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High-grade endometrial cancer: Revisiting the impact of tumor size and location on outcomes

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HIGHLIGHTS

- TS and LUS location have been largely studied in low-grade endometrial cancer with conflicting results.
- In high-grade endometrial cancer, both TS > 2 cm and LUS involvement are associated with pelvic nodal disease.
- Neither TS > 2 cm nor LUS involvement was independently associated with recurrence.

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ABSTRACT

Objective. Research on tumor size (TS) and intracavitary tumor location in endometrial cancer has focused primarily on low-grade tumors. Data in patients with high-grade histology are limited. Our goal is to determine if TS or lower uterine segment (LUS) involvement, is associated with nodal disease and recurrence in women with high-grade endometrial cancer.

Methods. This is an IRB-approved, multi-institutional cohort study of patients with clinically early-stage, high-grade endometrial cancer who underwent comprehensive surgical staging. Records were reviewed for demographic, pathologic, and treatment data. Nodal involvement and recurrence as a function of TS and location were estimated with odds ratios and hazard ratios.

Results. From 2005 to 2012, 208 patients were identified. Of these, 188 patients had tumor location and 183 had TS reported. There were 75 endometrioid (36.1%), 35 serous (16.8%), 12 clear cell (5.8%), and 26 carcinosarcoma (12.5%) cases, and 60 (28.8%) undifferentiated or mixed histologies. There were 55 recurrences (median follow up 17.2 mo). LUS tumors were associated with pelvic and para-aortic nodal disease (OR 3.83, 95% CI 1.70–8.60, $p < 0.01$, OR 5.13, 95% CI 1.96–13.45, $p < 0.01$). TS ≥ 2 cm was associated with pelvic nodal disease (27.4% vs. 0%, $p = 0.01$; OR 10.00, $p = 0.01$). Neither TS nor LUS location was independently associated with recurrence.

Conclusions. In high-grade endometrial cancers, tumor involvement of the LUS and TS > 2 cm was associated with pelvic nodal disease, and LUS involvement was also significantly associated with para-aortic nodal disease. There was no association between LUS involvement or TS > 2 cm and recurrence.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States [1]. The mainstay of treatment involves surgery, which may include lymphadenectomy based on uterine risk factors. Tumor grade and histology, lymphovascular space invasion, and depth of myometrial invasion have been shown to be consistent predictors of extrauterine disease [2]. However, uterine risk factors have not always been predictive of metastatic disease in women with high-grade lesions such as uterine papillary serous carcinoma, as metastatic disease was detected even in cases where there was minimal uterine disease [3]. In a study by Schink et al. of predominantly low-grade histology, tumor size greater than 2 cm was found to confer an increased risk of lymph node metastasis (15% for ≥2 cm tumors vs. 4% for <2 cm) and decreased overall survival (98% vs 85%) [4].

In addition to tumor size, tumor location within the lower uterine segment has been studied with regards to its impact on nodal disease and risk of recurrence. However, these data have been conflicting [5–11]. The literature to date has focused primarily on patients with low-grade endometrioid histology. While women with high grade histologies represent a minority of the endometrial cancer cases, they

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represent a majority of the recurrences and subsequent deaths from disease. Therefore, the goals of our study were to evaluate tumor size and location of the tumor within the lower uterine segment as a predictor of lymph node metastasis and recurrence among clinical early stage high-grade endometrial cancer patients. We also sought to evaluate the impact of tumor location on patterns of recurrence, with the goal of further informing the choice adjuvant treatment.

Methods

A multicenter, retrospective analysis of patients with clinical early stage, high-grade endometrial cancer who were comprehensively surgically staged was conducted following Institutional Review Board approval from University of North Carolina, Chapel Hill, NC and Greater Baltimore Medical Center, a comprehensive cancer center in Baltimore, MD. The study period was from January 2005 to January 2012. The inclusion criteria were comprehensive surgical staging (hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, +/− omentectomy). High-risk patients included grade 3 endometrioid, papillary serous, clear cell, carcinosarcoma, or mixed histologies. Operative reports were abstracted for extent of surgical staging and lymph node counts were collected from pathology reports. All patients had clinically stage I disease and underwent primary surgical management between January 4, 2005 and January 16, 2012.

Clinical data was abstracted including operative reports, pathology reports, and inpatient hospital and outpatient records. Original pathology reports were reviewed for tumor grade, histologic type, depth of invasion, lymphovascular space invasion, cervical/adnexal involvement, nodal involvement, tumor size, and tumor location within the corpus. Location was classified as lower uterine segment, mid-corpus, and fundus. The lower uterine segment is defined pathologically by the narrowest portion between the cervical os and the uterine fundus. On histology from these sections, pathologists can see the junctional area of mucosa that is the zone between the endocervical mucinous glands and the endometrial glands. Reports stating involvement of "entire endometrium" were coded with all three locations. Reports that did not explicitly state tumor location were coded as "Not Reported" (NR). Tumor size was determined by the average of the two largest diameters [4] as previously described. Tumor size reported as "diffuse" or otherwise qualitative in nature, without measurements given, was coded as NR.

