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Is lower uterine segment involvement a prognostic factor in endometrial cancer?

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Background/aim: The purpose of this study is to investigate the prognostic significance of lower uterine segment (LUS) involvement in endometrial cancer (EC).

Materials and methods: We reviewed the patients who were operated at our institution between July 2007 and March 2015 with the diagnosis of EC. Tumors localized in the corpus and involving the LUS or localized entirely in the LUS formed Group A, while tumors in the uterine corpus without LUS involvement formed Group B. Clinicopathological characteristics and survival of the patients were compared in both groups.

Results: A total of 500 patients were included in the study. There were 139 patients who had tumors involving the LUS and formed Group A, while 361 patients with endometrial tumors in the uterine corpus without LUS involvement formed Group B. We did not detect a significant difference between survival of the patients in group A and group B (78 months vs. 87 months, respectively; $P > 0.05$).

Conclusion: We found that LUS involvement was not an independent prognostic factor for poor survival, but it is associated with other poor prognostic factors such as deep myometrial invasion, uterine serosal involvement, lymphovascular space invasion, lymph node metastasis and higher FIGO grade.

Key words: Endometrial cancer, lower uterine segment, prognosis, survival

1. Introduction

Endometrial cancer (EC) is the fourth most common cancer among women and the most common malignancy of the female genital system (1). EC arises from the uterine corpus (UC), but in 3%–6% of EC cases, the localization of the tumor is the lower uterine segment (LUS) (2–4). LUS-originated tumors are located between the UC and the uterine cervix and show histological characteristics of both parts, which sometimes complicates the differential diagnosis of EC and cervical adenocarcinomas when determination of the primary tumor is essential for further treatment and prognosis (2). Tumors originating from the LUS or involving the LUS also differ from UC tumors with thin mucosal and myometrial layers and poor hormonal response to estrogen (5). Since EC cases that originate from the LUS are rare, a small number of studies have compared the characteristics of LUS tumors with UC-originated tumors. There have been conflicting reports on the effect of LUS involvement as a prognostic factor in endometrial cancer. In this study we aimed to compare the clinical and pathological characteristics and overall survival of endometrial carcinoma cases involving the LUS with UC tumors without LUS involvement.

2. Materials and methods

This study was conducted at Zekai Tahir Burak Women's Health Training and Research Hospital, Ankara, Turkey, after obtaining the approval of the institutional ethics board. The clinical records and pathology reports of the patients who were operated on with the diagnosis of endometrial carcinoma in the Gynecologic Oncology Department of our hospital between July 2007 and March 2015 were reviewed retrospectively.

Inpatient and outpatient records, operation and pathology reports, and clinical and demographic data of the patients were reviewed. The pathological records of patients included in this study were reviewed and tumor localizations were identified. Tumor localizations were grouped as UC tumors with LUS involvement and UC without LUS involvement.

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During the study period, the surgical management protocol for endometrial carcinoma of our department changed; patients with histopathologically proven endometrial carcinoma before 2013 underwent comprehensive surgical staging including total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omental biopsy, peritoneal cytology, and pelvic and paraaortic lymph node dissection, regardless of intraoperative frozen section. However, after 2013, women with nonendometrioid histologic subtypes, >1/2 myometrial invasion (MI), grade 3 disease, or tumor size >2 cm in the frozen section result of the hysterectomy specimen were surgically staged in the above-mentioned manner, while the women without any these above-mentioned risk factors had only TAH-BSO and peritoneal cytology. A gynecologic pathologist in the Pathology Department of our institution reviewed all the specimens. Patients who were operated on at other institutions and patients with postoperative diagnosis of cervical adenocarcinoma or tumor suspicion of other primary locations were excluded. Follow-up was carried out in our Gynecologic Oncology Department every 3 months in the first 2–3 years, every 6 months for 2 years, and then annually. Clinicopathological characteristics of the patients including age, serum CA-125 levels, tumor staging according to the International Federation of Gynecology and Obstetrics (FIGO), and survival of patients were determined. Pathological findings including tumor histology, FIGO grade, tumor diameter, cytology positivity, lymphovascular space invasion (LVSI), and MI status were also recorded.

