

Investigating the Association of Lower Uterine Segment Involvement with Deep Myometrial Invasion in Endometrial Adenocarcinoma

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Abstract

Background: Endometrial carcinoma is the most common cancer of the female genitalia and its prevalence is 2% to 3% along the females' lifetime. This adenocarcinoma is diagnosed in the early stages because the patients become symptomatic early in the course of disease. The correlation of the lower uterine segment involvement (LUSI) with the recurrence, and the survival rates in patients with endometrial adenocarcinoma are always questionable. Confirming the prognostic significance of LUSI can fundamentally improve the current state of patients' surveillance. The current study aimed at investigating the association of lower uterine segment involvement with deep myometrial invasion in endometrial adenocarcinoma.

Methods: In the current retrospective cohort study, 54 patients with stage I endometrial endometrioid adenocarcinoma who underwent surgery in Mirza-Koochak-Khan Hospital, Tehran, Iran, from 2004 to 2014 were divided into 2 groups according to the presence of LUSI. In the current cohort study, the data from the patients exposed to LUSI were obtained by questionnaires to measure deep myometrial invasion besides post-operative adjuvant radiotherapy. The median of follow-up period was 48 months for all of the patients, which started after their surgery, and the measurement period for variables were similar to those of the follow-up period, which was 48 months. They were compared regarding to age, tumor grade, depth of myometrial invasion, lymphovascular involvement, extra uterine diseases, the extent of lymphadenectomy, adjuvant therapy, recurrence rate, time, and location. The data analysis was conducted by the SPSS v.16 statistical software (Chicago, IL, USA) at the significance level of 5%. In the investigation, Chi-square, the Kolmogorov-Smirnov, t test, and the Mann-Whitney U tests were used.

Results: Group 1 consisted of 13 patients with LUSI and group 2 had 41 patients without LUSI divided by a non-random sampling method. According to the results of the Mann-Whitney U test, there was a significant difference between the mean age of patients with LUSI and that of the ones without LUSI ($P = 0.03$). It showed that the mean age in the former group was significantly higher than that of the latter. A Chi-square test showed no significant association between the lymphovascular involvement and the presence of LUSI ($P = 0.1$). The Fisher exact test showed that patients with LUSI had significantly higher rate of radiotherapy after surgery rather than the ones without LUSI ($P < 0.001$).

Conclusions: In conclusion, there was a significant association between the lower uterine segment involvements with deep myometrial invasion in the endometrial endometrioid adenocarcinoma. In other words, there was a significant difference in the depth of myometrial invasion between the groups, and the patients with LUSI had deeper myometrial invasion (the Mann-Whitney U test, $P < 0.001$).

Keywords: Endometrioid Adenocarcinoma, Lower Uterine Segment, Myometrial Invasion, Adjuvant Radiotherapy

1. Background

Endometrial adenocarcinoma is the most common gynecological malignancy responsible for about half of different kinds of females' cancers in the United States (1). This cancer is the 4th common cancer among females in the developed countries (2). Each year, endometrial cancer arises in more than 319,000 females worldwide and causes the death of about 76,000 females (3). Symptoms develop at an early stage, which causes the primary diagnosis easier, and an increased survival rate is a result of that (4). Several researches conducted in the national cancer institute's surveillance, epidemiology and end results program

proved that 73% of such patients had stage I cancer at diagnosis, while 10% were diagnosed with stage II cancer (5, 6). This heterogeneous cancer has 2 types (7). Cancers categorized as type I, which are estrogen-dependent and include 70% to 80% of the cases, present with a low grade at an early stage and type II cancers, which are less differentiated, become symptomatic at a later stage and have a higher recurrence rate (7, 8). The endometrium is apparently composed of 2 components, the uterine corpus (UC) and the lower uterine segment (LUS) (8). LUS has a thin mucosal membrane and a decreased responsiveness to hormonal stimulation, compared with UC (6). Endometrial adenocarcinoma mainly develops in the uterine corpus en-

