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The Association between Lower Uterine Segment Involvement in Corpus Located Endometrioid Adenocarcinoma with the (International Federation of Gynecology and Obstetrics) Grade and Stage

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Abstract

BACKGROUND: Although lower uterine segment (LUS) is regarded as an anatomically defined part that possess some histological differences, it is involvement by carcinoma have not been included in the criteria for definition in the staging system for endometrial carcinoma and there are few conflicting data focused on the effect of LUS involvement as a prognostic factor in endometrial cancer.

AIM: To find the association between LUS involvement in corpus located endometrioid carcinoma with the grading and staging system established by the international federation of gynecology and obstetrics (FIGO).

METHODS: This was a retrospective study involving data collected from achieves of histopathology departments of teaching laboratories within successive 4 years period in Medical City complex at Bagdad. Pathological analysis of 70 hysterectomy specimens of corpus located endometriod adenocarcinoma was done, histological sections from each case of endometrioid adenocarcinoma carcinoma were microscopically reviewed for appropriate grading and staging, in addition, meticulous search was applied for histological finding consistent with LUS involvement. The statistical comparison between the results was done using either independent sample t-test (for continuous data; mean ± SD) or Chi-square test at a significant $p < 0.05$.

RESULTS: The study enrolled 70 histological samples of endometrioid adenocarcinoma, the majority of the samples were of low grade and stage at presentation. Of total sample, 46 (65.71%) showed LUS involvement by tumor cells. There was a significant statistical relationship between LUS involvement and FIGO stage while a non-significant statistical association with FIGO grade was found.

CONCLUSION: LUS involvement by corpus located endometrioid adenocarcinoma is associated with an advanced FIGO stage at presentation while non-significant relationship was found between patient age and tumor grade.

Introduction

Endometrial carcinoma is the most common uterine cancer in developed nations that involves layer of cells forming the lining (endometrium) of the uterus [1], it is of many histological type the most common type which representing type up to 80% of endometrial carcinoma is endometrioid [2], [3]. The majority arises in a background of endometrial hyperplasia due to prolonged unopposed estrogenic stimulation without progestational agents which tend to be of low grade and stage at presentation [4]. Women who had endometrial hyperplasia particularly when post-menopausal carry a definite risk of acquiring endometrial cancer at their lives, the risk of progression from endometrial hyperplasia to endometrial carcinoma relies on the existence and severity of cytologic atypia achieved by a careful histologic examination “Atypia is defined as enlarged rounded irregular nuclei, prominent nucleoli, loss of polarity and occational cytoplasmic eosinophelia” [5], [6]. Endometrial carcinoma tends to occur in the middle age group with a mean age at diagnosis is in the fifth decade of life [3], [7]. Endometrial adenocarcinoma most frequently arises in the corpus proper and it is of variable gross appearances and sizes but the vast majority are exophytic and friable in texture with vaguely demarcated Tumor/myometrial interface which is an important landmark for assessment the degree of myometrial invasion, however, some originate in the lower uterine segment (LUS) which has a unique set of clinical and pathologic characteristics [8]. Regarding microscopical features of endometriod adenocarcinoma, confluent or back to back glands lacking any intervening stroma is considered as the key architectural pattern together with cribriform, microaciner and villoglandular configuration, other morphologic variants include endometrioid carcinoma with altered differentiation/metaplasia, Papillary type variants, Microglandular hyperplasia-like, Spindled,

Corded/Hyalinized and Mixed (combination of at least 2 endometrial histologic subtypes most frequently endometrioid and serous) [1], [2]. The most powerful prognostic factors in endometrial cancer are histological grade and surgical stage [4]. The "International Collaboration on Cancer Reporting" recommended to stage endometrial cancers by using the "2009 international federation of gynecology and obstetrics (FIGO)" staging system which is largely concordant with The "TNM" staging system [9], [10], [11]. Medical Oncology presurgical and postsurgical guidelines for "adjuvant treatment," are made almost entirely on the pathologic informations given in the histopathology report [12], [13], [14], tumor grade and clinical stage in endometrial carcinoma are important prognostic factors that drive the treatment regimen [15]. The uterus is anatomically subdivided into the corpus, isthmus, and cervix, isthmus or LUS is defined as the region constitute the transition between the endocervical tissue and the lower part of the uterine corpus, this term (LUS\isthmus) is used for descriptive purposes in obstetric and it is an important landmark for the gynecological pathologist when describing cancers of the uterine corpus, since it located between the uterine body and cervix, it posses morphological features of both endometrium and cervix in the glandular epithelium and interstitium, the fact that endometrial mucosa in the isthmus is thinner than that of the uterine body responsible for poor response to hormonal stimulation, muscular layer of the isthmus is less well developed than in the corpus to facilitate effacement and dilation during labor [8], [16]. Although it is regarded as an anatomically defined part that possess some histological difference, it is involvement by carcinoma have not been included in the criteria for definition in the staging system of endometrial carcinoma, in addition only few puplished data were focused on the effect of LUS involvement as a prognostic factor in endometrial cancer were recorded to date [17]. This study was conducted to search for the relationship between LUS involvement by the most common endometrial cancer and the most powerful prognostic factors (FIGO grade and stage) in an attempt to find the prognostic significance of this association among Iraqi patients with endometrioid adeno carcinoma.

