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Retrospective Clinico-epidemiological Study of Endometrial Carcinoma, Mansoura Experience

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Authors' contributions

This work was carried out in collaboration among all authors. Author AAFH designed the study, wrote the protocol and the draft. Author FME performed the statistical analysis, managed the literature searches and wrote the draft of the manuscript . Authors RMAL, AMMNE, AH managed the literature search, participated in writing the draft and revised the whole work. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Determining epidemiological characteristics and treatment outcome of endometrial carcinoma (EC) patients treated at Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt from Jan 2000 to Dec 2013 inclusive.
Study Design: Retrospective study.
Place and Duration of Study: Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt.
Methodology: Clinical data of 226 EC patients were retrospectively abstracted from the records. Data collected included presenting symptoms, detailed examination and investigations, the treatment protocol, and the outcome.
Results: Post-menopausal females were 183 (81%). The incidence of disease was 75.7% among cases with BMI 30-39.9. Forty-two (18.6%) were diagnosed with positive family history.

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Postmenopausal bleeding was the most common presenting symptom (79.6%). Endometrioid adenocarcinoma was the most common pathology (85.4%) and 48 (21.2%) were diagnosed as grade III.Eighty-four (37.2%) were stage IB and 62 (27.4%) were stage 1A.EC was classified into Low-risk cases (FIGO 2009 stage IA, grade 1 or 2, of endometrioid type histology, intermediate-risk cases (stage IA grade 3 endometrioid EC&IB grade 1,2) and high-risk cases(FIGO stage IB of grade 3 or non-endometrioid histology, stage II, and any stage with non-endometrioid histology). Most of our patients were intermediate risk [95 patients (42.1%)] followed by high risk [81 patients (35.8%)]. Adjuvant treatment was received by 183 patients (90% of whom were intermediate and high risk). Combined EBRT plus brachytherapy was not given to low-risk patients. The 5- year DFS & OS were 46.4% & 65.1% respectively.BMI, ECOG, tumour grade, staging, using EBRT plus VBT and using combined chemotherapy and radiotherapy were the significant prognostic factors.

Conclusion: The majority of our EC cases were obese post-menopausal women having early stages and intermediate-risk disease. Serious investigation of postmenopausal bleeding is a must and tailoring the therapy of EC based on the risk category is worthy.

Keywords: Endometrial cancer; clinico-epidemiological study; cancer uterus; female genital tract cancer; brachytherapy.

1. INTRODUCTION

Globally, endometrial cancer (EC) accounts for 4.8% of all cancers diagnosed in women [1]. It is the most common malignancy of the female reproductive tract in developed countries, and the second most common in developing countries [2]. In Egypt, corpus uteri cancer is ranked as the tenth most common cancer among women. Egypt is considered the lowest compared to other countries in the Middle East [3].

The peak of disease occurrence is between 55 and 70 years with an average age of 60. The incidence increases with the increase in body mass index (BMI), being diabetic or hypertensive and nulliparity [4-6]. Approximately 2%–5% of EC is associated with hereditary gene alteration. A smaller subset of sporadic cancers is associated with ageing and unique molecular changes, producing aggressive variants (serous/clear cell type) [7].

Most cancers of the endometrium are of endometrioid histology, followed by serous and clear cell types [8]. Tumour stage is determined according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system. The majority of EC cases are diagnosed at an early stage, with approximately 72% stage I, 12% stage II, 13% stage III, and 3% stage IV.

For early-stage disease, surgery alone or in combination with local therapy is generally curative. The standard surgical approach for stage I EC consists of total hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy [1]. Adjuvant radiation therapy is not recommended in low- risk patients (with stage IA grade 1–2 endometrioid EC) [9]. For patients with intermediate-risk factors (stage IA grade 3 endometrioid EC&IB grade 1,2), vaginal brachytherapy alone is preferred over EBRT, providing excellent vaginal control without impacting the quality of life [10]. On the other hand, in patients with high- risk disease (Stage IB grade 3, stage II & III endometrioid EC and tumours with unfavourable histologies), EBRT remains the standard treatment [11], however, the combination of adjuvant chemotherapy and radiation therapy seems most effective to maximize recurrence-free survival [1]. Patients with Stage IV disease are candidate for systemic chemotherapy [1]. Serous and clear-cell carcinomas are indeed aggressive and show higher rates of metastatic disease with lower 5-year survival rates, so they require complete staging [12]. The different risk categories differ in their prognosis [13,14].

2. MATERIALS AND METHODS

This was a retrospective study of 226 EC patients who were treated at Clinical Oncology & Nuclear Medicine Department, Mansoura University Hospital during the period from January 2000 to December 2013, inclusive. Data were collected from the patient's files and then analysed.

Patient eligibility criteria:

- Patient's age >18 years.
- Pathologically proven EC.

- No renal or liver impairment.
- No associated other malignancy.

A clinical sheet for all cases was designed and the following data were collected:

1. Clinical assessment of patients:

a. History: Age, parity, menopausal status, family history, medical history, use of hormone replacement therapy (HRT), and patient complaints.
b. Clinical examination included determination of body weight and calculating BMI (body weight in kilograms divided by the square of height in meters). Assessment of the general condition of the patient was through the Eastern Cooperative Oncology Group (ECOG) scale. Detailed general and gynaecological examination were documented.

2. Investigations:

a. Lab investigations: complete blood count (CBC), kidney functions, liver functions, and glucose level.
b. Radiological investigations: Transvaginal us (TVUS), MRI of abdomen &pelvis, and CT chest to exclude distant metastasis.
c. Pathological evaluation: Detailed macroscopic and microscopic details of the surgical specimen with the definition of grading and staging.

3. Treatment options:

a. Surgery:

- Total abdominal hysterectomy with bilateral salpingo-oophorectomy with or without complete staging.
- Biopsy only if inoperable tumour.

b. Radiotherapy(RTH): either

*External beam radiotherapy (EBRT), which may be

1. Postoperative if there were high-risk pathological features.
2. Palliative for inoperable disease or local recurrence.

EBRT dose was 45–50 grey in 25–28 daily fractions using 6–15 MV photon beams, 5fractions/ week. The target volume is defined by GTV of the entire uterus in inoperable cases. CTV includes vaginal cuff, obturator nodes, external, internal and common iliac nodes. The planning target volume is calculated as CTV plus 0.5–1 cm.

*Brachytherapy either alone or with EBRT.

A vaginal cylinder of the largest feasible diameter was applied. The radiation was delivered with high dose rate radiotherapy.

c. ChemotherapyCTH): either

1. Postoperative: in the serous, clear cell, and high- risk endometrioid histology.
2. Palliative chemotherapy: was given to advanced, metastatic and inoperable cases.

Regimens were platinum-based as carboplatin (AUC 5-6) given by intravenous infusion over 1hour plus taxol (175 mg/m2) given by intravenous infusion over 3 hours every 3 weeks. Moreover, the combination between cisplatin (50 mg/m2) given at d1 by intravenous infusion over 1 hour and doxorubicin (60 mg/m2) given by intravenous infusion over 10 minutes at d1 every 3 weeks was used as well.

4. Response assessment:

The response was assessed after 2-3 cycles in advanced and metastatic EC patients according to Response Evaluation Criteria in Solid Tumour (RECIST). The toxic effects of the treatment were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

5. Follow up:

Clinical examination was done every 3-6 months for 2-3 years then annually. Imaging was performed as clinically indicated.

Endpoints of the study were the determination of treatment toxicity, survival, and prognostic factors.

Disease-free survival (DFS) was calculated in all patients from the date of complete cure till the date of recurrence, death from any cause or last follow up if no recurrence or death occurred.

Overall survival (OAS) was defined as the time from diagnosis till death (including deaths with or without recurrence) or lost follow up.

Progression-free survival (PFS) was the length of time during and after the treatment of cancer, that a patient lives with the disease without getting worse.

Statistical analysis: Quantitative data were summarized as medians & minimum-maximum values, while qualitative data as percentages. Comparisons of group medians were done using the Mann Whitney U test (z test), and Kruskal-Wallis test (χ^2) while comparisons of percentages were done by Chi-square test. TUKEY correlation test was used to correlate the risk factors with the different pathological types of EC.