dometrium and is exceptionally derived from the LUS (9). Due to vaginal bleeding and diagnosis in early stage, most patients can be treated just by surgery (5, 10). The prognosis of this carcinoma is usually excellent with an approximately 5-year survival of 85% (11). Poor prognostic factor in stage I endometrial adenocarcinoma consist of tumor grade, depth of myometrial invasion, lymphovascular involvement, and histological subdivision (5). Although the stage of malignancy has the main role in the prediction of the disease outcome, other factors can be indirectly affect the survival rate (12). Progression in clinical management of early stage endometrial cancers requires more predictive prognostic biomarkers to prevent 10% to 20% recurrence in such cases (2). Confirming a factor with high prognostic value can fundamentally improve the current state of patients' surveillance who repeatedly receive postoperative care. The current study aimed at investigating the association of lower uterine segment involvement with deep myometrial invasion in endometrial adenocarcinoma.

2. Methods

The current retrospective cohort study was conducted on 54 patients in Mirza-Koochak-Khan Hospital in Tehran, Iran, from 2004 to 2014. In the current cohort study, the data of the patients exposed to LUSI were obtained by questionnaires to measure deep myometrial invasion as well as post-operative adjuvant radiotherapy. The records of patients with stage I endometriod adenocarcinoma who had surgical operation were reviewed. In other words, they varied in the depth of myometrial invasion and the need for post-operative adjuvant radiotherapy based on the LUSI. They were divided into 2 groups according to the presence of LUSI by a non-random sampling method as follows: Group 1 consisted of 13 patients with LUSI and group 2 consisted of 41 patients without LUSI. All the subjects underwent complete surgical staging based on the International Federation of Gynecology and Obstetrics (FIGO) criteria. They also underwent pelvic and para-aortic lymphadenectomy based on the depth of myometrial invasion, grade, and size of tumor.

The median of the follow-up period was 48 months for all of patients, which started after their surgery, and the measurement period for variables were similar to those of the follow-up period, which was 48 months. If the lower uterine segment involvement was confirmed by the microscopic or gross pathologic studies in the pathologic reports, then it was classified as LUSI positive. Then, the tissue specimens were assessed by a gynecologic pathologist. After surgery, radiotherapy was started on patients based on the depth of myometrial invasion, grade, and histological type of the tumor. For each patient, a data form

was prepared. Forms were filled by investigating the medical records, surgical reports, and the pathologic results of the patients. Data collection was conducted based on the patients' age, tumor grade, depth of myometrial invasion, lymph-vascular space involvement, extra-uterine disease, extent of lymph node resection, lower uterine segment involvement, follow-up duration, adjuvant therapy, recurrence rate, recurrence location, recurrence time, and death time. Other accessory data such as age, menopausal status, the main complaint of the patients and endometrial biopsy results were analyzed on the basis of lower uterine segment involvement. The data analysis was conducted by the SPSS v.16 statistical software (IBM, Armonk, NY, USA). In the descriptive analysis of data, frequency, mean, and mode and standard deviation were used. Level of significance was set to 5% in all of the statistical analysis. Chi-square test (Chi2) was used to determine the association between the lower uterine segment involvement with postoperative adjuvant radiotherapy, vascular involvement, lymph node involvement, and extra uterine involvement. To investigate the mean age of the patients, the mean follow-up duration and depth of myometrial invasion with LUSI, in the first step, the Kolmogorov-Smirnov (KS) test were applied to check the distribution of data. Afterwards, non-parametric tests such as the Mann-Whitney U test were used.

3. Results

A total of 54 patients with stage I endometrial adenocarcinoma who underwent surgery participated in the current study, 13 patients had LUSI. After following-up the patients, it was realized that except 1 patient who died of coronary disease, none of them in the 2 groups died. The following data were gathered from the patients enrolled in the current study: employment, menopausal condition, hypertension, diabetes, cigarette smoking, the number of previous pregnancies, menopausal age, the time interval between onset of the first symptoms and diagnosis, CA125 and patients' initial complaints, family history of endometrial cancer and abnormal Pap smear test. Some clinicopathologic features such as age was also reviewed. Table 1 shows the result of a non-parametric test on two independent samples (the Mann-Whitney U test) indicating a significant difference between the age of patients with/without LUSI ($P=0.03$). The table shows that the mean age in the former group was significantly higher than that of the latter.