Materials and Methods

This was a retrospective original study involving data extracted from the archives of histopathology departments of teaching laboratories in the Medical City complex at Bagdad in the period from January 2015 to December 2019. In this study formalin-fixed paraffin embedded labeled blocks of 70 hysterectomy specimens of corpus located endometriod carcinoma that were stored in the archive of the aforementioned pathology laboratries were collected by matching their labeled numbers with the registered numbers in the archived histology reports of all endometrioid adenocarcinoma diagnosed within the period of this study. All specimen in which grossly and or microscopically showed cancer that originating from LUS were exclude from this study. Histological sections from each case of endometrioid carcinoma were microscopically reviewed by one pathologist for appropriate grading and staging by applying the widely used FIGO grading and staging system for endometrial carcinoma. "The three tier grading system widely used based on the degree of glandular differentiation are Grade 1 tumors that exhibit ≤5% solid non-glandular, non-squamous growth; grade 2 tumors from 6% to 50%; and grade 3 tumors >50%" [4]. Pathological Stage of endometrial carcinoma depending on histological finding observed in each hysterectomy specimen done by applying the most recent American joint cancer committee system which came into effect in January 2018 [18] (Table 1). Myometrial invasion which is an important criteria that define the FIGO stage was assessed with appreciation to all it is possible patterns as illustrated in (Table 2) [2]. In addition, meticulous search was done for histological findings consistent with LUS involvement using a certain histologic criteria [11] which is not usually reported in pathology reports using a light microscope (Leica DM500).

Table 1: FIGO staging system for uterine carcinoma [18]

FIGO stage	Stage description
I	Involve the uterus. It may also involve the cervical glands, but not involve the supporting connective tissue of the cervix
IA	Endometrial involvement and<50% through the myometrium
IB	Endometrial involvement and more than 50% through the myometrium but not beyond the body of the uterus
II	Involvement of the cervical stroma. But not outside the uterus
III	Outside the uterus, but not to the inner lining of the rectum or urinary bladder
IIIA	Involvement of serosa and/or to the adnexa
IIIB	Involvement of vagina or to the parametrium
IIIC1	Uterine body involvement. and or to nearby tissues or pelvic lymph nodes, but is not into the bladder or rectal mucosa
IIIC2	As in IIIc1 and has also spread to lymph nodes around the aorta (para-aortic lymph nodes) but not to the distant sites
IVA	Involvement of the rectum or urinary bladder mucosa and or nearby lymph nodes but not to distant organs
IVB	Involvement of inguinal (groin) lymph nodes, the upper abdomen, the omentum, distal organs as the lungs, liver, or bones

FIGO: International federation of gynecology and obstetrics.

The only available clinical data is the patient age which was gathered from the archival records. This study was approved by the ethical committee of the national center for educational laboratories (ethical clearance file number 68/19) and agreed all institutional policy. Photomicrographs were taken for this study using the camera (Leica Icc 50E).

Table 2: Microscopic patterns of myometrial invasion [2]

Patterns of myometrial invasion	Histological description
Conventional pattern	• Traverses outward the irregular endomyometrial junction either pushing or infiltrative border • Stromal response consists of fibroblastic proliferation, edema, and inflammatory cells
Microcystic, ELongated and Fragmented (MELF)	• Fragmented microcystic, elongated glands with flattened or histiocytoid epithelial lining • Distinctive fibromyxoid stromal response with acute inflammation
Adenoma malignum	• Diffusely infiltrative malignant glands with irregular shape, invading myometrium in clusters • No or minimal associated stromal response

Data analysis was done by (Statistical Package for the Social Sciences, version 4.0). It was represented in form of mean ± SD for continuous data or total number/percentage for categorical data. Independent sample Student t-test and Chi- square test was used for comparisons between them respectively. Calculated $p \leq 0.05$ set as statistically significant.