Patients were classified into two groups based on LUS involvement. Tumors localized in the UC and involving the LUS or localized entirely in the LUS formed Group A, while tumors in the UC without LUS involvement formed Group B.

Patients with gross cervical or vaginal involvement, deep MI, grade 3 disease, or positive LVSI were consulted for radiation therapy, while patients with nonendometrioid subtypes, positive lymph nodes, or metastatic disease were referred to platinum-based chemotherapy for the adjuvant setting.

All data were analyzed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Differences between groups were assessed using the chi-square test, Fisher's exact test, and the Mann–Whitney U test for categorized variables and Student's t-test for continuous variables. We used the Kaplan–Meier method to estimate the overall survival of the patients, and overall survival rates were compared using the log-rank test. Cox proportional hazard analysis was used to assess the prognostic significance of the different characteristics. The Cox regression model was used in multivariate analysis. Risk of death was expressed as the hazard ratio (HR) with the 95% confidence interval (CI). $P < 0.05$ was considered significant.

3. Results

There were 527 patients operated on with the diagnosis of endometrial carcinoma at our institution from July 2007 through March 2015. Tumor localizations were defined in the pathology reports of 500 patients out of 527 while 27 patients were excluded from the analysis. Median follow-up time was 34 months.

The median age of the patients was 59 years. Thirty-seven patients (7.4%) had TAH with BSO and peritoneal washing, while the remaining 463 patients (92.6%) underwent a systematic surgical staging including pelvic and paraaortic lymph node dissection up to the renal veins and omental biopsy. Fifty-two patients (10.4%) had positive pelvic nodes, while 40 patients (8%) had positive paraaortic nodes.

There were 139 patients who had tumors involving the LUS and formed Group A, while 361 patients with endometrial tumors in the UC without LUS involvement formed Group B. There were 14 patients (2.8%) who had tumors limited to only the LUS, while 125 patients (25%) had tumors involving both the UC and LUS. No mortality occurred among that subgroup of patients and these patients were included in Group A. The average age at diagnosis, serum Ca-125 levels, histological subtypes, and peritoneal cytology results were similar in both groups. However, larger tumor diameter (>5 cm), higher FIGO grade (Grade 3), deep MI (>1/2 MI) and serosal invasion, LVSI, adnexal involvement, and pelvic and paraaortic lymph node involvement were more common for patients in Group A. Clinicopathological characteristics of the patients are summarized in Table 1.

Overall survival was slightly inferior in Group A compared to Group B (median survival 78 vs. 87 months, 95% CI, respectively); 5-year estimated overall survivals were 82.3% and 80.1%, respectively, but this was not statistically significant ($P > 0.05$). Figure 1 shows survival curves for Groups A and B. We further stratified patients according to histological subtypes as endometrioid and nonendometrioid subtypes. In patients with the endometrioid subtype, median overall survivals were 84 vs. 90 months for Group A and Group B, respectively (95% CI, $P > 0.05$), while 5-year estimated overall survivals were 84.5% vs. 86.4% for Groups A and B, respectively (log-rank test, $P > 0.05$); neither was statistically significant. In patients with nonendometrioid histology, median overall survivals were 59 vs. 75 months for Groups A and B, respectively (95% CI, $P > 0.05$), while 5-year estimated overall survivals were 59.8% vs. 65.1% for Groups A and B, respectively (log-rank test, $P > 0.05$), and again it was not statistically significant. Figures 2A and 2B show survival curves of Groups A and B according to histological subtypes.

Table 1. Comparison of endometrial carcinoma with isolated LUS tumors and uterine corpus tumors without LUS involvement.