A Chi-square test showed that although the sample contained more patients with LUSI who experienced lymph vascular involvement, there was no significant association between the lymph vascular involvement and pres-

ence of LUSI ($P = 0.1$). According to the results of the Chi-square test (the Fisher exact test), patients with LUSI had significantly higher rate of radiotherapy after surgery than the ones without LUSI. Therefore, there was a significant association between the post-operative adjuvant radiotherapies and the presence of LUSI ($P < 0.001$).

Table 1. The Statistical Tests Between the Patients With and Without LUSI

Variable	With LUSI	Without LUSI	P Value
Mean age of the patients, y	55.23 (25 - 81)	47.17 (25 - 80)	0.03
Lymph vascular involvement, %	15.4	2.4	0.1
Postoperative adjuvant radiotherapy (Pelvic and para-aortic radiotherapy), %	50	5	< 0.001
Depth of myometrial invasion, %	53.8	7.2	< 0.001

Table 1 showed that patients with LUSI had higher rates of deep myometrial invasion. Moreover, there was a significant difference in the depth of myometrial invasion between the groups, and the patients with LUSI had deeper myometrial invasion (the Mann-Whitney U test, $P < 0.001$). It is also noteworthy that by defining the 50% of myometrial invasion as an index to opt the deep myometrial invasion, the odds ratio statistics could be derived. The odds ratio for the association between the presence of LUSI and deep myometrial invasion was large at 15.167, reflecting the large difference in deep myometrial invasion and thus a strong relationship between the 2 variables in the current sample.

4. Discussion

LUS is an anatomical part of uterus, which is also a histologically transitional area between endocervical glands and endometrial tissue. As an anatomical and histological view, it has non-mucinous, non-cycling type of epithelium without any fibrous elements of cervical stroma. However, there is always a debate on the prognostic value of LUSI in patients with endometrial cancer. It was also demonstrated that LUSI in patients with postoperative adjuvant radiotherapy with pelvic and para-aortic lymphadenectomy had no association with any poor prognosis or rate and location of recurrence. However, the authors knew that an increase in the follow-up period would enrich the paper, and let them provide survival models such as the Cox regression, and the Kaplan-Meier statistics, as they measured recurrence rate, recurrence location, recurrence time, and death time. The authors detected LUSI in 24% of the patients, which was identical to the results achieved in

the study performed by Lavie et al. (5). In other previous studies, upper or lower rates were reported ranging from 5% to 58% (13); including the studies by Gemer et al. that reported 18% (14), Phelan et al. 42% (13), Ben-Arie et al. 19.3% (15), Kizer et al. 46.4% (2), and Brown et al. 57% (1). In the current study, there was no significant difference between the 2 groups with and without LUSI in the lymph node ($P = 0.1$), which was similar to the study by Phelan et al. (13). While in the study by Brown et al. on 147 potential patients with endometrial adenocarcinoma, complete surgical staging, and negative lymph nodes, LUSI was truly associated with nodal involvement ($P = 0.005$) (1). As confirmed by the current study, deep myometrial invasion was a factor with statistically significant association with LUSI, which was the same as the results achieved by Brown et al.; in contrast to those of Phelan et al. who reviewed 98 cases in 2 groups with and without LUSI (1, 13). Although there was a positive trend between the patients with LUSI who had lymphovascular involvement in the current study, no statistical difference was observed between the 2 groups that was in contrast with the studies by Brown et al. and Gemer et al. (1, 14) and similar to the results of Phelan et al. (13). Mean age of the patients was a factor with significant association with LUSI in both groups in the current study ($P = 0.03$). In contrast, there was no significant difference between the 2 groups in some previous investigations (1, 2, 13). In the research done by Phelan et al. there were no significant differences in many of the factors examined between the 2 groups including diabetes mellitus, hypertension, and the frequency of adjuvant radiotherapy (13), which were similar to the results of the current study except adjuvant radiotherapy that was significantly associated with LUSI ($P < 0.001$). Phelan et al. found no difference in the histopathological factors in patients with and without LUSI (13). In a study by Gupta et al. adjuvant radiotherapy results in 4.1% overall survival improvement in patients with high-intermediate risk stage I endometrial cancer (16). In the current study, after following-up the patients, it was found that except 1 patient who died of coronary artery disease, none of them died. Moreover, none of the patients in the 2 groups encountered recurrence. In the study by Gemer et al. no difference was detected in the survival rate between the 2 groups (17). But among the 481 patients included in the study by Kizer et al. 80 cases (16.6%) died and 36 (7.5%) had recurrences during the research (2). According to the study by Phelan et al. which had the mean follow-up duration of 37.3 months, 10.2% of the patients had recurrence and 4.8% died of their diseases (13). In the current study, post-operative adjuvant radiotherapy was significantly associated with LUSI ($P < 0.001$). In contrast to the study by Kizer et al. no priority was detected in patients with LUSI ($P = 0.32$) (2). It was similar to the study by Phelan (13).