Results

This study enrolled 70 samples of formalin-fixed paraffin-embedded blocks of hysterectomy specimen diagnosed histologically as endometrioid carcinoma with the mean age was 55.8 ± 10.77. Of total sample, 46 (65.71%) showed LUS involvement by tumor cells. 48 (68.6%) were grade I (Figure 1), I, 14 (20.0%) were grade (Figure 2) II, 8 (11.4%) were grade III (Figure 3). The majority were stage IA at presentation.

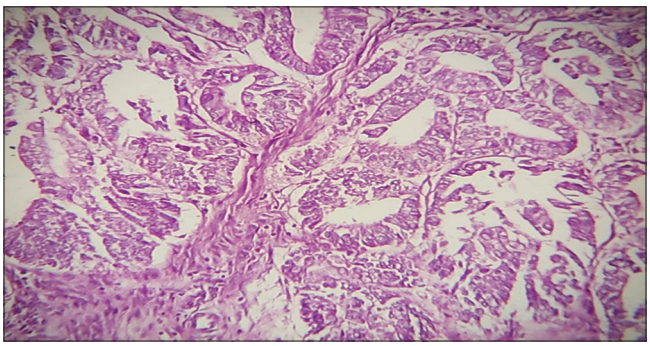

Figure 1: Well differentiated grade I endometriod adenocarcinoma (Hematoxyline and eosin stained histological section 100×)

The mean age in females in whom LUS was involved was less than 55.39 ± 11.17 years vs. 58.33 ± 10.33 years in females without involvement with no significant statistical variance, p = 0.28. The association between LUS involvement and FIGO Grade revealed no significant statistical relationship with p = 0.57 (Table 3).

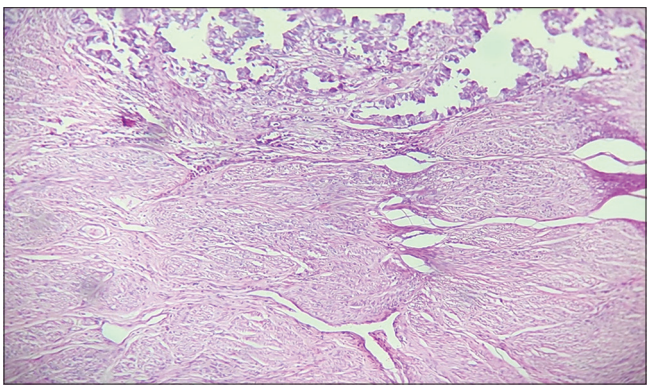

Figure 2: Lower uterine segment involvement by grade II endometriod adenocarcinoma identified by the characteristic fibrous stroma (Hematoxyline and eosin stained histological section 100×)

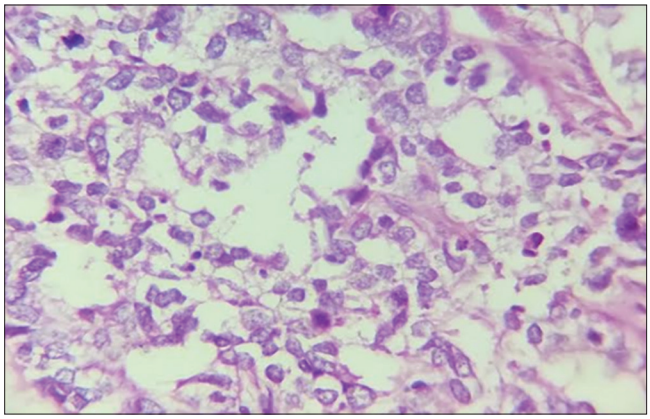

Figure 3: Grade III endometriod adenocarcinoma (Hematoxyline and eosin stained histological section 100×)

While the association between LUS involvement and FIGO stage is best to be illustrated in (Table 4) which revealed a significant association at as significant p = 0.045.

Table 3: The association between lower uterine segment involvement by endometrioid ca and FIGO grade

Parameter	LUS involved (%)	LUS not involved (%)	Total (%)	p-value
Grade I	32 (69.6)	16 (66.7)	48 (68.6)	0.57
Grade II	10 (21.7)	4 (16.7)	14 (20.0)	
Grade III	4 (8.7)	4 (16.7)	8 (11.4)	
Total	46 (100)	24 (100)	70 (100)	

Chi-square test, FIGO: International federation of gynecology and obstetrics, LUS: Lower uterine segment.