Variables	Group A N = 139, LUS involvement	Group B N = 361, without LUS involvement	P-value
Age at diagnosis (mean years, ± SD)	58.2 ± 9.7	57.9 ± 9.6	>0.05
Tumor diameter (mean, cm)	4.7 ± 2.3	2.8 ± 1.6	<0.01
Ca-125 (U/mL, mean)	31.8	27.5	>0.05
FIGO Grade 1 2 3	 63 (45.3%) 36 (25.9%) 40 (28.7%)	 236 (65.3%) 73 (20.2%) 52 (14.4%)	<0.0001
Histological subtype Endometrioid Serous Clear Mucinous Mixed type Carcinosarcoma Others	 105 (75.5%) 8 (5.7%) 13 (9.3%) 2 (1.4%) 8 (5.7%) 2 (1.4%) 1 (0.7%)	 284 (78.6%) 21 (5.8%) 13 (3.6%) 6 (1.6%) 30 (8.3%) 4 (1.1%) 3 (0.8%)	>0.05
Myometrial invasion (N, %) No invasion MI <1/2 MI ≥1/2	 6 (4.3%) 65 (46.7%) 68 (48.9%)	 58 (16%) 213 (59%) 89 (24.6%)	<0.001
Serosal involvement (N, %) Positive Absent	 17 (12.2%) 122 (87.7%)	 12 (3.3%) 349 (96.6%)	<0.001
LVSI (N, %) Positive Negative	 58 (41.8%) 81 (58.2%)	 73 (20.2%) 288 (79.8%)	<0.001
Peritoneal cytology (N, %) Positive Negative	 17 (12.2%) 122 (87.7%)	 28 (7.7%) 333 (92.3%)	>0.05
Adnexal involvement Adnexa positive Adnexa negative	 16 (11.5%) 123 (88.5%)	 21 (5.8%) 340 (94.2%)	>0.05
Pelvic LN metastasis (N, %) Positive Negative	 25 (18%) 114 (82%)	 27 (7.5%) 334 (92.5%)	<0.001
Paraaortic LN metastasis (N, %) Positive Negative	 19 (13.6%) 120 (86.4%)	 21 (5.8%) 340 (94.2%)	<0.005
Status Dead Alive	 20 (14.4%) 119 (85.6%)	 33 (9.1%) 328 (90.9%)	>0.05

LUS: Lower uterine segment; MI: myometrial invasion; LVSI: lymphovascular space invasion; LN: lymph node.

