Comparative study between type I and type II endometrial cancer

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ABSTRACT

Objective: The aim of our study was to compare the clinical and pathological characteristics of two different types of endometrial cancer (EC) managed at a single institution.

Materials and methods: A retrospective study was conducted regarding the patients who were diagnosed with EC and received treatment at King Hussein Medical Centre, Amman, Jordan. Data were extracted from the files and reports of patients during the period from January 2010 to January 2018. A total of 263 patients with EC were included in this study. Two groups were created. The first group had patients with endometrioid type cancer. The second group had patients with non-endometrioid types of cancer, which include papillary serous and clear cell adenocarcinomas but not uterine sarcomas. The collected data involved patient characteristics, tumour characteristics, type of surgery performed, adjuvant treatment provided, tumour stage, recurrence and survival rate. International Federation of Gynecology and Obstetrics (FIGO)staging system 2009 edition was applied. Data were revised, arranged in tables and statistically analysed with comparison between the two groups. $P < 0.001$ was considered statistically significant.

Results: A total of 263 cases were enrolled in the study. Among all cases, 214 cases (81.3%) had endometrioid type adenocarcinoma (type I) and 49 cases (18.7%) had papillary serous or clear cell adenocarcinomas (type II). The mean age for the first group was 52.1 years as compared to 61.8 years for the second group. Abnormal vaginal bleeding was the most common presenting symptom for both groups. For patients ≤ 50 years old, the incidence of type I cancer was 29% in comparison to only 10.2% for type II. As a primary treatment, surgery was performed for 87.9% of type I tumours as compared to 71.4% for type II tumours. Pelvic radiotherapy was the main treatment approach in 13/214 cases (6.1%) of type I EC, with no cases in type II EC. Patients received chemotherapy accompanied with or without radiotherapy in 3.7% and 20.4% of the cases in the type I and II groups, respectively. The most common stage at the time of diagnosis was stage one for type I disease (75.3%) as compared to stage four for type II disease (42.9%). Type I disease showed a better 5-year survival rate (90.7%) compared to type II disease, which showed a lower percentage (60.9%).

Conclusion: Among Jordanian women, type I EC is more common, and the response to treatment has a higher survival rate than type II EC.

Keywords*:* endometrial cancer, endometrioid, serous.

RMS August 2023; 30 (2): 10.12816/0061606

Introduction

Tumours of the uterus mainly arise from the endometrial cavity, which is called the endometrium. Worldwide, endometrial adenocarcinoma is the most common cancer of the female genital tract, with an incidence which exceeds all other types of female genital tract malignancies combined [1].

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Submission date: 8 June 2021 , Acceptance date: 11August 2022 , Publication date: August 2023

Moreover, its incidence is still rising by 1-2% yearly [2]. Endometrial cancer (EC) has a 2.5% lifetime risk of development [3]. These tumours usually present with vaginal bleeding. Most of the patients are diagnosed at an early stage with tumour limited to the uterus, leading to a 5-year survival rate of more than 90%.

Two pathogenetic subtypes (type I and type II) have been described. According to Bokhman et al., this difference was based on histology and clinical outcome, which depend on the differences in endocrine and metabolic factors [4] .

Type I is the most common, accounting for about 65-70% of all ECs and is strictly endometrioid type in histopathological terms [5] . It is formed from glandular epithelium that arises from endometrial hyperplasia. Moreover, it is considered an oestrogen-dependent tumour that develops in women who have conditions associated with hyperoestrogenism, such as obesity, infertility, polycystic ovary syndrome, late menopause and prolonged anovulation. It is characterized by a well to moderately differentiated morphology of the carcinoma, superficial invasion into the myometrium and high sensitivity to progesterone [6] . This type is mostly discovered at an early stage and therefore has a somewhat favourable prognosis.