Survival of patients was displayed by Kaplan-Meier survival curve. Multivariate analysis was performed using a Cox regression analysis using the survival predictors that showed significance in the univariate analyses. The results were considered significant if the p-value was ≤0.05. All statistical analyses were performed using a software tool (SPSS 15.0).

3. RESULTS

This retrospective study enrolled 226 patients diagnosed with EC who were registered at the Clinical Oncology and Nuclear Medicine Department of Mansoura University Hospital in the period between January 2000 and December 2013 inclusive.

Patients and tumour characteristics: The different patients and tumour characteristics are displayed in Table 1. The median age was 61 with an age range from 28 to 78 years. Post-menopausal females were 183 women (81%).

Among all patients, 62 patients (27.4%) were nulliparous; whereas 128 patients (56.6%) had 3 children or less.

The incidence of disease was 75.7% among those with BMI ranging from from 30-39.9 Kgm/m2.

Most of the patients had medical comorbidities, 111 patients (49.1%) were hypertensive, 126 patients (55.8%) were diabetic, and 24 patients (10.6%) were cardiac.

Regarding using HRT, it was not clear in the records of 126 patients (55.8%) whether they received HRT or not, while only 34% of cases were reported to be on HRT at time of disease diagnosis.

Positive family history was documented in only 42 patients (18.6%).

Most of the patients in our study presented with good performance status (89.5% were less than ECOG2). Postmenopausal bleeding (PMB) was the most common symptom (79.6%).

As regard to histopathological types, endometrioid adenocarcinoma was the most common (85.4%), followed by serous carcinoma (7.1%). Figs. 1 and 2 represent the different pathological types included in the manuscript. Grade II was the commonest [116 patients (51%)]. According to the FIGO System, stage I was the commonest (64%). Intermediate- risk and high –risk patients represented 42.1% and 81% respectively.

Figs. 3, 4 and 5 represent the MRI details of one of the cases.

Correlation of the different risk factors with the different types of the pathology of EC is shown in Table 2.

Treatment modalities: Two hundred and eight patients (92%) underwent radical surgery. Lymphadenectomy was performed in 44 patients (21%). Adjuvant treatment whether radiotherapy or chemotherapy or combined was received by 183 patients (90% of whom were intermediate and high risk). Combined EBRT plus brachytherapy was not given to low-risk patients, however, it was given to 20% and 31% of the intermediate and high –risk categories respectively. Detailed treatment modalities are shown in Table 3.

Eighteen patients didn't undergo surgery and so received either palliative chemotherapy (10 patients) and/or radiotherapy (8 patients). Ten patients developed disease progression while on first-line treatment and started a second line. Eight of those progressed and 2 patients were stable. Response to first and second-lines of CTH is shown in Table 4.

Table 5 shows treatment failure patterns. Fifty-four patients (23.9% of all study population) developed either local (48.2%) or distant

recurrence (51.8%). Lymph nodes were the most common site of metastasis (33% of cases with failure). Forty-five percent of the failures were in stage 3. At the end of the study, one hundred twenty-four patients (54.9%) died, while 102 (45.1%) were still alive.

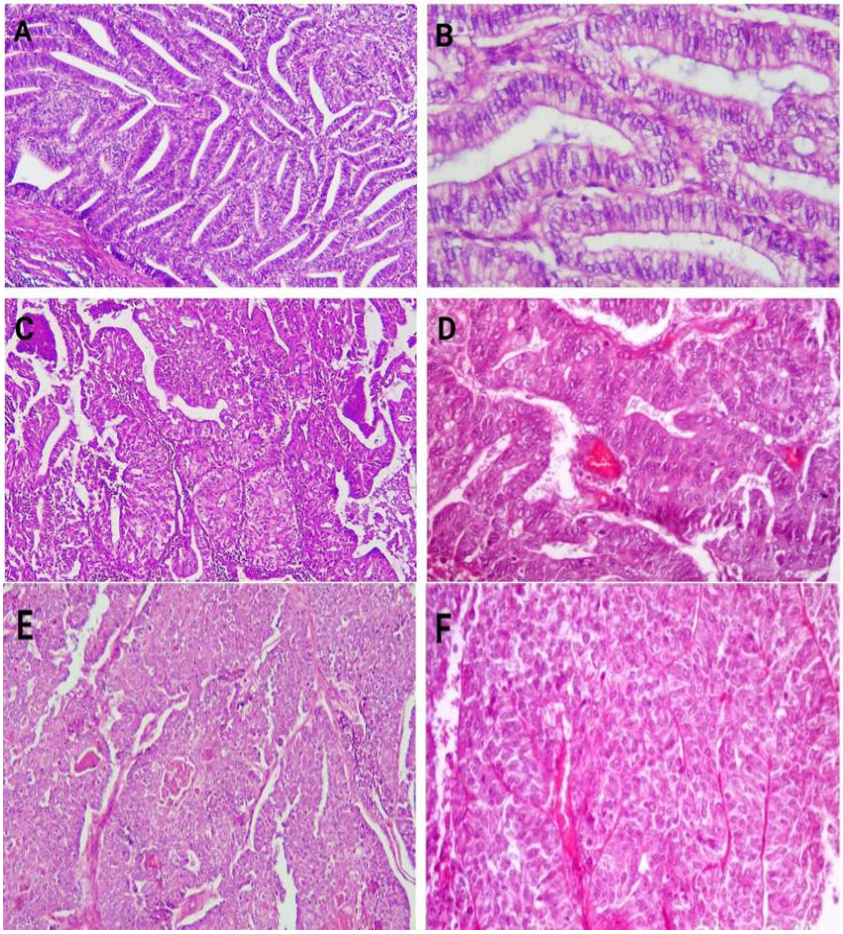
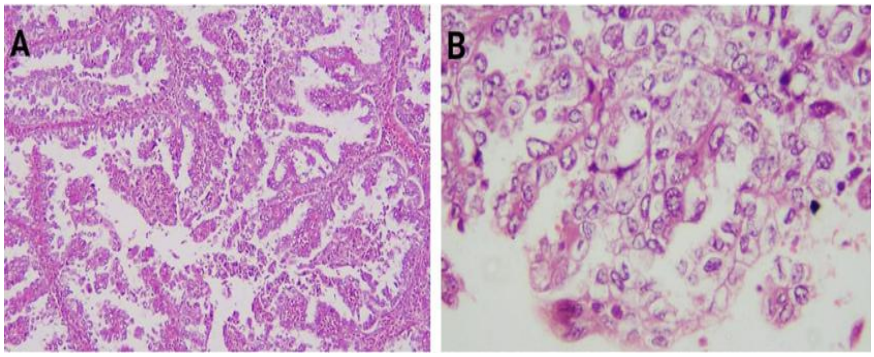


Fig. 1. Endometrioid carcinoma. A, B: FIGO grade I endometrioid carcinoma, formed predominantly of glandular structures in more than 95% of the tumour with low-grade cytological features (H&E, x200,x400). C, D: Grade II endometrioid carcinoma showing glandular differentiation with small solid areas occupying less than 50% of the tumour (H&E, x100,x200) E, F: A case of grade III endometrioid carcinoma, formed predominantly of solid sheets occupying more than 50% of the tumour (H&E, x100, x200)