In the study by Phelan, the frequency of adjuvant radiotherapy was similar in patients with (24.4%) and without (22.8%) LUSI; there were no statistically significant differences between the groups. In current survey, no recurrence occurred. The possible reason for lack of recurrence in the patients was the initiation of postoperative adjuvant therapies on time. In a recent study by Kizer et al. (2) on the largest population of patients to date, the negative LUSI association with the disease-free survival and overall survival in patients with the stage I and II of the disease was confirmed. Since the depth of myometrial invasion has a considerable impact on the patients' prognosis, elimination of this factor can be beneficial to evaluate LUSI as an independent factor in these 2 groups in future studies. The current investigation as a retrospective cohort study design with a very small study population on a really challenging issue raises the need for larger studies to survey the effect of LUSI as an independent prognostic factor in stage patients with endometrial cancer.

Footnote

Conflict of Interests: The authors declared no conflict of interest.

References

- 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**(1):55-8. doi: [10.1016/j.ygyno.2006.10.058](https://doi.org/10.1016/j.ygyno.2006.10.058). [PubMed: [17157904](https://pubmed.ncbi.nlm.nih.gov/17157904/)].
- Kizer NT, Gao F, Guntupalli S, Thaker PH, Powell MA, Goodfellow PJ, et al. Lower uterine segment involvement is associated with poor outcomes in early-stage endometrioid endometrial carcinoma. *Ann Surg Oncol.* 2011;**18**(5):1419-24. doi: [10.1245/s10434-010-1454-9](https://doi.org/10.1245/s10434-010-1454-9). [PubMed: [21181281](https://pubmed.ncbi.nlm.nih.gov/21181281/)].
- Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 France: International Agency for Research on Cancer; 2014. Available from: <https://www.iarc.fr/Default.aspx>.
- Lax SF. Pathology of Endometrial Carcinoma. *Adv Exp Med Biol.* 2017;**943**:75-96. doi: [10.1007/978-3-319-43139-0_3](https://doi.org/10.1007/978-3-319-43139-0_3). [PubMed: [27910065](https://pubmed.ncbi.nlm.nih.gov/27910065/)].
- Lavie O, Uriev L, Gdalevich M, Barak F, Peer G, Auslender R, et al. The outcome of patients with stage I endometrial cancer involving the lower uterine segment. *Int J Gynecol Cancer.* 2008;**18**(5):1079-83. doi: [10.1111/j.1525-1438.2007.01150.x](https://doi.org/10.1111/j.1525-1438.2007.01150.x). [PubMed: [18081795](https://pubmed.ncbi.nlm.nih.gov/18081795/)].
- Trimble EL, Harlan LC, Clegg LX, Stevens JL. Pre-operative imaging, surgery and adjuvant therapy for women diagnosed with cancer of the corpus uteri in community practice in the United States. *Gynecol Oncol.* 2005;**96**(3):741-8. doi: [10.1016/j.ygyno.2004.11.041](https://doi.org/10.1016/j.ygyno.2004.11.041). [PubMed: [15721420](https://pubmed.ncbi.nlm.nih.gov/15721420/)].
- Carlson MJ, Thiel KW, Leslie KK. Past, present, and future of hormonal therapy in recurrent endometrial cancer. *Int J Womens Health.* 2014;**6**:429-35. doi: [10.2147/IJWH.S40942](https://doi.org/10.2147/IJWH.S40942). [PubMed: [24833920](https://pubmed.ncbi.nlm.nih.gov/24833920/)].