Type II is the other less common form (10-20%), which is known as the non-endometrioid type [5] . It is histopathologically formed from clear cell, papillary serous and undifferentiated carcinomas similar to those cancers arising from the ovary and fallopian tubes. It develops within the atrophic endometrium and progresses from precancerous intraepithelial lesions. While not much is known about this malignant growth, it may be caused by a genetic mutation [7 ,8] . By definition, this tumour is poorly differentiated, with a tendency for deep invasion to the myometrium, and has a high frequency of metastatic spread. It was first described by Hendrickson et al. in 1982 as a highly malignant subtype with a poor prognosis [9] . Patients with serous carcinoma are diagnosed at an older age, with an average of 5 years older than those with endometrioid carcinoma. Although it accounts for about 10-20% of all endometrial carcinomas, type II is responsible for about 40% of cancer-related mortality [4 ,5 ,10] .
An important recent development is the ancillary immunohistochemistery(IHC) P53 optimization and validation , which has become a reliable adjunct in subclassification of gynaecological cancers[11].

Materials

The database of the Gynaecologic Oncology Clinic at King Hussein Medical Centre, Amman, Jordan, was reviewed from January 2010 to January 2018. The records of patients were reviewed, and systemic research was performed through the pathology records of patients reported as having EC. A total of 310 cases with uterine malignancies were recognized during the mentioned period of study. Out of the total, 30 cases were uterine sarcomas and another 17 cases had incomplete data in their files. Therefore, these 47 patients were excluded, and 263 patients with EC were included in this study.

Two groups were created. The first group was composed of patients with endometrioid type endometrial adenocarcinoma and mucinous ECs. The second group was composed of patients with serous,and clear cell ECs. Cases with histopathological reports that showed uterine sarcomas were not included in this study. The extracted data involved patient characteristics, tumour characteristics, modality of management performed and the final outcome, which included stage of tumour, recurrence and survival. Patient characteristics at the time of diagnosis were age, parity, menopausal status and presenting symptoms. Tumour characteristics included type, grade, size, location, depth of myometrial invasion (MI), presence of lymphovascular space invasion (LVSI) and presence of malignant cells at peritoneal cytology. Modality of treatment included primary and secondary surgeries, adjuvant chemotherapy and radiotherapy.

Statistical analysis

The categorical data were expressed in frequencies and percentages , the scale variables were expressed in mean±SD ,chi square of independence was used to test association between categorical data , p value set at <0.05 deemed statistically significant and SPSS IBM software ver 25 language was used to analyze data.

Results

Out of 263 patients, 214 cases (81.3%) had endometrioid type adenocarcinoma (type I) and 49 cases (18.7%) had papillary serous and clear cell adenocarcinomas (type II). The mean age for the first group was 52.1 years as compared to 61.8 years for the second group, with nearly 10 years difference in mean age.

Table I shows a comparison of patient characteristics between the two groups. For both groups, most patients were above the age of 50 years at the time of diagnosis, with a higher incidence among the type II group (accounting for 89.8%). In addition, 29% of patients who were diagnosed with a type I tumour were ≤ 50 years old. Regarding parity and menopausal status, most of the patients in both groups were grand multiparas and postmenopausal, with a higher percentage, which was not statistically significant. Abnormal vaginal bleeding was the most common presenting symptom, with the remainder of the patients presenting with other less common symptoms with percentages of only 1.9% and 20.4% for type I and II, respectively. This observation was considered statistically significant, as it is demonstrated in Table I.

A comparison of different tumour characteristics between the two groups is illustrated in Table II below. The presence of LVSI, high-grade tumour differentiation and positive peritoneal cytology for malignancy were obviously evident and statistically significant in type II patients with non-endometrioid cancer, which reflects its aggressiveness at presentation. In spite of the high percentage of cases with deep invasion of half or more of the myometrium in type II in comparison to type I (71.4% and 45.2%, respectively), its P-value was 0.004, which is not considered statistically significant.

Different modalities of primary treatment and adjuvant therapies that were provided for the patients are demonstrated in **Table III** below.Total abdominal hysterectomy with or without removal of adjacent lymph nodes or omentum was the most commonly used modality of primary treatment among both groups. Surgery was performed for 87.9% of patients with type I tumours as compared to 71.4% for type II tumours. Simple abdominal hysterectomy with bilateral salpingo-oophorectomy was performed in more than half of the type I cases compared to 14.3% for the type II cases with a P-value < 0.001. The addition of lymphadenectomy plus or minus omentectomy to the previous procedure occurred in 71/214 cases (33.2%) of type I disease and 28/49 cases (57.1%) of type II disease. Pelvic radiotherapy as a primary treatment was received by 6.1% of type I patients, with no cases for type II patients. Chemotherapy with or without radiotherapy was used for 20% of type II cases in comparison to only 3.7% of type I cases (P < 0.001). Hormonal and palliative care were not considered widely for primary treatment.