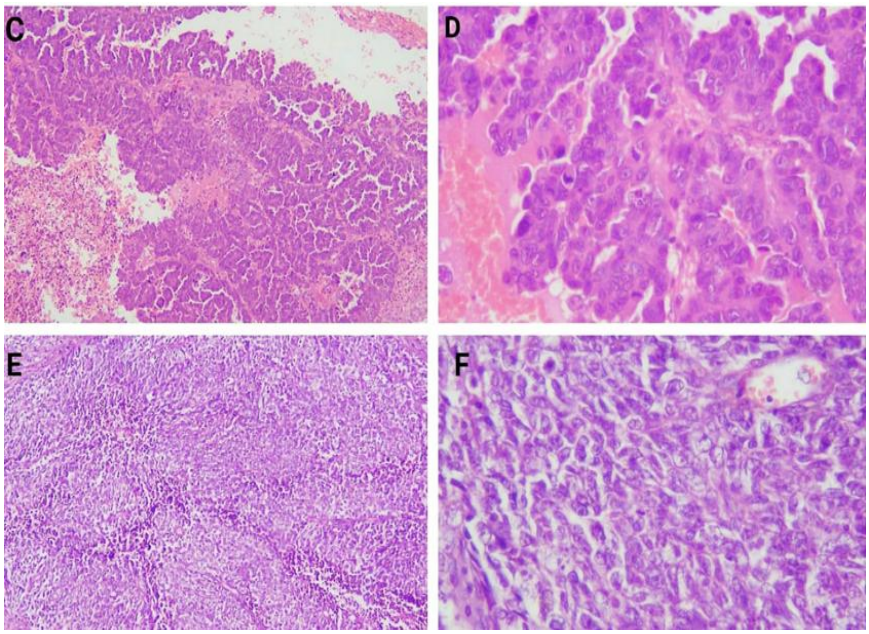


Fig. 2. Non-endometrioid carcinoma: A, B: Clear cell carcinoma tubulocystic papillary pattern. The papillae are covered by cuboidal cells with clear cytoplasm and high-grade nuclei with some hyaline globules (H&E, x200,x 400). C, D: Serous carcinoma: Papillary structures with extensive budding and tufting covered by highly atypical epithelial cells with frequent mitotic activity (H&E, x100,x400). E, F: Undifferentiated endometrial carcinoma formed of monotonous discohesive cells with vesicular nuclei and frequent mitotic activity (H&E, x200, x400)

Table 1. Patient and tumour characteristics

Variable	Number (226)	Percentage (%)
Age		
≥60y	135	59.7
<60y	91	40.3
Mean ± SD	59.52 ± 10.07	
Median (Range)	61 (28 – 78)	
Menopausal status		
Post-menopausal	183	81.0
Pre-menopausal	43	19.0
Parity		
Nulliparous	62	27.4
≤3	128	56.6
>3(grand multipara)	20	8.8
Not mentioned	16	7.1
Mean ± SD	1.38 ± 2.21	
Body mass index (BMI)		
Underweight	9	4
Normal	20	8.8
Overweight	26	11.5
Obese	171	75.7
Mean ± SD	36.75 ± 7.93	
Medical comorbidities		
Diabetic	126	55.8
Hypertensive	111	49.1
Cardiac	24	10.6
Normal	11	4.9

Variable	Number (226)	Percentage (%)
Hormone Replacement Therapy		
Not assessed	126	55.8
Yes	77	34
No	23	10.2
Family History		
Negative	140	62
Positive	42	18.6
Not assessed	44	19.4
ECOG		
1.00	153	67.7
0.00	48	21.2
2.00	23	10.2
3.00	2	0.9
Symtoms at presentation		
Post-menopausal bleeding	180	79.6
Pre-menopausal bleeding	46	20.4
Abdominal pain	21	9.3
Other symptoms	6	2.7
Histo-Pathologic types		
Type (I) Endometrial carcinoma		
Endometrioid adenocarcinoma	193	85.4
Type (II) Endometrial carcinoma		
Serous carcinoma	16	7.1
Clear cell carcinoma	13	5.8
Undifferentiated carcinoma	4	1.8
Grade		
I	62	27.4
II	116	51.4
III	48	21.2
Risk		
High- risk	81	35.8
Intermediate- risk	95	42.1
Low- risk	50	22.2
Surgical staging (FIGO)		
IA	62	27.4
IB	84	37.2
II	40	17.7
IIIA	22	9.7
IIIB	5	2.2
IIIC	7	3.1
IVA	4	1.8
IVB	2	0.9

Table 2. Correlation of risk factors with the pathology types(the first 2 factors are presented as mean and SD while the rest are presented by numbers)

Risk factor	Endometrioid pathology	Non-endometrioid pathology	*P*-value
Age(presented as mean and SD)	59.7+/-9.9	58.3+/-11.1	.4
BMI(presented as mean and SD)	33.9+/-13.3	31.4+/-10.4	.3
Hypertension(presented as	110	14	.2
Diabetes	90	18	.06
Cardiac disease	22	0	.05
Postmenopausal	156	24	.07

There was no significant difference between the different pathological types as regards the correlation with the risk factors except cardiac disease

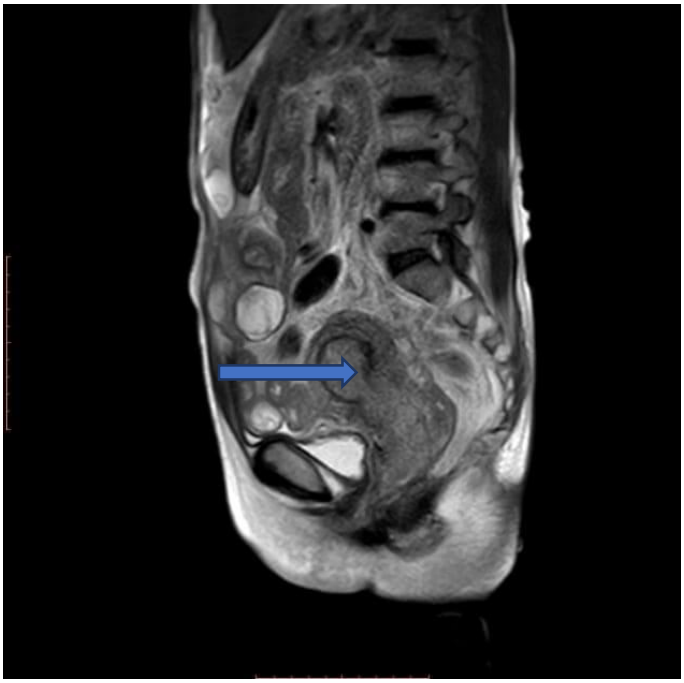


Fig. 3. Non-contrast sagittal T2 weighted image showing soft tissue mass filling the endometrial cavity(arrow), extending to the cervical canal with infiltration of the junctional zone

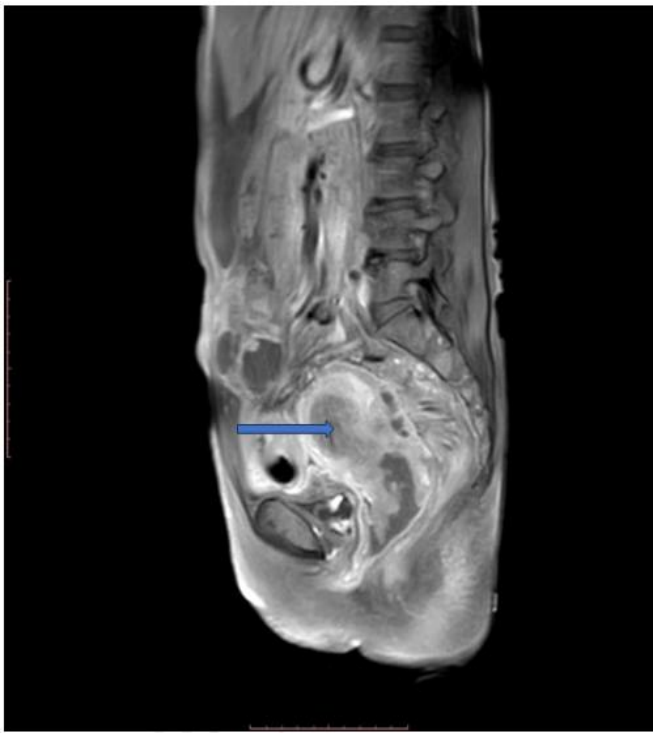


Fig. 4. Postcontrast sagittal T1 weighted image showing mild heterogeneous enhancement of the same mass (arrow)

Table 3. Treatment modalities

Variable	Number	Percentage (%)
Primary Treatment		
Surgery	208	92.0
Chemotherapy	10	4.4
Radiotherapy	8	3.5
Type of surgery		
Radical surgery +/- lymphadenectomy	208	92%
Biopsy	18	8
Lymph node dissection		
Lymphadenectomy not done	164	78.8
Lymphadenectomy done	44	21.1
Chemotherapy	37	(16.3%)
Adjuvant	27	11.9
Palliative	10	4.4
Regimen of Adjuvant		
Taxol& Carboplatin	26	11.5
Cisplatin& Adriamycin	11	4.8
No. of cycles		
6	19	8.4
3	8	3.5
4	6	2.6
1	4	1.8
Type of radiotherapy	146	64.6
Adjuvant	138	61.1
Palliative	8	3.5
Radiotherapy technique	146	64.6
External beam radiotherapy	112	49.5
Brachytherapy	16	7
Both	16	7

Table 4. Response to treatment in non- operable patients

Response to 1st line treatment	Number of patients (18 cases)
Complete response	0
Partial response	4
Stable disease	4
Progression	10
Response to 2nd line treatment	
Complete response	0
Partial response	0
Stable disease	2
Disease progression	8

Survival: The median DFS, OAS &PFS were 56.05, 66.08& 19.04 months respectively, While the 5- year DFS &OAS were 46.4%& 65.1% respectively (Figs. 6-8).

