAH	12 (7.5%)
Papillary serous	4 (2.5%)
Clear cell	3 (1.9%)
Carcinosarcoma	3 (1.9%)
Undifferentiated	3 (1.9%)
Endometrial stromal sarcoma	1 (0.6%)
Benign/non-endometrial primary	15 (9.3%)

Table 2. — *UW and LVSI.*

Uterine weight (g)	Negative LVSI	Positive LVSI	Total number of patients in each group (%)	Percentage of patients with positive LVSI in each group (%)
≤ 50	9	1	10 (9.7%)	10.0%
51-100	40	1	41 (39.8%)	2.4%
101-150	23	3	26 (25.2%)	11.5%
151-200	8	3	11 (10.7%)	27.3%
201-250	1	4	5 (4.9%)	80%
> 250	9	1	10 (9.7%)	10%
Total	90	13	103	12.6%

Table 3. — *UW and incidence of LNM.*

Uterine weight (g)	Negative LNM	Positive LNM	Total number of patients in each group (%)	Percentage of patients with positive LNM in each group (%)
≤ 50	10	0	10 (10.4%)	0%
51-100	40	0	40 (41.7%)	0%
101-150	21	3	24 (25%)	12.5%
151-200	8	1	9 (9.4%)	11.1%
201-250	1	4	5 (5.2%)	80.0%
> 250	6	2	8 (8.3%)	25.0%
Total	86	19	96	19.8%

LVSI, 96 had LNM, and 116 had stage reported. On final pathologic analysis there were 120 (89.6%) endometrioid, 12 (2.5%) CAH, four (2.9%) papillary serous, three (2.2%) clear cell, three (2.2%) carcinosarcoma, three (2.2%) undifferentiated, and one (0.7%) endometrial stromal sarcoma histologies (Table 1). Among the entire cohort, the incidence of LNM was 19.8% and LVSI was 12.6%. Increasing UW was associated with increase in LVSI ($p = 0.003$) (Table 2). , LN metastasis ($p = 0.000$), and stage ($p = 0.010$). On further analysis, the cohort was examined as two separate groups, UW < 200 *vs.* > 200 grams. UW > 200 grams is associated with significant increase in LVSI ($p = 0.045$) and LNM ($p = 0.0005$). There were no LNM in patients with UW < 100 grams (Table 3).

Discussion

EC is the most common gynecologic cancer; the American Cancer Society estimates that there will be 61,380 new cases diagnosed in 2017 [1]. The cornerstone of the treatment of EC is surgery. Controversy exists regarding which patients should undergo comprehensive surgical staging, including pelvic and para-aortic lymphadenectomy, in addition to hysterectomy with bilateral salpingo-oophorectomy. The principle benefit to comprehensive surgical staging is defining the full extent of disease, providing the greatest amount of information to triage appropriate adjuvant therapy and prognosis. This information results in the use of less pelvic radiation and more vaginal cuff brachytherapy, which is associated with less side effects and overall improved quality of life [2, 3]. However, lymphadenectomy is not without risks. The major risks attributed to nodal dissection include increase blood loss, longer operative times, risk of neurovascular injury, ileus, lymphocyte formation, and lymphedema [4, 5]. The question that continues to be debated is, which patients can be considered low enough risk for nodal disease, that they can comfortably avoid lymphadenectomy, and also avoid pelvic radiation without fear of under treatment and recurrence? Several tumor specific features have been identified as risk factors for nodal disease, including tumor size and LVSI. Multiple studies have demonstrated an association between increasing tumor size and poor outcomes, including increase in nodal disease and advanced stage at diagnosis [6-10]. Additionally, LVSI is an independent poor prognostic factor and is associated with high rate of LN metastasis. Up to 27% of patients with LVSI will have positive pelvic LN and 19% of patients will have positive para-aortic LN [11]. However, the implications of overall UW at the time of hysterectomy for EC are unknown.

The present results demonstrate that increasing UW at the time of hysterectomy for EC is associated with negative prognostic indicators. This includes increase in LN metastasis, stage, and LVSI. The present authors found a significant increase in LNM and LVSI associated with UW > 200 grams. Notably they found no incidents of LNM in patients with UW < 100 grams. Taken together these results suggest that nodal dissection can safely be omitted in patients with UW < 100 grams and can be considered in low risk patients with UW < 200 grams. A scale can be used intra-operatively and accurately at the time of hysterectomy to guide the decision-making process on whether or not to proceed with nodal dissection. Studies have assessed the use of intra-operative frozen section (FS) and examination of tumor specific features, including tumor size and depth of invasion. However, intra-operative FS is subject to observation bias and may not correlate with final pathology. The sensitivity of FS for myometrial invasion ranges in the literature from 66.7-98.1% [12-14]. Therefore, basing management decision on this alone can be inaccurate and mis-

leading. The addition of UW to this technique may improve accuracy and lead to better intra-operative management. Subsequently, leading to less morbidity related to nodal dissection and unnecessary over use of pelvic radiation, without increase in local regional recurrence. The major limitation to this study is its small sample size. A larger, prospective study should be conducted to confirm these results.

Conclusions

Increasing UW at the time of hysterectomy for EC is associated with increase in LVSI, LN metastasis, and stage.

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