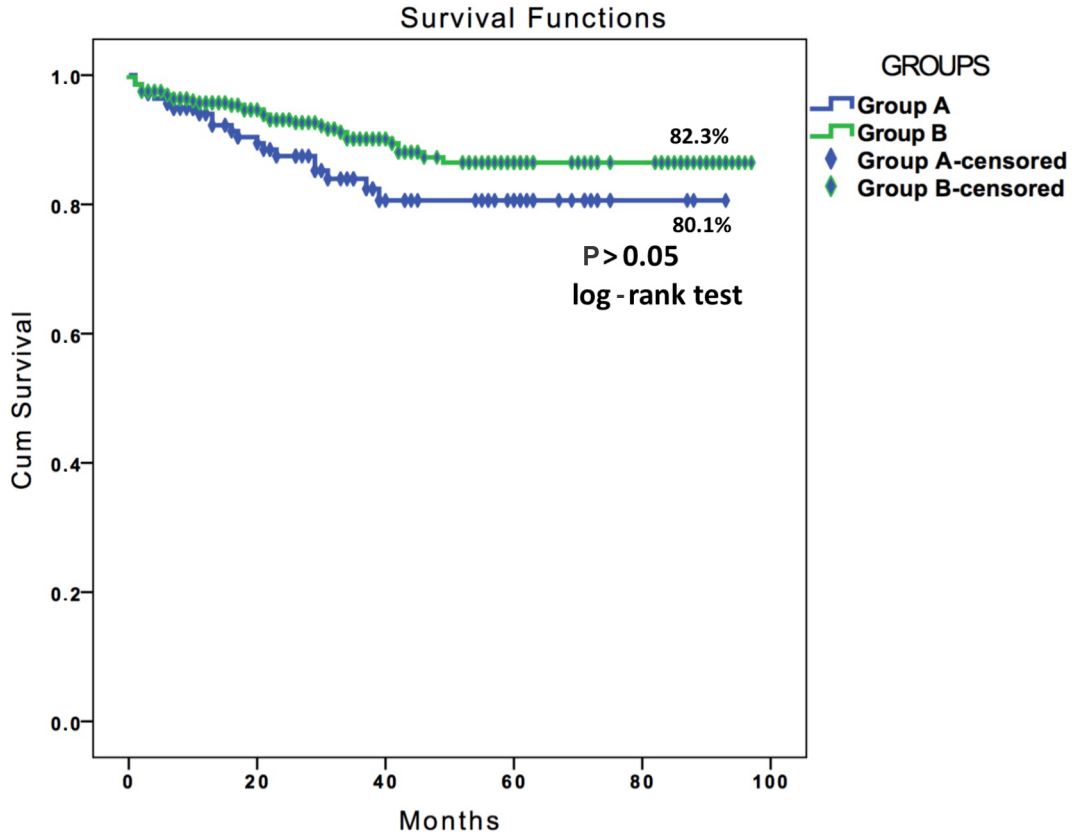

Figure 1. Overall survival curves for Groups A and B, all patients.

In univariate analysis, nonendometrioid histologic subtype, older age of the patients (>65 years), larger tumor size (>5 cm), FIGO Grade 3 histology, advanced stage of the disease, peritoneal cytology positivity, lymph node involvement, LVSI, and MI were significantly related to poor survival. However, LUS involvement was not associated with decreased overall survival in univariate analyses. In the multivariate analysis, MI (HR 3.22, 95% CI 1.42–7.29, P < 0.005) and tumor grade (HR 6.57, 95% CI 3.59–12.04, P < 0.001) were the only independent prognostic factors for survival (Table 2).

4. Discussion

The LUS is the anatomical and histological landmark of transition of endometrial tissue to endocervical epithelium between the UC and the cervix. In our patient cohort, 27.8% of the endometrial cancer patients had tumors involving the LUS. This case-comparison study is the first report that assesses the clinical and pathological features of endometrial carcinoma regarding the tumor localization in the LUS. There have been limited studies in the literature considering the LUS involvement in cases of endometrial carcinoma with conflicting results, hypothesizing that endometrial carcinoma of the LUS may be a worse prognostic factor. In our study we separated the cases into two groups as tumors in the UC involving the LUS or tumors entirely in the LUS (Group A) and tumors in the UC without LUS involvement (Group B), and we found that LUS involvement was not an independent prognostic factor for poor survival, but it is associated with other poor prognostic factors such as deep MI, uterine serosal involvement, LVSI, lymph node metastasis, and higher FIGO grade.

The thickness of the myometrial wall in the LUS is less than that in the UC, and also the lymphatic drainage differs. Therefore, the behavior of LUS tumors was hypothesized to be more diversified than that of UC tumors with their clinical and pathological characteristics.

Endometrial carcinoma is basically defined as type 1 or type 2 cancer (6). Carcinoma of the LUS mainly shows characteristics of type 2 endometrial cancer, seen in elder women, whereas endometrial atrophy plays a role instead of estrogen exposure and it is presumed to be due to weak response of the thin endometrial layer of the LUS to estrogen and shows similar immunohistochemical characteristics with type 2 endometrial cancer (2,7). Conversely, Westin et al. reported that patients with LUS-isolated tumors were significantly younger than the ones with UC tumors and