Regarding adjuvant therapy, 43.1% of endometrioid tumour cases required no further treatment, 43.1% required radiotherapy alone and 4.8% (nine cases) required chemotherapy alone. Seventeen cases out of 188 cases (9%) required both radiotherapy and chemotherapy (P = 0.02). Contrary to type I tumours, only three

cases of type II non-endometrioid cancer (8.6%) required no further adjuvant treatment, whereas 60% of them received chemotherapy, 8.6% received radiotherapy and 22.9% necessitated both modalities.

Table IV compares the stage of tumour and survival rate between the two groups. Early stage disease (stages I and II) was diagnosed among 84.1% of type I patients, while late stage disease (stages III and IV) was diagnosed among 28/49 (57.1%) of type II patients. The most common stage at the time of diagnosis was stage one for type I disease (75.3%) as compared to stage four for type II disease (42.9%) ($P < 0.001$). Ninety-seven out of 107 cases (90.7%) of type I disease showed more than 5 years of survival compared to 14/23 cases (60.9%) of type II disease ($P < 0.001$), which is considered statistically significant.

Table I: Patient characteristics

Characteristics		**Type I (214/263) (81.4%)**	**Type II (49/263) (18.6%)**	**X^2**	**P-value**
Age	**≤50**	62 (29.0%)	5 (10.2%)	7.40	0.007
	>50	152 (71.0%)	44 (89.8%)		
Parity	**0-2**	46 (21.5%)	6 (12.2%)	2.2	0.1
	≥3	168 (78.5%)	43 (87.8%)		
Menopause	**Pre**	26 (12.1%)	7 (14.3%)	0.17	0.7
	Post	188 (87.9%)	42 (85.71%)		
Presenting symptoms	**Vaginal bleeding**	210 (98.1%)	39 (79.6%)	27.2	<0.001
	Other	4 (1.9%)	10 (20.4%)		

Table II: Tumour characteristics

Characteristics		**Type I (N= 188) N (%)**	**Type II (N=35) N (%)**	**X^2**	**P-value**
LVSI*	**Positive**	25 (13.3%)	19 (54.3%)	31.30	<0.001
	Negative	163 (86.7%)	16 (45.7%)		
Myometrial invasion	**<50%**	103 (54.8%)	10 (28.6%)	8.11	0.004
	≥50%	85 (45.2%)	25 (71.4%)		
Grade	**1**	96 (51.1%)	-		N/A
	2	72 (38.3)	-		N/A
	3	20 (10.6)	35 (100%)	4.1	<0.001
Cytology	**Positive**	24 (12.8%)	25 (71.4%)	59.2	<0.001
	Negative	164 (87.2%)	10 (28.6%)		

*LVSI:lymphovascular space invasion

Table III: Primary and adjuvant therapies

Characteristics			Type I N/Total (%)	Type II N/Total (%)	X^2	P-value
Primary treatment	Surgery	TAH+BSO	117/214 (54.7%)	7/49 (14.3%)	26.1	<0.001
		TAH+BSO+ LND± Oment	71/214 (33.2%)	28/49 (57.1%)	9.8	0.002
	Radiotherapy alone		13/214 (6.1%)	0/49 (0%)	1.2	0.08
	Chemotherapy ± Radiotherapy		8/214 (3.7%)	10/49 (20.4%)	17.4	<0.001
	Hormonal		1/214 (0.5%)	0/49 (0%)	1.2	0.6
	Palliative		4/214 (1.9%)	4/49 (8.2%)	5.4	0.02
Adjuvant therapy	No therapy		81/188 (43.1%)	3/35 (8.6%)	14.9	<0.001
	Radiotherapy alone		81/188 (43.1%)	3/35 (8.6%)	14.9	<0.001
	Chemotherapy alone		9/188 (4.8%)	21/35 (60%)	77.3	<0.001
	Both		17/188 (9.0%)	8/35 (22.9%)	5.7	0.02