The 5-year DFS for low, intermediate& high- risk groups were 83%& 77% & 36% respectively. While the 5- year OAS were 82% & 62% & 37% respectively .

Correlation of prognostic factors with survival:

Univariate analysis: Age, menopausal status, parity, family history, HRTand hypertension did not show any significant impact on survival. On the other hand, DM had a statistical significant negative impact on both DFS and OS respectively (*P*=.043 & .006).

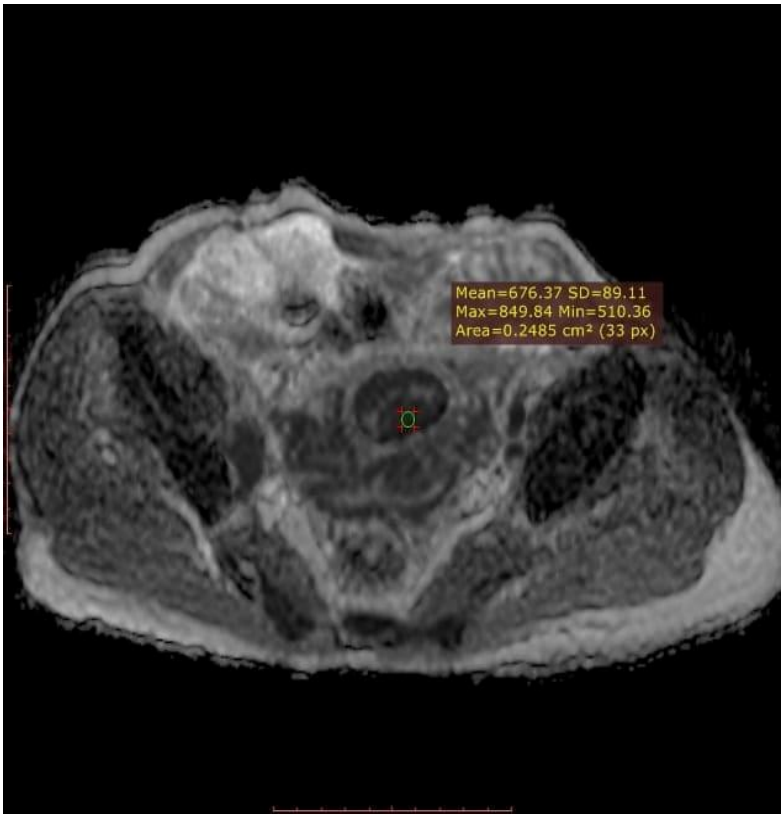


Fig. 5. The axial map showed restricted diffusion with ADC value about $0.67x10^{-3}$

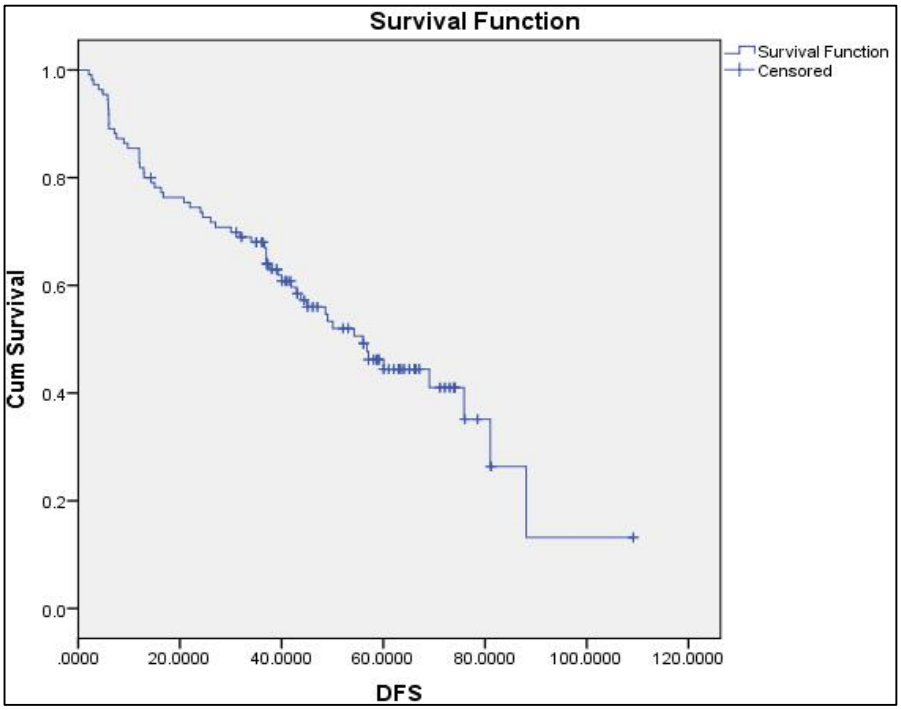


Fig. 6. Kaplan-Meier DFS survival curve of all studied population

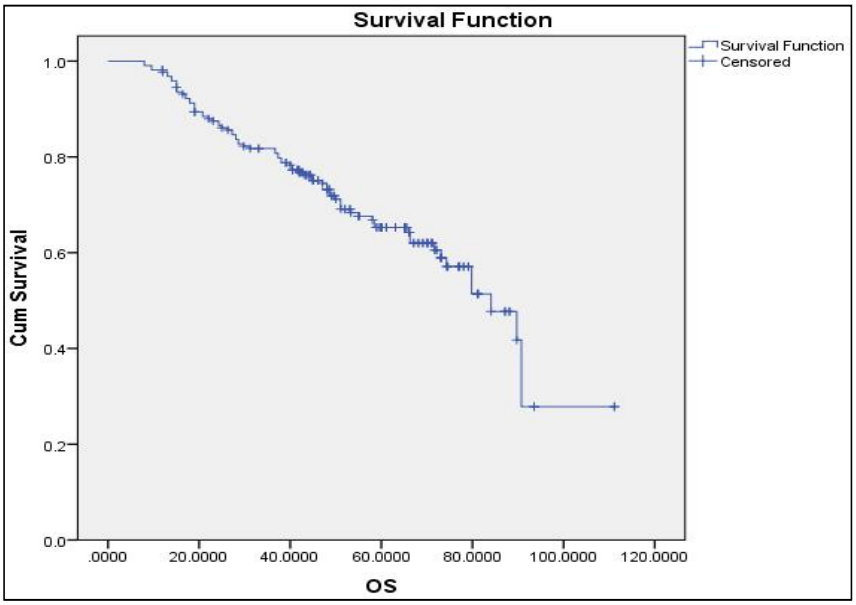


Fig. 7. Kaplan-Meier OAS curve of all studied population

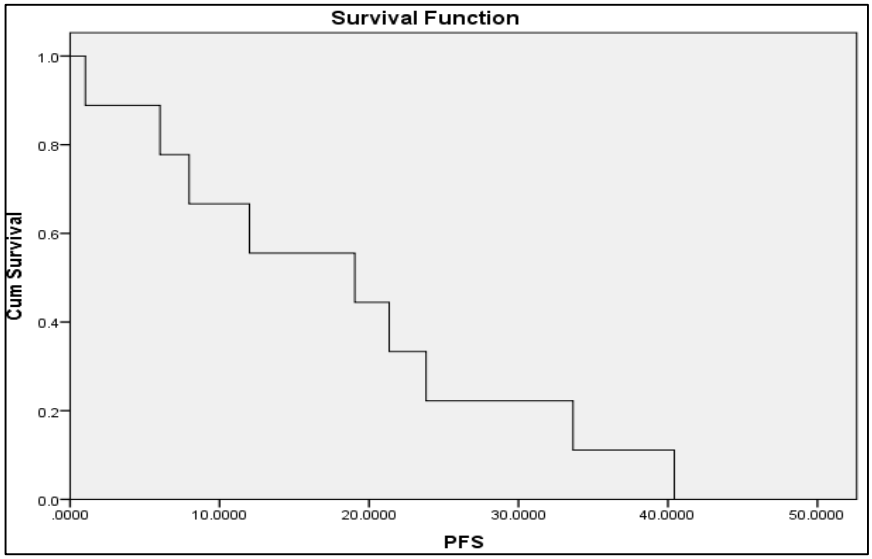


Fig. 8. Kaplan-Meier PFS curve

Patients who presented with abdominal pain either alone or associated with vaginal bleeding had statistically worse DFS & OS than those who presented with vaginal bleeding alone (*P* =.020 & .026 respectively).

