Role of Hormone receptor status, Ki-67 expression and body mass index in endometrial carcinoma: clinical value and survival

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Abstract: Background: The most known risk factors for developing endometrial cancer are high estrogen levels and obesity which associated with excessive levels of estrogen. Expression of Ki-67 has independent role on prognosis. Effect of hormone receptor, body mass index (BMI) and Ki-67 on disease free survival in endometrial carcinoma and their association with other clinicopathological features was evaluated in this study.
Methods: Fifty-three adult female patients were included in this prospective study with histologically confirmed endometrial cancer (EC). Those patients treated and followed up at Tanta University Hospitals. Hormone receptor status and ki67 was detected by immunohistochemical exam. Body mass index was calculated at time of presentation. Hormonal status, ki-67 and BMI were studied and compared with other clinicopathological criteria. Survival was assessed and compared by Kaplan-Meier curves and log-rank test
Results: Positive expression of ER and PR was detected in 54.7% and 49.1% ofpatients respectively and significantly associated with less myometrial invasion, low Ki-67, BMI>30kg/m^2 and endometrioid type. Interestingly BMI **>30** kg/m^2, was significantly associated with earlier stage and endometrioid type (*P*=0.04 and 0.003 respectively). Multivariate Cox regression analysis detected that myometrial invasion, tumor grade and ER expression remained statistically significant with DFS.
Conclusion: Our study investigatedthat different molecular factors such as ER, PR and Ki-67 in addition to obesity, significantly associated with tumor characteristics and survival.
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1. Introduction:

Endometrial cancer (EC) is common malignant cancer of the endometrial epithelium of female reproductive tract that is diagnosed in premenopausal and postmenopausal females [(1)].

Studies have reported that endometrial cancer accounts for about20-30%of female reproductive tract tumors and the incidence of endometrial cancer is increasing [(2)].About 80% of EC patients have endometrioid adenocarcinoma (type I) and presented early with good prognosis [(3)]but a subset of these patients failed to reach 5-year overall survival even those with low-grade or early-stage EC[(4)].More urgent and accurate studies are needed, to identify high-risk patients with grade I–II EC precisely[(5)].

Estrogen and progesterone receptors are most validated prognostic biomarkers for endometrial cancer [(5)]Gene expression of these receptors were found significantly associated to the protein expression of ERα and PR by immunohistochemistry, respectively [(6)].Body mass index (BMI),physical activity and diet may explain up to 80% of the risk of endometrial cancer [(7)].

Molecular biomarkers that have shown independent prognostic role in endometrial cancer, focusing on survival and/or lymph node metastases include TP53 mutation, loss of hormone receptors, and Ki67[(8)].

BMI is a simple index commonly used to classify underweight, normal weight, overweight in adults. Obesity is defined as BMI ≥30 kg/m^2[(9)].

Obesity contributed to about 10% of post-menopausal breast cancers, 11% of colon cancer and 37% of esophageal cancers. While obesity participated in 39% of EC patients[(10)].Several studies suggested that waist circumference can be used as a measure to predict EC risk[(11,12)].

Type I endometrial cancer is known to be influenced by obesity because of the changes in endogenous hormone metabolism[(13)].

2. Patients and Methods

Our prospective study included 53 adult female patients with histologically confirmed EC. Those patients treated and followed up at Tanta University Hospitals through the period from January 2015 to December 2018. The entire patient underwent surgical staging with total hysterectomy, bilateral salpingo-oophorectomy, retroperitoneal node dissection and peritoneal washing cytology. The tumor stage,

histologic diagnosis and grading of each patient were classified under International Federation of Gynecology and Obstetrics (FIGO) 2009 criteria. Postoperative adjuvant treatment and follow up was administered according to published guidelines [14].

The study was conducted in accordance with the local ethical committee, and all the participants gave an informed consent for use of the specimens. Formalin-fixed, paraffin-embedded specimens were pathologically examined.

Data on the following parameters were collected: age, parity, BMI at time of diagnosis were measured (BMI=kg/m^2), status of menopause, stage, grade, status of lymphovascular invasion (LVSI), tumor histological subtypes, cervical involvement, hormone receptor status, ki67, date of recurrence or death, and last follow-up date. Patients who undergone incomplete surgical staging and those with stage IV EC were excluded from the study.

Immunohistochemical examination:

We assessed ER, PR and ki67 expression by IHC, using paraffin-embedded sections. Antigen retrieval was performed by treatment with citric acid (pH 6.0) for 20 minutes. Non-specific antibody binding was blocked by incubating with 10% fetal calf serum for 20 minutes. Mouse anti-human ER (1:200 Glostrup, Denmark), PR monoclonal antibody (1:100, Dako, Glostrup, Denmark) ki67 or (1: 100, MIB 1 DAKO, Glostrup, Denmark) were added for 1 hour at room temperature. Sections were then washed with phosphate-buffered saline (PBS) and incubated with biotinylated anti-mouse IgG (Dako, Glostrup, Denmark) for 30 minutes and after washing, sections were incubated with streptavidin-conjugated horseradish peroxidase (Dako, Shanghai, China) for 30 minutes. Antigen–antibody complexes were visualised using 3,3Diaminobenzidine (DAB) and counterstained with haematoxylin. Staining in normal endometrial tissues surrounding the tumor served as internal positive control to avoid false negative results.