*TAH: Total Abdominal Hysterectomy, BSO: Bilateral Salpingo-oophorectomy, LND: Lymphadenectomy, Oment: Omentectomy

Table IV: Stage and survival

Characteristics		Type I N/Total (%)	Type II N/Total (%)	X^2	P-value
Stage	I A	105/214 (49.1%)	9/49 (18.4%)	15.3	<0.001
	I B	56 /214 (26.2%)	10/49 (20.4%)	0.70	0.4
	II	19/214 (8.9%)	2/49 (4.1%)	1.2	0.3
	III	16/214 (7.5%)	7 /49 (14.3%)	2.3	0.1
	IV	18/214 (8.4%)	21/49 (42.9%)	37.5	<0.001
Survival	>5 years	97/107 (90.7%)	14/23 (60.9%)	13.5	<0.001

Discussion

The most widely accepted model to divide ECs into type I and type II was based on differences in metabolic and endocrine factors. This model had been proposed by Bokhman et al. [4].

In our study, type I EC accounted for the majority of 214 cases (81.3%), while type II EC accounted for 49 cases (18.7%). These findings are considered similar to previously published data that shows endometrioid type accounting form the majority of ECs [5], and a study in the Middle East recently performed in Egypt concluded nearly similar results with 73.1% for type I ECs and 26.9% for type II ECs [12].

ECs share many risk factors, such as parity, age of menarche, use of oral contraceptives, cigarette smoking and diabetes. While body mass index tends to affect the incidence of type I [13] more , high-grade endometrioid tumours and type II tumours have the same risk factor patterns [7] . Age was considered the most common risk factor for type II EC [14].The majority of patients were aged between 50 and 65 years at the time of primary diagnosis, according to a study done by Prudie et al. [16].Our data showed that the mean age for diagnosis of type I disease was 52.1 years as compared to 61.8 years for type II disease. Nearly a 10-year difference in mean age was observed. This is in agreement with other previous reports[12,16]. In addition, many patients with high-grade EC were of advanced age compared to those with type I disease [7] . Another study reported that women with type II EC were more likely to be older at diagnosis, of non-white race, have a history of additional primary tumours and less likely to be obese [5] .

Although parity has been well documented as having a negative correlation with the incidence of EC [17,18], our data showed the opposite finding, with the majority of our patients having three or more children at the time of primary diagnosis with EC. No statistically significant difference was noted between both studied groups regarding the effect of parity on both types of EC. In one study, 91.8% of type I cases and 94.4% of type II cases presented during the postmenopausal period [12], and our data is in accordance, as about 88% of type I patients and nearly 86% of type II patients were postmenopausal.

The main symptom of EC is abnormal uterine bleeding (AUB), although occasionally, women with EC can present with abnormal findings on cervical cytology without having any symptoms. It is reported that about 75-90% of women with EC present with AUB [19,20], which is consistent with our results. Nevertheless, 20% of our patients with type II EC presented with symptoms other than bleeding. This can be explained by the aggressive nature of this cancer and tendency for fast distal metastasis.

In this study, there was no difference between the two EC subtypes regarding MI, which showed statistical non-significance (P = 0.004). This could be attributed to the fact that type II EC has been shown to metastasize without deep MI [21].

ECs are primarily graded based on their architecture according to the World Health Organization and International Federation of Gynecology and Obstetrics (FIGO)[22] as follows:

- Grade 1: less than 5% non-squamous or non-morular solid growth pattern
- Grade 2: 6% to 50% non-squamous or non-morular solid growth pattern
- Grade 3: more than 50% non-squamous or non-morular solid growth pattern

By definition, all type II ECs are considered high grade tumours. The serous type is usually a papillary or glandular tumour. The nuclei are classically defined as “high grade” [23], while endometrial clear cell carcinomas are rare. In our study, all type 2 EC II cases showed high grade architecture, and the same

findings were reported in a study by Creasman et al. who reported that type II EC was mostly diagnosed at an advanced stage with a high grade tumour [24].

