Immunohistochemical Expression of Estrogen and Progesterone Receptors in Endometrial Carcinoma in Relation to Clinic-Pathological Parameters

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ABSTRACT:

BACKGROUND:

Carcinoma of the endometrium is the most common gynecologic malignancy in developed countries. Estrogen and progesterone receptors are present in most cases of endometrial adenocarcinoma of endometrioid type, with low-grade tumors being almost invariably positive.

OBJECTIVE:

Evaluation of estrogen and progesterone receptors expression in endometrial carcinoma and their correlation with age, grade and stage of tumor.

MATERIALS AND METHODS:

This is a retrospective study using data collected form archived materials from Teaching Laboratories of Baghdad Medical City ,the period of the study (from February 2020 to December 2020) including formalin fixed, paraffin embedded tissue blocks. Three sections of 5µm thickness were taken from each block, the first was stained with (H&E) for histological revision, the second section was stained for ER and the third section was stained for PR to determine the signal specificity.

RESULTS:

Twenty five cases of endometrial adenocarcinoma were studied. In this study, the peak incidence of endometrial carcinoma was found to be in the range of (61-70) years old. Most cases showed grade I (40%) and grade II (44%). Seventy two percent were positive for estrogen receptor and (60%) of all tumors reacted positively for progesterone receptor. Co-expression of both estrogen receptor and progesterone receptor were noted in (52%) of cases.

CONCLUSION:

Majority of cases with endometrial carcinoma were found to be of grade I and grade II (low grade) and confined to the uterus (stage I & II) at time of diagnosis and most of them express ER and PR and half of the cases express both.

KEYWORDS: Estrogen receptor, progesterone receptor, endometrial carcinoma.

INTRODUCTION:

Carcinoma of the endometrium is the most common gynecologic malignancy in developed countries.[1] It typically occurs in elderly individuals, 80% of the patients being postmenopausal at the time of diagnosis.[2] Most endometrial adenocarcinomas occurring in women aged 40 years or younger are of endometrioid type, well to moderately differentiated, and early stage disease.[3] Conversely, tumors of elderly patients are more likely to be grade 2 or 3 and to have more advanced disease at the time of diagnosis.[4] Estrogen and progesterone receptors are present in most cases of endometrial adenocarcinoma of endometrioid type, with low-grade tumors being almost invariably positive.[5]

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Estrogen and progesterone receptors belong to the steroid hormone superfamily of nuclear receptors.[6]This steroid receptors regulate the growth, development, and physiology of the reproductive system in human.[6] Estrogen also affects the neuroendocrine, skeletal, adipogenic and cardiovascular system.[6]

MATERIAL AND METHODS:

This is a retrospective study using data collected form archived materials from teaching laboratories of Baghdad medical city, the period of the study (from February 2020 to December 2020) including formalin fixed, paraffin embedded tissue blocks of patient diagnosed with primary endometrial adenocarcinoma in which all patients received total abdominal hysterectomy and bilateral salpingooophorectomy in period from 2016 –2020from which data was collected. Study group included 25 cases of endometrial adenocarcinoma.

Clinicopathological parameters such as age, histological grade and pathological stage of the tumors were obtained from the available reports. Three sections of 5µm thickness were taken from each block, the first was stained with (H&E) for histological revision, the second section was stained for ER and the third section was stained for PR to determine the signal specificity using rabbit monoclonal (clone EP1 for ER and EP2 for PR). Semi-quantitative analysis of ER and PR stained tissue sections was performed following the Allred scoring system guidelines.[7] **(Table 1)**

Table 1: Allred scoring of Estrogen receptor (ER) and progesterone receptor (PR) by immunohistochimstry.

Proportion score	Positive cell %	Intensity	Intensity score
0	0	None	0
1	1%	weak	1
2	1-10%	intermediate	2
3	11-33%	strong	3
4	34-66%	sum of proportion score and intensity score 0-2 Negative 3-8 positive	
5	67-100%		

Statistical Analysis:

Statistical analysis was performed with **SPSS** v26 (Statistical package for social sciences). Data analysis was done using t-test, chi-square test for tables with frequencies, percentages, ranges. Values were considered Statistically significant when p-value is equal or less than **0.05**.