Women with BMI ≥ 25 had significantly shorter OAS survival than those with normal BMI (*P* =.007).

ECOG 0 & 1 had significant superiority regarding DFS & OS over those with ECOG III (*P*= .001 & <.001) respectively.

Endometrioid adenocarcinoma significantly exceeded serous & clear cell carcinoma as regard DFS and OS (*P*=.001 & .016).

Women with low-grade tumours, early-stage disease and low- risk category had much better DFS & OAS (*P*<0.001) (Tables 6 and 7).

Table 8 showes that lymph node dissection didn't add any survival benefit on both DFS& OAS. Patients who received RTH showed better DFS&OAS than those who did not receive it (P-value =.004 & <.001) respectively. Moreover,

combined use of RTH+CTH caused better DFS&OAS than the use of each alone (P-value <.001).

Table 9 showes that the combined use of EBRT and brachytherapy caused better DFS survival than the use of each alone in only the high- risk category (p=0.032).

Multivariate analysis: In multivariate analysis, presentation by abdominal pain, tumour grade, stage, application of both EBRT & brachytherapy and the use of combined RTH and CTH caused a statistically significant impact on DFS (*p*=<0.05) (Table 10). On the other hand, body weight, ECOG status, presentation by abdominal pain, tumour grade, stage, the combined use of RTH and CTH had a significant impact on OAS (*p*,0.05) (Table11).

With our RTH, the most common toxicity was abdominal pain which occurred in 36 patients (25.7%) while diarrhoea and dysuria occurred in 30 patients (21.4%) as shown in Table 12. All such toxicities were of grade I & II.

The most common CTH toxicity was alopecia and haematological toxicities (each representing 32%). Fortunately, the different grade III toxicities did not exceed one-tenth of the cases (Table 13).

4. DISCUSSION

In this study, we retrospectively analysed the clinic-epidemiological features, treatment, and treatment outcome of 226 EC patients who were registered at Clinical Oncology & Nuclear Medicine Department, Mansoura University Hospitals in the period from January 2000 to December 2013 inclusive. The epidemiologic criteria of our study population were generally in harmony with worldwide reports. Around 59.7% of patients in our study were ≥ 60 years old with a median age 61 years and thus similar to the median age reported by Setakornnukul et al. [15] and Signorelli et al. [16]. Post-menopausal patients were more than two-thirds(81%) in our study which coincides with Gottwaldov et al. [17] & Van den Bosch and Mertens [18] respectively, who reported incidence figures of 87.3 & 70% respectively. Grand multipara represented 8.8% of our cases similar to Wan Nor Asyikeen et al. [19]. Seventy-five percent of our patients were obese with BMI >30 kg/m2, which agrees with different literature [20-22]. On the contrary, Jimñnez-López et al. [23] included 358 patients among whom only 31 patients (9%) were of BMI ≥ 30 kg/m2. Fifty percent of our study cases were diabetic or hypertensive coinciding with different literature [18,24-25]. Because most of our patients were from rural areas beside lack of data regarding HRT in many of the patient's records we were not able to assess the correlation between HRT and EC. Such correlations between HRT & EC were published [26-28]. Family history was not common in this study (62 % had negative family history)which is fitting with some reports [17,29] and contradicting with others [30]. Presentation mainly by postmenopausal bleeding, ECOG 1-2, type I EC, and high- risk category occurred but not in more than two-thirds of our cases which conforms with many literatures [15,19,23,24,31,32].

On follow up, 54 patients (23.9% of total cases) developed recurrence and the lymph nodes were the commonest site of failure which cope with different reports [17,23]. The recurrence rate was higher in our late- staged patients similar to Sasada et al. [33], Yen et al. [34].

Table 5. Treatment failure patterns among 54 cases with failure

Variable	Number	Percentage
Local recurrence	26	51.8%
Distant recurrence	28	48.2%
Sites of distant recurrence		
Lymph nodes	18	33%
Liver	10	18.5%
Omental	8	14.8%
Bone	8	14.8%
Lung	6	11.1%
Others	6	11.1%
Death		
Yes	124	54.9%
No	102	45.1%

Table 6. Univariate analysis of different prognostic factors affecting DFS

Parameter	Number	Disease-free survival (DFS)		
Age		**Median (Range)**	**P-value**	**HR**
<60	91	40.07 (2.66 – 81.15)		
≥60y	135	39.08 (2.07 – 109.14)	.803	1.402
Menopausal status				
Pre-menopausal	43	39.31 (2.66 – 81.15)		
Postmenopausal	183	40.76 (2.07 – 109.14)	.645	1.194
Parity				
Null-Para	62	41.74 (4.01 – 78.52)		
≤ 3	128	39.67 (2.07 – 109.14)		
>3	20	31.68 (4.84 – 73.06)	.829	0.955
Not assessed	16	36.05 (14.34 – 71.15)		
Hormone Replacement Therapy				
Not documented	126	40.93 (2.66 – 109.14)		
Yes	77	37.27 (2.07 – 81.15)		
No	23	45.1 (4.01 – 64.08)	565	1.027
Family history				
No	140	42.44 (2.07 – 109.14)		
Yes	86	33.06 (2.66 – 81.15)	.327	1.003
Hypertension				
No	115	39.08 (4.01 – 81.15)		
Yes	111	41.74 (2.07 – 109.14)	.372	0.787
Diabetes				
Yes	100	43.47 (2.66 – 109.14)		
No	126	37.04 (2.07 – 88.09)	.043	1.708
Presenting symptoms of the disease:				
-Post-menopausal bleeding				
Yes	180	41.42 (2.07 – 109.14)		
No	46	38.06 (2.66 – 81.15)	.275	1.117
-Premenopausal Bleeding				
No	180	41.42 (2.07 – 109.14)		
Yes	46	39.06 (2.66 – 81.15)	.275	1.097
-Abdominal pain				
No	205	40.76 (2.07 – 109.14)		
Yes	21	32.11 (5 – 52.07)	.020	1.663
Obesity& BMI				
Underweight	20	37.16 (6.02 – 67.11)		
Normal	9	41.74 (3.03 – 109.14)		
Overweight	26	36.66 (4.01 – 81.15)	.097	0.922
Obese	171	4.55 (2.07 – 53.09)		
ECOG				
0	48	36.7 (2.66 – 81.15)		
1	153	45.03 (2.07 – 109.14)	.001	1.399
2	23	16.74 (3.03 – 60.07)		
3	2	12.93		
Pathological types				
Endometrioid adenocarcinoma	193	41.74 (2.07 – 109.14)		
Serous carcinoma	16	15.28 (4.01 – 81.15)		
Clear cell carcinoma	13	7.58 (2.66 – 39.31)		
Undifferentiated carcinoma	4	32.70 (36.35 – 49.05)	<.001	1.336
Tumour grading				
I	62	47.04 (4.01 – 81.05)		
II	116	39.08 (2.07 – 109.14)		
III	48	27.80 (2.66 – 81.15)	<.001	1.047