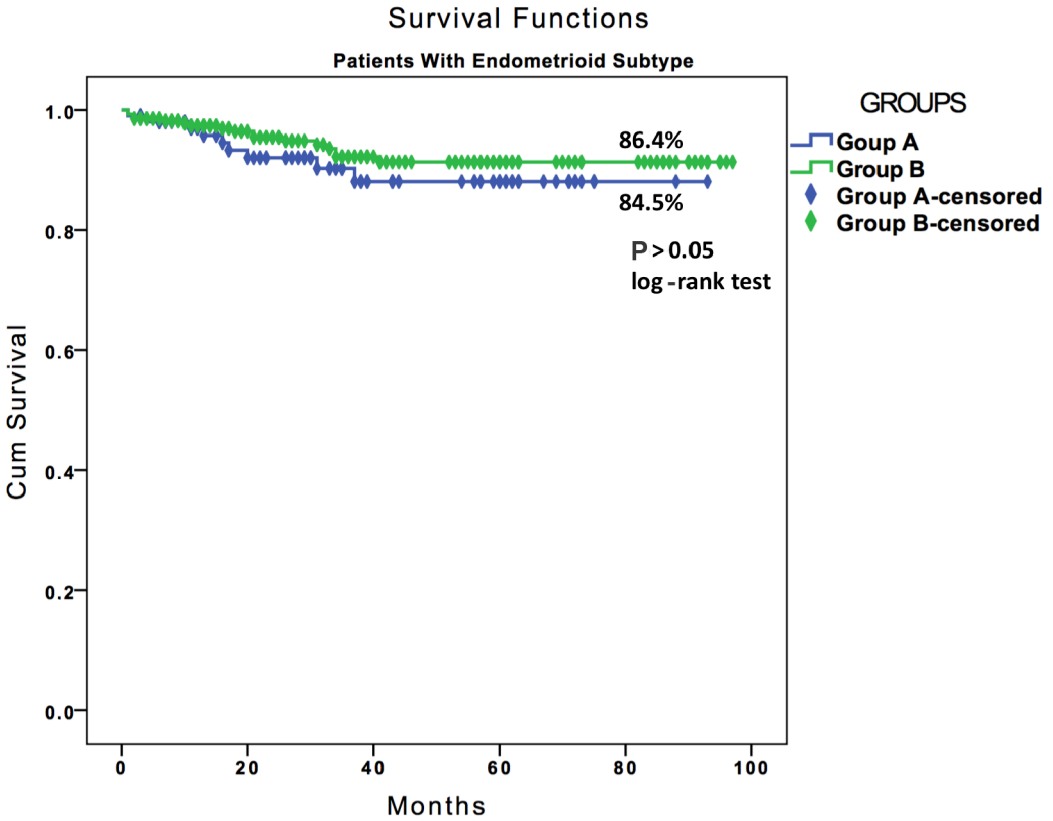

Figure 2. A) Overall survival curves for Groups A and B, patients with endometrioid subtype. B) Overall survival curves for Groups A and B, patients with nonendometrioid subtype.

Table 2. Factors that affect survival in Group A and Group B in multivariate analysis.

	HR (CI)	P-value
MI	3.22 (1.42–7.29)	<0.005
LVSI	1.216 (0.45–3.278)	0.700
Tumor size >5 cm	1.889 (0.899–3.966)	0.093
Grade 3 histology	6.57 (3.59–12.04)	<0.001
LUS involvement	1.29 (0.88–2.27)	>0.05

HR: Hazard ratio; MI: myometrial invasion; LVSI: lymphovascular space invasion; LUS: lower uterine segment.

the prevalence of LUS tumors was 9% in patients under 50 years of age (3). However, in our patient cohort, the age of the patients and the histological subtypes of the tumors were similar in both groups. Interestingly, we found that 5-year estimated survival rates in Groups A and B were quite similar for the endometrioid subtype (84.5% vs 86.4%), while the difference in survival rates was larger in Groups A and B for the nonendometrioid subtypes (59.8% vs 65.1%).

Phelan et al. (8) studied 98 women with stage 1 endometrial cancer with and without LUS involvement and reported that there was no significant difference between patients with or without LUS involvement in terms of grade, histology, LVSI, deep MI, pelvic recurrence, and 5-year disease-free survival. However, the authors included only stage 1 endometrial cancer patients and the prevalence of LUS involvement was 19%. Similar to these results, Mayr et al. (9) reported that tumor grade, histology, LVSI, and MI were similar between the stage 1 endometrial tumors of 106 patients with and without LUS involvement. In contrast, Hachisuga et al. reported that LUS involvement was correlated with lower median age, higher grade, deeper MI, and less favorable histology, but their study population included only 12 patients (4). Kizer et al. (10) evaluated 481 patients and reported decreased disease-free survival in patients with LUS involvement. In our study, we found slightly lower, but not statistically significant, overall survival in patients with LUS involvement compared to tumors without LUS involvement. Our study population was larger than those of previous studies, and while previous studies involved only stage 1 tumors, we included patients with all stages of tumors, which may have altered the survival rates. In nonendometrioid tumors, LUS involvement diminished survival slightly more compared to endometrioid subtypes, but the effect was still nonsignificant.