RESULT:

1. Age of study group:

The age of the patients ranged from 42 to 80 years, 3 (12%) of cases were aged from 40-50 years, 9 (36%) of cases were aged from 51-60 years, 12 (48%) of cases were aged from 61-70 years and only 1 (4%) of cases were aged from 71-80 years. as illustrated in (Table 2).

Table 2: Age of study group of 25 cases of endometrial adenocarcinoma.

Age group	NO. of cases (%)
40-50 y	3(12%)
51-60 y	9(36%)
61-70 y	12(48%)
71-80 y	1(4%)

2. Grading of the study group:

Tumors with grade I (well differentiated) were 10 **(40%)** cases, grade II (moderately differentiated) were 11 **(44%)** cases and grade III (poorly differentiated) were 4 **(16%)** cases illustrated in (**Figure 1**).

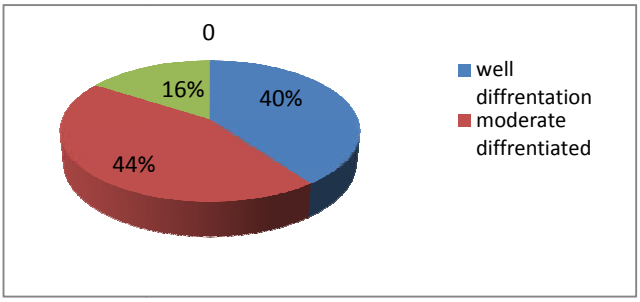

Figure 1: Grade in 25 cases of endometrial adenocarcinoma

3. Staging of the study group:

The tumor stage is very important for prognostic and therapeutic values, 25 cases of endometrial carcinoma were staged using FIGO staging system. Tumors with stage IA were 17 **(68%),** stage IB were 1 **(4%)**, stage II were 4 **(16%)** and stage IIIA were 3 **(12%)** as shown in **(Figure 2).**

4. Expression of ER and PR positivity:

The frequency of steroid receptor positivity in endometrial adenocarcinoma is summarized in **(Table 3).** Of all endometrial carcinoma, **(72%)** were positive for ER and **(60%)** of all tumors reacted positively for PR. Co-expression of both ER and PR were noted in only **(13%)** of cases where as loss of association between ER and PR were found in **(20%)** of cases in the form of (ER +/PR –) and **(8%)** in the form of (ER -/PR +). Negative expression of both ER and PR were found in only **(5%)** of cases.

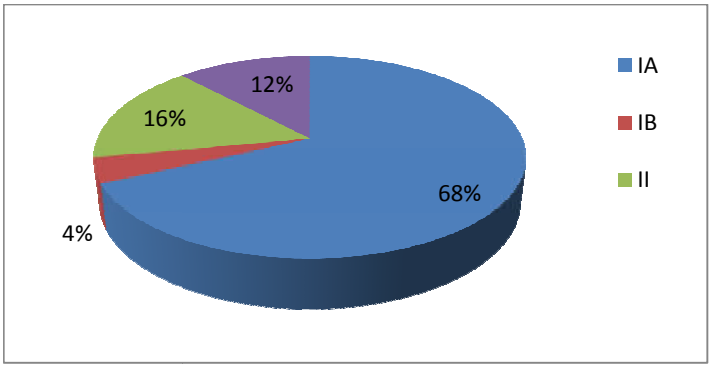

Figure 2: Stage in 25 cases of endometrial adenocarcinoma using FIGO staging system.

Table 3: Status of ER and PR positivity in 25 cases of endometrial adenocarcinoma .

Receptor	NO. (%)
ER +	18 (72%)
PR +	15 (60%)
ER + PR +	13 (52%)
ER +/PR –	5 (20%)
ER – PR -	5 (20%)
ER – PR +	2 (8%)

5. Score of ER and PR:

According to Allred scoring system, the final Allred score which was obtained from the sum of proportion of positivity and the intensity of ER showed that majority **(28%)** show score 8 and score 7 in **(20%)** of cases summarized in **(Figure 3)**.