Parameter	Number	Disease-free survival (DFS)		
Risk of disease				
Low-risk disease	50	58.09 (6.02 – 88.09)		
Intermediate risk disease	95	40.05 (2.07 – 109.14)		
High-risk disease	81	12.06 (2.66 – 81.15)	<.001	2.396
FIGO staging				
IA	62	54.28 (6.02 – 88.09)		
IB	84	40.09 (2.07 – 109.14)		
II	40	41.58 (2.66 – 81.05)		
IIIA	22	16.32 (5.82 – 56.78)		
IIIB	5	9.77 (6.02 – 12.93)	<.001	1.180
IIIC	7	15.03 (4.84 – 39.08)		
IV A	4	4.95 (4.01 – 7.58)		
IV B	2	7.48 (4.55 – 10.4)		

Table 7. Univariate analysis of different prognostic factors affecting OAS

Parameter	Number	Overall survival (OAS)		
Age		**Median (Range)**	**P-value**	**HR**
<60y	91	48.62 (4.01 – 93.52)	.252	1.534
≥60y	135	48.06 (5.0 – 111.15)		
Menopausal status				
Pre-menopausal	43	46.09 (4.01 – 93.52)	.863	1.468
Post- menopausal	183	48.55 (5.0 – 111.15)		
Parity				
Null-para	62	48.06 (12.01 – 88.13)	.396	
≤ 3	128	48.31 (4.01 – 111.15)		0.970
>3	20	44.05 (5 – 78.06)		
Not assessed	16	46.58 (16.38 – 73.13)		
Hormone Replacement Therapy				
Not documented	126	50.54 (9.57 – 111.15)	.193	
Yes	77	45 (7.96 – 93.52)		
No	23	55.03 (4.01 – 74.28)		1.021
Family history				
No	140	49.29 (4.01 – 111.15)	.493	1.007
Yes	86	45.10 (5.21 – 93.52)		
Hypertension				
No	115	48.06 (4.01 – 93.52)	.867	
Yes	111	48.55 (5.0 – 111.15)		1.678
Diabetes				
Yes	100	53.52 (4.01 – 111.15)	.006	2.074
No	126	47.07 (5.0 – 90.72)		
Primary presenting symptoms:				
-Post-menopausal bleeding				
Yes	180	48.31 (4.01 – 111.15)	.767	1.150
No	46	46.09 (5.21 – 93.52)		
-Premenopausal Bleeding				
No	180	48.31 (4.01 – 111.15)	.767	1.073
Yes	46	46.09 (5.21 – 93.52)		
-Abdominal pain				
No	205	48.55 (4.01 – 111.15)	.026	2.005
Yes	21	44.38 (5 – 53.29)		
Obesity& BMI				
Underweight	20	44.54 (11.94 – 71.09)	.007	
Normal	9	48.62 (5 – 111.15)		
Overweight	26	50.03 (4.01 – 93.52)		1.027
Obese	171	24.28 (5.21 – 60.07)		

Parameter	Number	Overall survival (OAS)		
ECOG				
0	48	45.58 (15.03 – 93.52)	<.001	
1	153	53.09 (7.96 – 111.15)		
2	23	36.68 (4.01 – 65.1)		1.075
3	2	18.98		
Pathological types				
Endometrioid adenocarcinoma	193	49.08 (5.21 – 111.15)	.016	1.290
Serous carcinoma	16	28.05 (4.01 – 93.52)		
Clear cell carcinoma	13	24.28 (9.21 – 84.08)		
Undifferentiated carcinoma	4	40.54 (46.05 – 55.03)		
Tumour grading				
I	62	59.70 (11.94 – 89.74)	.018	
II	116	48.06 (4.01 – 111.15)		1.050
III	48	41.14 (5.0 – 93.52)		
Risk of disease				
Low-risk disease	50	60.07 (11.94 – 90.72)	<.001	
Intermediate risk disease	95	49.36 (12.01 – 111.15)		2.093
High-risk disease	81	26.78 (4.01 – 93.52)		
FIGO staging				
IA	62	58.95 (11.94 – 90.72)	<.001	
IB	84	48.55 (12.01 – 111.15)		
II	40	49.13 (16.38 – 89.74)		
IIIA	22	40.36 (9.57 – 84.08)		
IIIB	5	18.98 (7.96 – 26.32)		1.151
IIIC	7	27.24 (7.96 – 49.08)		
IV A	4	6.48 (4.01 – 9.21)		
IV B	2	8.12 (5.21 – 11.02)		

Table 8. Effect of different treatment modalities on survival in univariate analysis

Treatment modality			DFS		OAS	
Lymph node dissection			**Median(range)**	**P value**	**Median(range)**	**P value**
No	164		41.9 (17.6 – 60.84)	.808	55.03 (27.19 – 82.86)	.795
Yes	44		45.03 (36.30 – 53.75)		71.67 (46.83 – 96.52)	
Radiotherapy						
Yes	146		41.84 (2.07 – 81.15)		51.05 (4.01 – 93.52)	<.001
No	80		29.77 (2.66 – 109.14)	.004	40.99 (7.96 – 111.15)	
Chemo-radiotherapy						
CTH or RT	Yes	138/27	12.06 (2.66 – 66.41)		27.65 (4.01 – 76.94)	<.001
RTH+CTH	No	14	45.03 (15.03 – 81.15)	<.001	65.27 (22.07 – 93.52)	

In this study, the 5-years OAS was 65.1%, this is similar to Craighead et al. [35] who reported a 5 – year survival of 65% but lower than the figure reported by Karateke et al. [36] (76.9%) and better than that of Jhingran et al. [37] (42%).This survival figures variability might be explained by different ratios of low risk versus the other risk categories and the variability of the health care services provided by the different nations.

Indeed, there is variability in the reported independently significant prognostic factors among the different publications. Age was not among the significant prognostic factors in our study similar to some literature [17,36,38] and contradicting others [19,23]. Menopausal status and parity were not proved of prognostic significance in our work similar to Nicholas et al [24] but unlike the results of Gottwald et al. [17]. Increased BMI but not diabetes had a prognostic impact in our study coping with several publications [24,39-42]. The endometriod pathology was not our most preferable pathology regarding prognosis unlike literature [1,31]. This might be due to the limited number of non endometiod cases. However, Craighead [35]

Table 9. Difference between the effect of the EBRT alone, brachytherapy alone, both EBRT and brachytherapy on survival in the different risk groups

RTH type	Number	DFS			OAS		
Low risk	**No**	**Median (Range)**	**HR**	**P value**	**Median (Range)**	**HR**	**P value**
External beam radiotherapy	10	60.07 (6.02 – 76.05)			68.09 (18.94 – 87.14)		
Brachytherapy	8	62.08 (40.44 – 70.06)	1.428	.153	70.09 (48.55 – 76.06)	0.714	.475
Intermediate risk							
External beam radiotherapy	56	41.09 (2.07 – 78.52)			51.09 (12.01 – 88.13)		
Brachytherapy	14	39.08 (38.06 – 75.89)			43.98 (42.63 – 79.80)		
Both	14	72.07	4.997	.082	79.08	2.959	.228
High risk							
External beam radiotherapy	30	36.97 (5.82 – 81.15)			42.01 (15.03 – 93.52)		
Brachytherapy	2	46.12			49.64		
Both	10	50.07 (36.97 – 66.41)	6.861	.032	58.42 (45.03 – 76.94)	2.789	.248

Table 10. Multivariate analysis of variables on DFS

Parameter		B	SE	P value	Odds ratio	95% of Odds ratio
Medical History	Diabetes	0.191	.314	.543	1.210	2.240-.654
ECOG	ECOG			.375		
	ECOG II	7.741	62.272	.901	2301.243	.000-2.333E+056
	ECOG III	7.222	62.272	.908	1368.588	.000-1.387E+056
Primary presenting symptoms	Abdominal Pain	-1.834	.629	.004	.041	.002-.676
Pathologic types	Endometrioid carcinoma	-.601	1.194	.614	.548	0.53-5.68
	Others	-3.823	5.750	.506		.000-1714.43
Tumour grade	Grade 1			.273		
	Grade 2	-1.059	.830	.202	.100	.006-1.616
	Grade 3	-1.212	.778	.030	.079	.006-.974
Risk	Low risk			.508		
	Intermediate risk	.292	1.652	.860	3.808	1.543-9.452
	High risk	1.082	1.082	.318	6.311	.992-40.156
Stage of disease	Stage IA			.172		
	Stage IB	-2.889	1.388	.037	.128	.011-1.463
	Stage II	-3.196	1.431	.025	2301.243	.000-2.333E+05