- Aminimoghaddam S, Shahrabi-Farahani M, Mohajeri-Tehrani M, Amiri P, Fereidooni F, Larijani B, et al. Epistatic interaction between adiponectin and survivin gene polymorphisms in endometrial carcinoma. *Pathol Res Practice.* 2015;**211**(4):293-7. doi: [10.1016/j.prp.2014.11.012](https://doi.org/10.1016/j.prp.2014.11.012). [PubMed: [25613698](https://pubmed.ncbi.nlm.nih.gov/25613698/)].
- Masuda K, Banno K, Yanokura M, Kobayashi Y, Kisu I, Ueki A, et al. Carcinoma of the Lower Uterine Segment (LUS): Clinicopathological Characteristics and Association with Lynch Syndrome. *Curr Genomics.* 2011;**12**(1):25-9. doi: [10.2174/138920211794520169](https://doi.org/10.2174/138920211794520169). [PubMed: [21886452](https://pubmed.ncbi.nlm.nih.gov/21886452/)].
- Westin SN, Lacour RA, Urbauer DL, Luthra R, Bodurka DC, Lu KH, et al. Carcinoma of the lower uterine segment: a newly described association with Lynch syndrome. *J Clin Oncol.* 2008;**26**(36):5965-71. doi: [10.1200/JCO.2008.18.6296](https://doi.org/10.1200/JCO.2008.18.6296). [PubMed: [19001318](https://pubmed.ncbi.nlm.nih.gov/19001318/)].
- Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin.* 2010;**60**(5):277-300. doi: [10.3322/caac.20073](https://doi.org/10.3322/caac.20073). [PubMed: [20610543](https://pubmed.ncbi.nlm.nih.gov/20610543/)].
- Ghaemmaghami F, Aminimoghaddam S, Modares-Gilani M, Mousavi A, Khazaeipour Z, Fereidoni F. Assessment of gross examination and frozen section of uterine specimen in endometrial cancer patients. *Arch Gynecol Obstet.* 2010;**282**(6):685-9. doi: [10.1007/s00404-010-1387-3](https://doi.org/10.1007/s00404-010-1387-3). [PubMed: [20213133](https://pubmed.ncbi.nlm.nih.gov/20213133/)].
- 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**(3):513-7. doi: [10.1006/gy.2001.6407](https://doi.org/10.1006/gy.2001.6407). [PubMed: [11733964](https://pubmed.ncbi.nlm.nih.gov/11733964/)].
- Gemer O, Gdalevich M, Voldarsky M, Barak F, Arie AB, Schneider D, et al. Lower uterine segment involvement is associated with adverse outcome in patients with stage I endometrioid endometrial cancer: Results of a multicenter study. *Eur J Surg Oncol.* 2009;**35**(8):865-9. doi: [10.1016/j.ejso.2008.10.007](https://doi.org/10.1016/j.ejso.2008.10.007). [PubMed: [19013746](https://pubmed.ncbi.nlm.nih.gov/19013746/)].
- Ben-Arie A, Tamir S, Dubnik S, Gemer O, Ben Shushan A, Dgani R, et al. Does hysteroscopy affect prognosis in apparent early-stage endometrial cancer? *Int J Gynecol Cancer.* 2008;**18**(4):813-9. doi: [10.1111/j.1525-1438.2007.01076.x](https://doi.org/10.1111/j.1525-1438.2007.01076.x). [PubMed: [17961159](https://pubmed.ncbi.nlm.nih.gov/17961159/)].
- Gupta V, McGunigal M, Prasad-Hayes M, Kalir T, Liu J. Adjuvant radiation therapy is associated with improved overall survival in high-intermediate risk stage I endometrial cancer: A national cancer data base analysis. *Gynecol Oncol.* 2017;**144**(1):119-24. doi: [10.1016/j.ygyno.2016.10.028](https://doi.org/10.1016/j.ygyno.2016.10.028). [PubMed: [27793358](https://pubmed.ncbi.nlm.nih.gov/27793358/)].
- Gemer O, Uriev L, Harkovsky T, Peled R, Ben-Dor D, Barak F, et al. Significance of lower uterine segment involvement in women with stage I endometrial adenocarcinoma. *J Reprod Med.* 2004;**49**(9):703-6. [PubMed: [15493559](https://pubmed.ncbi.nlm.nih.gov/15493559/)].