Regarding PR, the final Allred score which was obtained from the sum of proportion of positivity and the intensity of PR showed that majority **(44%)** show score 8 and score 3 in **(12%)** of cases summarized in **(Figure 4)**.

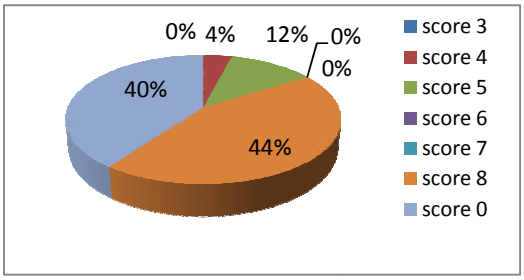

Figure 4: The sum of proportion of positivity and intensity of ER(final score).

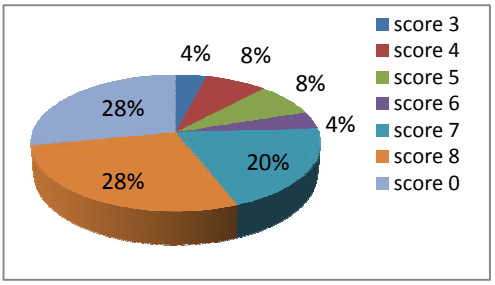

Figure 3: The sum of proportion of positivity and intensity of PR (final score).

6. Relation of ER and PR score with the age:
Among all cases, 3**(12%)** of cases were aged from 40-50 years (4% show co-expression of ER and PR , 4% express only PR and 4% in this range loss expression of both), 9 **(36%)** of cases were aged from 51-60 years (28% show co-expression of ER and PR, 4% express only ER and 4% show loss expression of both), 12 **(48%)** of cases were aged from 61-70 years (20% show co-expression of ER and PR, 12% show expression of ER only and 16% loss expression of both) and only 1 **(4%)** of cases were aged from 71-80 years and express both ER and PR. The p value was **0.216** (>0.05) and the result was not significant so there was no relation between the age groups and expression of ER and PR as illustrated in **(Table 4)**.

Table 4: Correlation between the age of the patients and ER and PR expression.

Age group	ER+\PR+	ER+\PR-	ER-\PR+	ER-\PR-	Total	P value
40-50 y	1(4%)	0(0%)	1(4%)	1(4%)	3(12%)	0.216
51-60 y	7(28%)	1(4%)	0(0%)	1(4%)	9(36%)	
61-70 y	5(20%)	3(12%)	0(0%)	4(16%)	12(48%)	
71-80 y	1(4%)	0(0%)	0(0%)	0(0%)	1(4%)	

7. Relation of the ER and PR score with the grade:
Relation of ER score with the grade was significant with p-value **0.0417** (<0.05); so, there was a relation between ER expression and tumor grade as shown in **(Table 5)**.
Relation of PR score with the grade was insignificant with p-value **0.283** (>0.05); so, there was no relation between PR expression and tumor grade as shown in **(Table 6)**.
Relation of co-expression of ER and PR with the grade was insignificant with p-value **0.103** (>0.05); So, there was no relation between co-expression of ER and PR and tumor grade as shown in **(Table 7)** .

Table 5: Association between tumor grade and ER expression in 25 cases of endometrial carcinoma.

Tumor grade	3	4	5	6	7	8	Total	ER-	P value
GI	0(0%)	1(4%)	0(0%)	0(0%)	3(12%)	3(12%)	7(28%)	3(12%)	0.0417
G II	1(4%)	1(4%)	2(8%)	1(4%)	2(8%)	3(12%)	10(40%)	1(4%)	
G III	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(4%)	1(4%)	3(12%)	

Table 6: Association between tumor grade and PR expression in 25 cases of endometrial carcinoma.