Parameter		B	SE	P value	Odds ratio	95% of Odds ratio
	Stage III	-2.305	1.421	.105	1368.588	.000-1.387E+056
	Stage IV	-2.537	1.281	.048	.160	.047-.548
Radiotherapy	EBRT			.927		
	Brachytherapy	.613	1.147	.401	.900	.095-8.529
	Both	-1.932	.620	.005	1.845	.548-6.216
Radiotherapy+chemotherapy		-.105	.691	.026	2.517	.650-9.750

Table 11. Multivariate analysis of variables on OAS

Parameter		B	SE	P value	Odds ratio	95% of Odds ratio
Medical History	Diabetes	.036	.254	.887	1.037	.630-1.706
Bodyweight	Underweight			.005*		
	Normal	1.337	.464	.004	.347	1.763-.068
	Over weight	1.842	.944	.051	.298	.065-1.367
	Obese	-2.053	1.242	.098	1.339	.053-34.151
ECOG	ECOG I			.036		
	ECOG II	-.972	.517	.060	.378	.138-1.042
	ECOG III	1.259-	.495	.011	.284	.108-.750
Primary presenting symptoms	Pain	-1.703	-1.703	.000	.182	.077-.431
Pathological types	Endomeriod	-.310	1.090	.776	0.733	.087-6.207
	Others	-2.344	1.887	.214	.096	.002-36.878
Tumour grading	Grade 1			.155		
	Grade 2	.344	.616	.577	1.410	.421-4.717
	Grade 3	-.143	.617	.040	.266	.258-2.905
Risk	Low risk			.666		
	Intermediate risk	-.816	1.373	.552	.442	.030-6.520
	High risk	-.042	1.018	0.967	.959	.130-7.059
Stage of disease	Stage IA			.043		
	Stage IB	-2.490	1.370	.069	.083	.006-1.215
	Stage II	-3.149	1.115	.005	.043	.005-.381
	Stage III	-3.058	1.202	.011	.047	.004-.495
	Stage IV	-3.273	1.241	.008	.038	.003-.431
Radiotherapy		-.658	.831	.122	.633	.354-1.130
Radiotherapy+chemotherapy		.293	1.213	.004	2.000	.362-11.052

Table 12. Radiotherapy toxicity (all are grade I or II)

	Number	Percentages
Abdominal Pain	50	35.7%
Diarrhoea	30	21.4%
Dysuria	30	21.4%
Constipation	14	10.0%
Skin Toxicity	12	8.6%
Other GIT symptoms	12	8.6%

Table 13. Chemotherapy complications

Types	Total	n= 37					
		Grade1		Grade 2		Grade 3	
		No	%	No	%	No	%
Leucopenia	12	6	16.6%	4	11.1%	2	5.1%
Anaemia	20	15	41.6%	4	11.1%	1	2.7%
peripheral neuropathy	26	16	44.4%	8	22.2%	2	5.5%
Emesis	30	10	27.8%	12	33.3%	3	8%
Alopecia	32	32	88.9%	-	-	-	-
Hypersensitivity	1	1	2.7%	-	-	-	-

similarly reported a non-significant effect of the pathological type.The prognostic impact of histologic grade was proved in our work and in other publications as well [31,36,38,43]. Similarly, FIGO staging had statistically significant prognostic effect similar to many reports [19,23,31].

The value of undergoing lymphadenectomy in EC is a matter of debate. Some literature proved improved survival in all stages of the disease as that of Gottwald et al. [17] and in the early stages of the disease as Wright et al. [44]. However, there were studies that reported no benefit [45,46]. In our study 78.8% of patients didn't undergo lymphadenectomy, so we were not able to assess its value.

Our multivariate analysis confirmed the statistically better DFS of the high- risk cases who received EBRT plus VBT which was proved previously by univariate analysis. This result coincides with that of Sorbe et al. [47] who studied 527 cases. Moreover, our multivariate analysis proved that combined use of RT and CTH had a beneficial impact on both DFS and OS exceeding the effect of any modality alone. This result coincides with several literature [14,16,48,49,50,51] which generally pointed out that this combined treatment modalities should be for risky EC cases and that their effect is mainly on the DFS .

Our study limitations were the retrospective nature and the limited application of brachytherapy.

5. CONCLUSION

Our epidemiologic criteria were similar to many published data. The 5- years DFS & OS were 46.4% & 65.1% respectively. Factors that affected DFS by multivariate analysis were presentation by abdominal pain, tumor grade, stage, and the combined use of EBRT plus brachytherapy or CTH plus RTH in the risky categories. Factors that affected OAS were body weight, ECOG, abdominal pain at presentation, grade, stage and combined CTH and RT in the risky categories. New molecular subgroups will support treatment personalization and new targeted therapies. A larger multicentre retrospective study is needed to define all the prognostic factors of the Egyptian women with EC.

CONSENT

Patients has given their informed consent for publishing.

ETHICAL APPROVAL

The Ethical Committee of Faculty of Medicine, Mansoura University approved the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. NCCN Clinical Practice Guidelines in Oncology: uterine Cancer. NCCN; 2018. Available:http://www.nccn.org
2. Van Nyen T, Moiola CP, Colas E, Annibali D, Amant F. Modeling endometrial cancer: Past, present, and future. Int J Mol Sci. 2018;19(8):2348-2352.
3. Alshahrani S, Soliman AS, Hablas A, Ramadan M, Meza J, Remmenga S, et al. Changes in uterine cancer incidence rates in Egypt. Obstetrics and Gynecology International. 2018;2018:1-10.
4. Onstad MA, Schmandt RE, Lu KH. Addressing the role of obesity in endometrial cancer risk, prevention, and treatment. J Clin Oncol. 2016;34(35): 4225-4230.
5. Pant A, Bristow R. Cancer of the uterine corpus. In: Joseph, H. K., Guile, M. & Bienstock, J. (Eds.) John Hopkins manual of genecology and obstetrics. 4th Ed. Philadelphia: Lippincott Williams & Wilkins. 2011;50.
6. Balasubramaniam G, Sushama S, Rasika B, Mahantshetty U. Hospital-based study of endometrial cancer survival in Mumbai, India. Asian Pac J Cancer Prev. 2013; 14(2):977-980.
7. Jayaraman M, Radhakrishnan R, Mathews CA, Yan M, Husain S, Moxley K, et al. Identification of novel diagnostic and prognostic miRNA signatures in endometrial cancer. Genes & Cancer. 2017;8(5-6):566-576.
8. Conlon N, Leitao MM, Abu-Rustum NR, Soslow R. Grading uterine endometrioid carcinoma. Am J Surg Pathol. 2014; 38(12):1583-1587.
9. Kong A, Johnson N, Kitchener HC, Lawrie T. Adjuvant radiotherapy for stage I endometrial cancer: An updated cochrane systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(21):1625-1634.
10. Nout RA, Smit VT, Putter H, Jürgenliemk-SchulzI M, JobsenJ J, Lutgens LCHW, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): An open-label, non-inferiority, randomised trial. Lancet. 2010;375(9717):816–823.
11. Randall M, Filiaci V, McMeekin D, Yashar CM, Mannel R, Salani R, et al. A phase 3 trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high-risk, early-stage endometrial cancer: A gynecology oncology group study. Int J Rad Oncol Biol Phys. 2017;99(5):1313.
12. Patni R. Current concepts in endometrial cancer. USA: Springer. 2017;30.
13. Martin-Hirsch PPL, Bryant A, Keep SL, Kitchener H, Lilford R. Adjuvant progestagens for endometrial cancer. Cochrane Database Syst Rev. 2011;6: CD001040.
14. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A gynecologic oncology group STUDY. Gynecol Oncol. 2004;92(3):744-751.
15. Setakornnukul J, Petsuksiri J, Wanglikitkoon S, Warnnissorn M, Thephamongkhol K, Chasilp Y, et al. Long term outcomes of patients with endometrial carcinoma treated with radiation - Siriraj Hospital experience. Asian Pac J Cancer Prev. 2014;15(5):2279-2285.
16. Signorelli M, Lissoni AA, De Ponti E, Grassi T, Panti S, Fruscio R. Adjuvant sequential chemo and radiotherapy improves the oncological outcome in high risk endometrial cancer. J Gynecol Oncol. 2015;26(4):284-292.
17. Gottwald L, Pluta P, Piekarski J, Spych M, Hendzel K, Topczewska-Tylinska K, et al. Long-term survival of endometrioid endometrial cancer patients. Arch Med Sci. 2010;6(6):937-944.
18. Van den Bosch A, Mertens H. Implementation of laparoscopic surgery for endometrial cancer: Work in progress. Facts Views Vis Obgyn. 2016; 8(1):23.
19. Wan Nor Asyikeen WA, Siti-Azrin AH, Che Jalil NA, Zin AAM, Othman NH. Median survival time of endometrial cancer patients with lymphovascular invasion at the Hospital Universiti Sains Malaysia. Malays J Med Sci. 2016;23(6):44-51.
20. Raglan O, Kalliala I, Markozannes G, et al. Risk factors for endometrial cancer: An umbrella review of the literature. Int J Cancer. 2019;145(7):1719-1730.