Demographic information, dates of diagnosis and treatment, stage, types, sequence, and dose of adjuvant therapy, disease recurrence or progression, date and site of recurrence, salvage therapy, date of last follow-up and status at last follow up, and death dates, where applicable, were collected. Patients were followed as customary to the institutions (every 3 months for 2–3 years, every 6 months for 2 years, then annually).

Data were tabulated and medians and ranges for variables were calculated. Tumor location was labeled "Lower" for those with tumors of the LUS or LUS/mid-corpus. Tumor location was labeled "Upper" for tumors of the fundus, the mid-corpus, or fundus/mid-corpus. Tumors present in all sections of the uterus were removed from analysis. Odds ratios were estimated using logistic regression. Exact methods were used when needed due to sparse data. Follow-up time was calculated from date of surgery to date of recurrence or date of last recurrence–free visit. Recurrence–free survival curves were modeled using the Kaplan–Meier method. The Log-Rank test statistic was used to assess differences between groups. Hazard ratios for recurrence were estimated using Cox proportional hazards models. Multivariable models included adjustments for stage and adjuvant radiation, as these were the only baseline variables associated with recurrence in this cohort. Analyses were performed using SAS v9.2 (Cary, NC, USA).

Results

Of the 208 women who met inclusion criteria, there were 188 with tumor location identified within the pathology report and 183 with tumor size reported. For the entire cohort, the median age was 65 years (interquartile range 60–73) and median BMI was 30 (IQR 26–36). Median follow up time was 17.2 months (range of 0.2–67.6 months). There were 75 (36.1%) endometrioid, 35 (16.8%) UPSC, 12 (5.8%) clear cell, 26 (12.5%) carcinosarcoma, and 60 (28.8%) undifferentiated or mixed histologies. There were 19 (10.4%) tumors <2 cm and 164 (89.6%) tumors ≥2 cm. Thirty-five (18.6%) patients were classified as "Lower" tumors (LUS tumors +/− mid-corpus involvement), and 122 (64.9%) were classified as "Upper" (fundus only, mid-corpus only, or fundus/mid-corpus). There were 8 tumors confined only to the LUS. In 31 cases, the tumor spanned the endometrium (16.5%) (LUS, mid-corpus, and fundus) and these cases were excluded from the analysis.

Tumor location

There were no significant demographic differences between the Lower and Upper tumor location groups (Table 1) with regard to age, race, or BMI. Presenting symptoms, route of surgical procedure, extent of surgery, extent of residual disease and adjuvant treatment also did not vary between the two groups (Table 1).

Table 2 reports histologic details as related to tumor location. Differing types of high-grade histology were evenly distributed. However, there were important pathologic differences between the location groups. Lower location tumors were larger (72% > 4 cm vs. 42% > 4 cm, $p = 0.03$), were more likely to have LVSI (68.6% vs 40.2%, $p < 0.01$), deep myometrial invasion (57.1% vs. 26.2%, $p = .001$), and adnexal involvement (20% vs 6.6%, $p = 0.02$) as compared to upper location tumors. There were significantly more advanced stage patients in the lower location group, 57% (20/35) compared to the upper group, 29% (35/122), $p < 0.01$.

Lower tumors were significantly associated with pelvic nodal disease (OR 3.83, 95% CI 1.70–8.60, $p < 0.01$), para-aortic nodal disease (OR 5.13, 95% CI 1.96–13.45, $p < 0.01$), and advanced stage disease (OR 3.31, 95% CI 1.53–7.20, $p < 0.01$) than upper location tumors on univariable analysis (Table 3). There were a total of 40 recurrences among patients with tumor location reported, 37.5% ($n = 15$) of which occurred among lower location tumors. Lower tumor location was significantly associated with recurrence on univariable analysis (HR 2.21, 95% CI 1.16–4.20). However, in multivariable analysis, controlling for stage and adjuvant treatment, lower tumors were no longer independently associated with recurrence (HR of 1.67 95% CI 0.81–3.44), Table 4. Fig. 1 depicts the relationship between tumor location and recurrence.

Details on recurrence confirmation and pattern of recurrence are given in Table S1 (Supplementary). There was no significant difference in the pattern of local or distant recurrence among the groups (Table S1, Supplementary). Disease status at follow up did vary significantly. There were more patients dead of disease (6/34, 17.6%) (DOD) in the lower location tumors, compared to the upper (7/118, 5.9%), $p < 0.01$ on univariable analysis.

Tumor size

There were no significant demographic or histologic differences between patients with <2 cm and ≥2 cm lesions (Table 1). There were also no differences seen in surgical route, rate of optimal debulking, or tumor location. In terms of pathology, there was no difference in LVSI among the tumor size groupings. There were more patients with deep myometrial invasion in the >2 cm group (40.8% vs. 5.26%, $p = 0.001$).

There were no pelvic lymph node or para-aortic lymph node metastases in patients with tumors <2 cm. In comparison, the ≥2 cm lesions had significantly higher pelvic (27.4% (45/164), $p = 0.01$) and a trend toward increased para-aortic nodal involvement (15.2% (25/164), $p = 0.07$) rates (Table 2). Tumor size was significantly associated with pelvic nodal involvement (OR 10.00, $p = 0.01$) and stage 3 or 4 disease (HR 4.78, 95% CI 1.07–21.39). There was no association between