Tumor grade	4	5	8	Total	PR-	P value
G I	1(%)	0(0%	6(24%)	28%)	3(12%)	0.283
G II	0(0%)	2(8%)	5(20%)	28%)	4(16%)	
G III	0(0%)	0(0%)	1(4%)	4%)	3(12%)	

Table 7: Association between tumor grade and co-expression of ER and PR in 25 cases of endometrial carcinoma.

Tumor grade	ER+/PR+	ER+/PR-	ER-/PR+	ER-/PR-	Total	P value
GI	5(20%)	2(8%)	2(8%)	1(4%)	10(40%)	0.103
GII	6(24%)	3(12%)	0(0%)	2(8%)	11(44%)	
GIII	0(0%)	1(4%)	0(0%)	3(12%)	4(16%)	

8. Relation of the ER and PR score with the stage:
Relation of ER score with the stage was insignificant with p-value **0.926** (>0.05); So, there was no relation between ER expression score and tumor stage as shown in **(Table 8)**.
Relation of PR score with the stage was insignificant with p-value 0.403(>0.05); So, there was no relation between PR expression score and tumor stage as shown in **(Table 9).**
Relation of co-expression of ER and PR with the stage was insignificant with p-value **0.642** (>0.05); So, there was no relation between co-expression of ER and PR and tumor stage as shown in **(Table 10)**.

Table 8: Association of the tumor stage and ER expression in 25 cases of endometrial carcinoma histological specimens.

Tumor stage	3	4	5	6	7	8	Total	ER-	P value
IA	1(4%)	2(8%)	1(4%)	1(4%)	2(8%)	5(20%)	12(48%)	5(20%)	0.926
IB	0(0%)	0(0%)	0(0%)	0(0%)	1(4%)	0(0%)	1(4%)	0(0%)	
II	0(0%)	0(0%)	1(4%)	0(0%)	1(4%)	1(4%)	3(12%)	1(4%)	
IIIA	0(0%)	0(0%)	0(0%)	0(0%)	1(4%)	1(4%)	2(8%)	1(4%)	

Table 9: Association of the tumor stage and PR expression in 25 cases of endometrial carcinoma histological specimens.

Tumor stage				Total	PR-	P value
IA	2(8%)	2(8%)	7(28%)	11(44%)	6(24%)	0.403
IB	0(0%)	0(0%)	0(0%)	0(0%)	1(4%)	
II	0(0%)	0(0%)	3(12%)	3(12%)	1(4%)	
IIIA	0(0%)	0(0%)	1(4%)	1(4%)	2(8%)	

Table 10: Association of the tumor stage and co-expression of ER and PR in 25 cases of endometrial carcinoma histological specimens.

TumorStage	ER+/PR+	ER+/PR-	ER-/PR+	ER-/PR-	Total	value
IA	9	3	2	3	17(68%)	0.642
IB	0	1	0	0	1(4%)	
II	3	0	0	1	4(16%)	
IIIA	1	1	0	1	3(12%)	

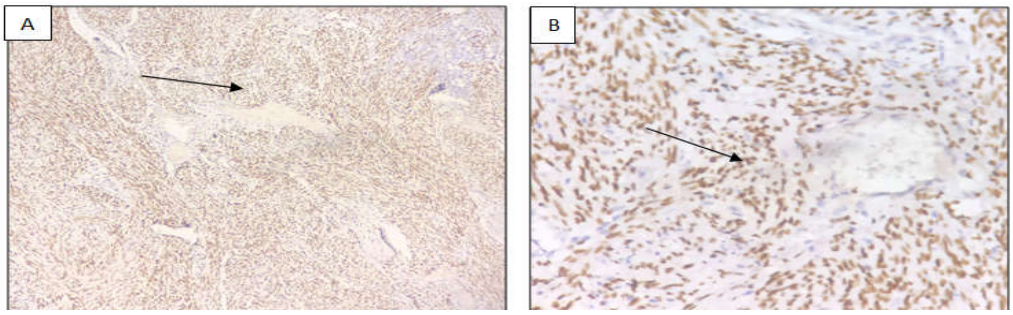

Figure 5: Immunohistochemical expression of estrogen receptor in poorly differentiated endometrial adenocarcinoma with positive estrogen receptor and nuclear score 8 (arrow):(A) at (10X) and (B) at (40X).