21. Jenabi E, Poorolajal J. The effect of body mass index on endometrial cancer: A meta-analysis. Public Health. 2015;129(7): 872-880.
22. Suskic A, Suskic SH, Opric D, Maksimovic S. Obesity as a significant risk factor for endometrial cancer. IJRCOG. 2016;5:(9): 2950-2951.
23. Jimñnez-López JS, Tejerizo-Garcia A, Álvarez-Conejo C, Guillen–Gamez C, Seoane-Ruiz JM, Perez-Sagaseta C, et al. Tumor recurrence and tumor-related mortality in endometrial cancer: Analysis in 276 patients. Indian J Cancer. 2015;52(4): 682-684.
24. Nicholas Z, Hu N, Ying J, Dodson M, Gaffney DK. Impact of comorbid conditions on survival in endometrial cancer. Am J Clin Oncol. 2014;37(2):131-134.
25. Saed L, Varse F, Baradaran HR, Moradi Y, Khateri S, Frigerg E, et al. The effect of diabetes on the risk of endometrial cancer: An updated a systematic review and meta-analysis. BMC Cancer. 2019;19(1):527.
26. Allen NE, Tsilidis KK, Key TJ, Dossus L, Kaaks R, Lund E, et al. Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European prospective investigation into cancer and nutrition. Am J Epidemiol. 2010;172(12):1394-1403.
27. Zaino R, Carinelli S, Ellenson L. Tumours of the uterine corpus: Epithelial tumours and precursors. WHO Classification of Tumours of the Female Reproductive Organs. 4th ed. Lyon, France: IARC Press. 2014;125.
28. Guinney J, Dienstmann R, Wang X, de Reynies, Schlicker A, Soneson C, et al. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015;21(11): 1350-1356.
29. Adekanbi AOA, Jimoh MA, Ajani Mustapha Akanji, Fawole Adeniran Olubukola. Endometrial cancer in Ibadan: Epidemiological and clinico-pathological Features-10 year review. New York Sci J. 2016;9(3):19-23.
30. Win AK, Reece JC, Ryan S. Family history and risk of endometrial cancer. Obstet Gynecol. 2015;125(1):89-98.
31. Pinar G, Ayhan A. Survival determinants in endometrial cancer patients: 5-years experience. Archives of Nursing Practice and Care. 2017;3(1):012-015.
32. Gao Y, Dai X, Chen L, Lee A, Tong M, Wise M, et al. Body mass index is positively associated with endometrial cancer in chinese women, especially prior to menopause. J Cancer. 2016;7(9):1169-1173.
33. Sasada S, Yunokawa M, Takehara Y, Ishikawa M, Ikeda S, Kato T, et al. Baseline risk of recurrence in stage I–II endometrial carcinoma. J Gynecol Oncol. 2017;29(1):e9.
34. Yen M-S, Chen T-H, Ke Y-M, Hsu K, Chen J, Yu M, et al. Clinicopathologic features and treatment outcomes in patients with Stage I, high-risk histology or high-grade endometrial cancer after primary staging surgery: A Taiwanese gynecologic oncology group study. J Clin Med. 2018; 7(9):254.
35. Craighead PS, Sait K, Stuart GC, Arthur K, Nation J, Duggan M, et al. Management of aggressive histologic variants of endometrial carcinoma at the Tom Baker Cancer Centre between 1984 and 1994. Gynecol Oncol. 2000;77(2):248-253.
36. Karateke A, Selcuk S, Asoglu MR, Namazov A, Tug N, Cam C, et al. Prognostic factors affecting survival in endometrial carcinoma. J Turk Soc Obstet Gynecol. 2012;9(1):42-46.
37. Jhingran A, Burke T, Eife P. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. Int J Radiat Oncol Biol Phys. 2003;56(2):1366-1372.
38. Bajracharya S, Juan F. Prognostic factors in endometrial cancer. Journal of Institute of Medicine. 2013;35(1):9-17.
39. Zanders MJ, Boll D, van Steenbergen L, Poll-France L, Haak H. Effect of diabetes on endometrial cancer recurrence and survival. Maturitas. 2013;74(1):37-43.
40. Arem H, Irwin ML. Obesity and endometrial cancer survival: A systematic review. Int J Obes (Lond). 2012;37(5):634-639.
41. Modesitt SC, Tian C, Kryscio R, Higpen JT, Randalld ME, Gallione HH, et al. Impact of body mass index on treatment outcomes in endometrial cancer patients receiving doxorubicin and cisplatin: A gynecologic oncology group study. Gynecol Oncol. 2007;105:(1):59-65.
42. Mauland KK, Trovik J, Wik E, Raeder MB, Nyolstad TS, Stefansson IM, et al. High BMI is significantly associated with positive progesterone receptor status and clinico-pathological markers for non-aggressive

disease in endometrial cancer. Br J Cancer. 2011;104(6):921-926.
43. Wright JD, Cham S, Chen L, Burke WM, Hou JY, Tergas AI, et al. Utilization of sentinel lymph node biopsy for uterine cancer. Am J Obs Gyn. 2017;216(6): 594.e1-594.e13.
44. Blake P, Swart AM, Orton J. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): Pooled trial results, systematic review, and meta-analysis. Lancet. 2009; 373(2):137-146.
45. Han AR, Kwon YS, Kim D, Kim JH, Kim YM, Kim YT, et al. Pregnancy outcomes using assisted reproductive technology after fertility-preserving therapy in patients with endometrial adenocarcinoma or atypical complex hyperplasia. Int J Gynecol Cancer. 2009;19(1):147-151.
46. Yoo S, Hegarty SE, Mishra MV, Patel N, Cantrell LA, Timothy N, Showalter TN. Definitive radiation therapy for stage I-II endometrial cancer. Am J Clin Oncol. 2017;40(6):582-589.
47. Sorbe B, Nordström B, Mäenpää J, Kuhelj J, Kuhelj D, Okkan S, et al. Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer. Int J Gynecol Cancer. 2009;19(5):873-878.
48. Therasakvichya S, Kuljarusnont S, Petsuksiri J, Chaopotong P, Achariyapota V, Srichaikul P, et al. Clinical outcomes of stage I endometrial carcinoma patients treated with surgery alone: Siriraj Hospital experiences. J Gynecol Oncol. 2016; 27(5):e48.
49. Creutzberg CL, Nout RA, Lybeert ML, Wárlám-Rodenhuis CC, Jobsen JJ, Mens JM, et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys. 2011;81(4): e631-638.
50. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): An open-label, multicentre, randomised, phase 3 trial. The Lancet Oncology. 2016;17(8):1114-1126.
51. Galaal KA, Moundhri MA, Bryant A, Lopes AD, Theresa A, Lawrie TA. Adjuvant chemotherapy for advanced endometrial cancer. Cochrane Database of Systematic Reviews. 2014;15(5):32-45.

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