The standard treatment for endometrial adenocarcinoma is surgery that includes a hysterectomy with bilateral salpingo-oophorectomy. Although performing omentectomy and selective pelvic and para-aortic lymphadenectomy is an essential part of surgical staging for type II ECs, its role for type I ECs remains controversial regarding overall and recurrence-free survival according to a large randomized controlled study (ASTEC trial) [25]. Another retrospective study (SEPAL study) reported a significant improvement in overall survival after performing both pelvic and para-aortic lymphadenectomies compared to those with pelvic lymphadenectomy only among patients with high and intermediate risks of recurrence involving cases of type II EC [26]. In our study, primary surgery was performed for 87.9% of type I EC cases and around 38% of them underwent omentectomy and lymphadenectomy compared to 70.4% for type II EC cases, of which 80% had omentectomy and pelvic lymphadenectomy. This difference in surgical approach can be related to the advanced tumour stage at the time of primary diagnosis for type II EC, which required primary chemotherapy for about 20% of our cases. Primary radiotherapy was required for 6.1% of type I EC cases, and this was attributed to cases that have been unfit for primary surgery due to associated medical co-morbidities, especially cardiovascular conditions.

Our data showed that peritoneal fluid cytology was positive in 71% of type II EC cases compared to only 13% in type I EC cases. This finding has been explained by many authors. Horn LC et al, wrote that the serous type spreads intra-abdominally like ovarian cancer [27], while Di Cristifano and Ellenson LH, mentioned that metastases happen at an early stage and present at the diagnosis for serous types of EC [28]. According to Chen et al., during diagnosis, hysteroscopy highly increases the probability of positive cytology [29]. This fact can explain the high number of positive peritoneal cytologies in our study, as our hospital uses hysteroscopy as the standard diagnostic tool for abnormal vaginal bleeding.

A study in Eygpt by Abd El-Wahed et al. revealed that 83.7% of type I EC cases were diagnosed at an early stage (stages I and II) compared to only 16.3% of cases at a late stage (stages III and IV) [12]. Another study showed it was 70% for early stage and 30% for late stage[30]. Our numbers were very similar to those published in the literature. This high detection rate in type I disease may be explained by the presentation of vaginal bleeding among those patients whose early diagnostic endometrial sampling was required. Regarding type II EC, a study by Vogel et al. reported that 40.9% of patients were diagnosed with stage I disease, 6.8% with stage II disease and 52.3% with stage III and IV disease [31]. A result that was similar to our data.

The protocol of adjuvant treatment for EC was published by the Gynecology Oncology Group (GOG) study where treatment depends on type, stage and grade of disease at initial diagnosis ²4. The best predictive factor for the need of adjuvant treatment might be the presence of lymphovascular invasion and stage of tumour [32]. Our data showed that there was not at the time indicated for adjuvant treatment in 43% of type I EC cases compared to only 8.6% of type II EC cases. Those numbers were exactly similar to those cases that required adjuvant radiotherapy. Although the published data (GOG study 33) showed that adjuvant radiotherapy is associated with a decrease in local recurrence, it was not associated with improvement in the overall survival rate, as shown by a large prospective clinical trial [33].

Adjuvant chemotherapy was indicated at that time for about 5% of type I EC cases compared to 60% of type II EC cases, as reported by our study where adjuvant chemotherapy had no role in early stage type I EC. According to a large retrospective study, patients with type II EC showed a significant reduction in recurrence with the addition of adjuvant platinum-based chemotherapy [34]. In our results, both adjuvant radiotherapy and chemotherapy were recorded among 9% of type I EC cases compared to 23% of type II EC cases. It is noteworthy that one study showed that the addition of any adjuvant treatment for patients with type II EC in early stages can lead to a significant improvement in overall survival [31].

In our study as well as many authors, patients with type I EC who maintained follow-up (97/107) showed more than 5 years of survival, accounting for 90.7% survival compared to 60.9% for II EC[35] type II EC. This may be related to the advanced stage at the time of primary diagnosis for type. Furthermore, another study reported that relapses occur among more that 50% of patients with type II EC [14], and many authors have reported that, although type II EC represents 10-20% of all ECs, it causes more than 40% of all EC deaths. [4 ,5 ,10 ,28].

Conclusion

Among Jordanian women, type I EC is more common. Type I endometrioid adenocarcinoma is diagnosed at an early stage, occurs at a younger age and shows a better response to treatment with a higher survival rate than type II EC.A future study can be designed using molecular/cytogenetic testing for EC detection.

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