Doll et al. (11) investigated tumor size and tumor localization of 208 patients with early-stage and high-grade tumors. Similar to our results, they noted that LUS tumors were associated with pelvic and paraaortic nodal involvement. The authors (11) also reported an association between tumor size and nodal involvement; comparable with our results, tumors involving the LUS were also larger in diameter.

Westin et al. (3) suggested that tumors arising in the LUS were a subtype of endometrial cancer. In fact, several studies reported that tumors involving the LUS were equivalent to UC tumors in regards to survival and did not imply a worse prognosis (8,12). We found that tumors with LUS involvement were associated with other poor prognostic factors such as deep MI, serosal involvement, LVSI, lymph node metastasis, and higher FIGO grade, but it was not an independent poor prognostic factor alone without other accompanying poor prognostic factors.

However, LUS tumors were considered as a poor prognostic factor with increased risk of pelvic recurrences and, even in the absence of other risk factors, adjuvant therapy was administered in some centers (9). Further studies will reveal the prognostic impact of LUS involvement on intra- and postoperative treatment plans. Just as decisions about lymph node dissection are made based on preoperative and intraoperative histopathological findings using modified Mayo Clinic criteria in most institutions, LUS involvement in frozen sections may influence lymph node dissection decisions for the surgeon (13).

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. CA Cancer J Clin 2008; 58: 71-96.
2. Jacques SM, Qureshi F, Ramirez NC, Malviya VK, Lawrence WD. Tumors of the uterine isthmus: clinicopathologic features and immunohistochemical characterization of p53 expression and hormone receptors. Int J Gynecol Pathol 1997; 16: 38-44.
3. Westin SN, Lacour RA, Urbauer DL, Luthra R, Bodurka DC, Lu KH, Broaddus RR. Carcinoma of the lower uterine segment: a newly described association with Lynch syndrome. J Clin Oncol 2008; 26: 5965-5971.
4. Hachisuga T, Kaku T, Enjoji M. Carcinoma of the lower uterine segment. Clinicopathologic analysis of 12 cases. Int J Gynecol Pathol 1989; 8: 26-35.
5. Sorvari TE, Laakso L. Histochemical investigation of epithelial mucosubstances in the uterine isthmus. Obstet Gynecol 1970; 36: 76-81.
6. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 1983; 15: 10-17.

7. Hachisuga T, Fukuda K, Iwasaka T, Hirakawa T, Kawarabayashi T, Tsuneyoshi M. Endometrioid adenocarcinomas of the uterine corpus in women younger than 50 years of age can be divided into two distinct clinical and pathologic entities based on anatomic location. Cancer 2001; 92: 2578-2584.

8. Phelan C, Montag AG, Rotmensch J, Waggoner SE, Yamada SD, Mundt AJ. Outcome and management of pathological stage I endometrial carcinoma patients with involvement of the lower uterine segment. Gynecol Oncol 2001; 83: 513-517.

9. Mayr NA, Wen BC, Benda JA, Sorosky JI, Davis CS, Fuller RW, Hussey DH. Postoperative radiation therapy in clinical stage I endometrial cancer: corpus, cervical, and lower uterine segment involvement--patterns of failure. Radiology 1995; 196: 323-328.

10. Kizer NT, Gao F, Guntupalli S, Thaker PH, Powell MA, Goodfellow PJ, Mutch DG, Zighelboim I. Lower uterine segment involvement is associated with poor outcomes in early-stage endometrioid endometrial carcinoma. Ann Surg Oncol 2011; 18: 1419-1424.

11. Doll KM, Tseng J, Denslow SA, Fader AN, Gehrig PA. High-grade endometrial cancer: revisiting the impact of tumor size and location on outcomes. Gynecol Oncol 2014; 132: 44-49.

12. Brown AK, Madom L, Moore R, Granai CO, DiSilvestro P. The prognostic significance of lower uterine segment involvement in surgically staged endometrial cancer patients with negative nodes. Gynecol Oncol 2007; 105: 55-58.

13. Walker JL, Piedmonte MR, Spirtos NM, Eisenkop SM, Schlaerth JB, Mannel RS, Spiegel G, Barakat R, Pearl ML, Sharma SK. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. J Clin Oncol 2009; 27: 5331-5336.