Discussion

Despite the fact that endometrial carcinoma in general and endometrioid histology, in particular, is generally considered a prognostically favorable cancer, worldwide more than 20% of women with endometrial cancer die and there is an actual rise in the incidence and mortality rate annually, the purpose of accurate and reproducible prognostication is to guarantee that patient will receive optimal management achieving better improvement in the patient outcomes overall [1], [2], [11].

Table 4: The association between lower uterine segment involvement by endometrioid carcinoma and FIGO stage

Parameter	LUS involved (Total no, %)	LUS not involved (Total no, %)	Total	p-value
Stage I a	26 (54.2)	20 (90.9)	46	0.045*
Stage I b	4 (8.3)	2 (9.1)	6	
Stage II a	10 (20.8)	0 (0.0)	10	
Stage III a	4 (8.3)	0 (0.0)	4	
Stage III c	2 (4.2)	0 (0.0)	2	
Stage IV b	2 (4.2)	0 (0.0)	2	
Total	48 (100)	22 (100)	70 (100)	

Chi-square test, FIGO: International federation of gynecology and obstetrics, LUS: Lower uterine segment.

Hence the first step is to discover other prognostic factors clarifying and discussing clinically relevant risk groups, and ultimately to plan management algorithms for those risk groups. The fact that only Scanty studies worldwide were done to investigate the prognostic significance of LUS involvement in endometrial carcinoma [17] and no such Iraqi study best clarify the purpose of the current study. The LUS is

often identified from histological slides that display the inactive or ciliated glands as well as the characteristic fibrous stroma of isthmus or also contain upper endocervix or from the section code when performed during grossing [11].

The current study showed that the mean age in females in whom LUS was involved in corpus located endometrioid adenocarcinoma is 55.39 ± 11.17 years versus 58.33 ± 10.33 years in females without such involvement with no significant statistical difference, it also showed that there is a non-significant statistical association with FIGO grade, this results disagree with one Turkish study done by Erkaya *et al*. [17] and one Iranian study done by Aminimoghaddam *et al*. [19] in which LUS involvement by endometrial carcinoma, in general, was used as a study group thus clarifying the disagreement with the current study. However, this is the only published studies worldwide searching for this purpose. Furthermore, the fact that only a minority of endometrioid carcinoma are of high grade at presentation is one of the major limitation of any study focused on finding a valuable association with FIGO grading in endometrioid adenocarcinoma.

The present study found that there is a significant association between LUS involvement by endometrioid ca and FIGO stage, these results agree with a similar study done by Ogden *et al*. [20], while Erkaya *et al*. [17] and Aminimoghaddam *et al*. [19] found a significant relationship between LUS involvement by endometrial ca in general and deep myometrial invasion which is an important criteria that define stage I endometrial cancer.

Clark *et al*. [21] and Kogan *et al*. [22] found that there is a significant association between LUS Involvement and FIGO stage in Grade 3 Endometrial Cancer. Kogan *et al*. [22] found that there is a significant association between LUS involvement and FIGO stage in type II endometrial cancer and the unique mutational profile of serous tumors. Additional three studies [23], [24], [25] found that LUS involvement is associated with poor outcome in patient with stage I endometrial ca.

THUS based on the fore mentioned analysis, LUS involvement by endometrial carcinoma has been reported to be associated with advanced stage; however, literature is limited particularly in regard to endometrioid carcinoma. This is the first study among Iraqi women with endometriod carcinoma and may regard as the starting idea about the importance of reporting LUS involvement in endometrial cancer in general and endometrioid histology in particular. Regarding endometrial cancer management, one of the powerful prognostic factors used in clinical decisions is the pathological stage, and the current study, as well as other published studies, found that LUS involvement significantly associated with a advance stage at presentation so a proposal for changes in a future revision of FIGO staging with incorporation the significant of LUS involvement is hopefully recommended, surely after large scale further prospective clinicopathological studies.

Conclusion

Grade I histology accounted for the majority of corpus located endometrioid adenocarcinoma cases. The mean age in females in whom LUS was involved was slightly less than that in females without involvement. LUS involvement by corpus located endometrioid carcinoma is associated with an advanced FIGO stage at presentation while no significant statistical association with FIGO grade and patient age.

Limitation

A single center with relatively small number of cases included in the study. limited clinical data about cases present in the records as in each retrospective study. Scant other worldwide studies with similar aims and no similar Iraqi study.

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Author's Contribution

First author: Data collection, data analysis and interpretation, editing the manuscript.

Second author: Data collection, Statistical analysis.

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