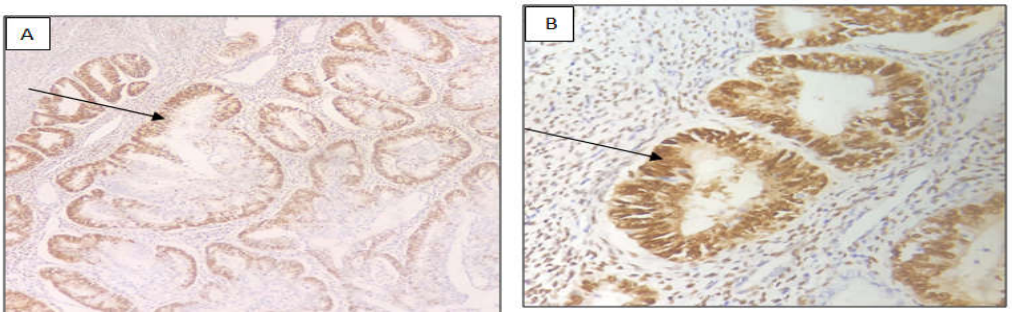

Figure 6: Immunohistochemical expression of progesterone receptor in well differentiated endometrial adenocarcinoma with positive progesterone receptor and nuclear score 8 (arrow):(A) at (10X) and (B) at (40X).

DISCUSSION:

In this study, the peak incidence of endometrial carcinoma was found to be in the range of (61-70) years old females followed by (51-60) years old represented by (48%) and (36%) of cases respectively. This agrees with other studies that show peak incidence between 55–65-year-old females and a mean age of 60.36 years. [8] In this study, carcinoma of the endometrium is uncommon before 40 years of age. This agrees with (Jemal A,2011).[8] Other studies show an increased incidence of endometrial adenocarcinoma after the age of 48 years.[9-14]

The grade of a tumor is a well-known prognostic factor for women with endometrial carcinoma.[15,16] In this study, most cases showed grade I (40%) and grade II (44%) and the remainder represented by grade III which constitutes (16%) of cases. This result was nearly similar to other studies [17,18] that show most of cases were grade as grade II (45.4%) with 40.9% and 13.7% of them had grade 1 and grade 3 disease at the final pathologic examination, respectively.[19] We chose to analyze histological grade, as it currently represents one of the major limitations to preoperative tumor staging along with depth of myometrial invasion to determine the surgical strategy.[20,21]

In this study, 25 cases staged according to (FIGO) staging system. Most cases were stage IA [17 (68%)], followed by stage II [4 **(16%)**] and stage IIIA [3 **(12%)**] and the least one was stage IB [1 **(4%)**]**.** In other words, in this study, (88%) of cases the tumor were confined to the uterus (stage I and II) that nearly agree with other studies (ANDREW BERCHUCK,1995)[22], (M.A. Elshaikh et al ,2012) [23]and (E.F. Dunn et al, 2012).[24]

In this study, (72%) of cases were express ER and (60%) of cases were express PR. This finding was in the ranges as reported by other studies: 32-77% for ER and 54-72% for PR expression (Fukuda et al., 1998; Jeon et al., 2006; Suthipinthawong et al., 2008). In an Indian study of 50 cases, an ER and PR positivity of 68% and 76% was observed. [25] Whereas positive rates in this study are lower in comparison to those reported in a Chinese cohort by Shen et al[26] which showed an overall rate of 85% for both ER and PR expression. In this study, nearly half of the cases (52%) were positive for both ER\PR and similar results were found in other study[27] in which co-expression of ER and PR were found in (51.6%) but against other study[28] in which 95.6% was found to have co-expression of both ER and PR. Different rates of hormonal receptors expression from various studies certainly depend on many factors, such as, proportion of low and high grade tumor which were reported to have higher and lower degree of hormonal receptors expression, respectively.[29]

Regarding ER and according to Allred scoring system, the final Allred score which was obtained from the sum of proportion of positivity and the intensity of ER showed that majority **(28%)** show score 8. Other study shows that (71.7%) of cases score 8 according to Allred scoring system.[26] Other study shows (38%) of cases were score 8 according to Allerd scoring system.[30] However, in both previous studies, score 8 account for the majority of cases.

Regarding PR and according to Allred scoring system, the final score which was obtained from the sum of proportion of positivity and the intensity of PR showed that majority **(44%)** show score 8. Other study shows that 55.9% of cases score 8 according to Allred scoring system.[26] Other study shows that (79.3%) were score between 4-8 according to Allred scoring system.[30]

As mentioned previously in this study, the peak incidence of endometrial carcinoma were found to be in the range of (61-70) years old which constitutes **(48%)** of cases (20% show co-expression of ER and PR, 12% show expression of ER only and 4% loss expression of both). The p value was **0.216** (>0.05) and the result was not significant so there was no relation between the age groups and expression of ER and PR. This agrees with other studies [30] that show no correlation between age and ER and PR expression with p value of 0.14 and 0.7 respectively. Limited studies show correlation between the ER and PR expression and the age with p value of 0.06(Jun Guan, 2019).[31]

The presence of estrogen receptor and progesterone receptor have been quantitatively associated with histological differentiation.[23,33] As EC grading is advanced ER and PR expression was found to be decreased.[34,35]

In this study, tumor grade shows significant statistical correlation with expression of ER with p value **(0.0417)** (<0.05) which agrees with other studies [36], while there was insignificant statistical correlation between PR and co-expression of both ER and PR with tumor grade with p value of **(0.283)** (>0.05) and **(0.103)** (>0.05) respectively.

This was against other studies that demonstrates a significant correlation between ER and PR immunostaining and histological grade in endometrial cancer.[36,37] This means that ER expression is a better indicator of grading compared to PR status. A few studies with low-grade endometrial adenocarcinoma presented independently with ER and PR, or their combination as a panel.[19-22] Some authors found no correlation between ER and PR status and histological grade[38], while others report a negative correlation.[39-42]

Among the cases were staged as IA, (48%) were positive for ER, and (44%) were positive for PR while stage IIIA only (8%) positive for ER and (4%) positive for PR stage. This result agreed with other studies[36,37] and support that a decrease in ER and PR expression is correlated to more advanced stages of EC.[36] In this study, tumor stage shows insignificant correlation with ER, PR and coexpression of both with p value of (**0.926, 0.403 and 0.642)** (>0.05) respectively. The majority of studies found a negative correlation between ER and PR expression and tumor stage.[42,43,44] This study disagrees with other studies that show significant correlation between tumor stage and ER and PR expression, with exception of PR (other than stage I) that shows insignificant correlation among other stages.[36,37] Few studies show similar result regarding association between steroid hormons expression and stage.[45,46] The variation in the results in comparison with other studies may result from one major analytic factor that has been shown to affect interlaboratory reproducibility of staining results. These preanalytic factors are related to tissue handling from the time of surgical excision to immunohistochemical staining. These variables include the nature and consistency of the excised tissue, the interval between excision and fixation, type of fixative, duration of fixation, thickness of the tissue block submitted for processing, type and duration of the processing method, and the time lapse between microtomy and use of the section for immunohistochemical analysis.

CONCLUSION:

The majority of cases with endometrial carcinoma were found to be of grade I and grade II (low grade). Most of the cases with endometrial carcinoma were found to be confined to the uterus (stage I & II) at the time of diagnosis. Most endometrial carcinoma express ER and PR and nearly half of the cases express both.

The absence of expression of ER and PR may be an important finding in the process of advancement of endometrial carcinogenesis. The presence of steroid receptors ER and PR has been quantitatively associated with histological differentiation. ER and PR expression was found to be decreased as EC grading advanced. Tumor grade shows a significant correlation with expression of ER, this makes ER expression a better indicator of grading compared to PR status. A decrease in ER and PR expression is correlated to more advanced stages of EC.

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