The expression of ER, PR and ki67 were analyzed by two experienced pathologists who were blinded to the patient characteristics and outcome. Staining of ER and PR was considered as positive if the tumor cell nuclei were stained in ≥1% of the cells, corresponding to the definition of positivity currently in clinical use. Ki67 expression was considered as positive if the tumor cell nuclei were stained in ≥10% of the cells **(figure 1)**.

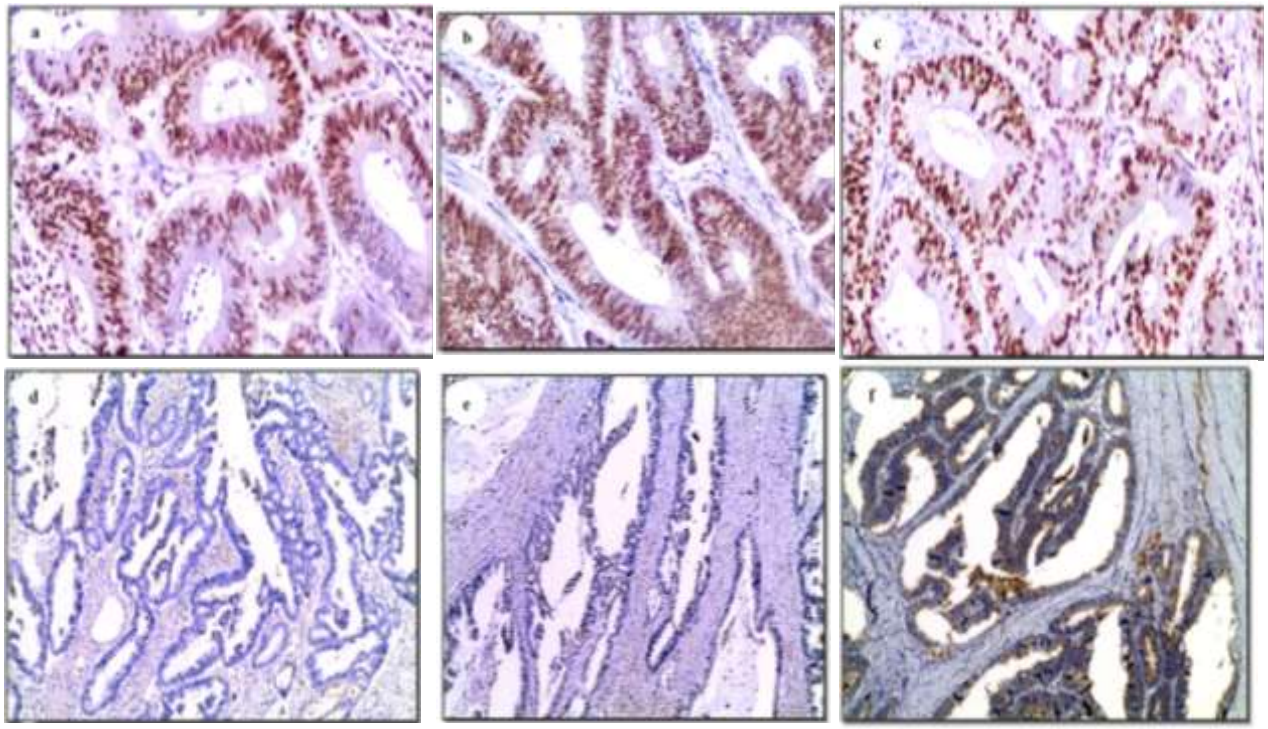

Figure (1): a, Positive ER immunostaining (X400), **b,** Positive PR immunostaining (X400), **c,** Positive Ki67 immunostaining (X400), **d**, Negative ER immunostaining (X100), **e**, Negative PR immunostaining (X100) **f**, Positive Ki67 immunostaining (X100).

Statistical analysis

Association of hormonal status, ki67 and BMI with other clinicopathological features were studied. Survival was assessed and compared using Kaplan-Meier curves and log-rank test. P-values < 0.05 were considered being significant. Disease free survival was calculated from date of diagnosis to either date of recurrence or death.

3. Results:

Fifty-three patients, diagnosed pathologically to have endometrial carcinoma, were included in our prospective study. Median age was 57 years (range 31-72). Stage II was reported in 19 patients (35.8%). Twenty-nine patients (54.7%) had grade 2 tumor. Most of patients had endometroid type (79.2%). Clinicopathological features were gathered in **table (1)**.

Table (1): Patient characteristics

Characteristics of all population	**(n=53)**	**%**
Age group		
≤57	21	39.6
>57	32	60.4
Myometrial invasion		
≤1/2	31	58.5
>1/2	22	41.5
Cervical involvement		
No	37	69.8
Yes	16	30.2
Stage		
I	16	30.2
II	19	35.8
III	18	34
Tumor grade		
G1	6	11.3
G2	29	54.7
G3	18	34
Lymphovascular invasion		
Absent	42	77.4
Present	11	22.6
Histological type		
Endometrioid	41	79.2
Non endometrioid	12	20.8
ER expression		
Positive	29	54.7
Negative	24	45.3
PR expression		
Positive	26	49.1
Negative	27	50.9
Ki 67		
<10%	40	75.5
≥ 10%	13	24.5
BMI		
≤ 30kg/m^2	24	45.3
>30 kg/m^2	29	54.7

Positive ER and PR expression was detected in 54.7% and 49.1% of EMC patients respectively and both were significantly associated with less myometrial invasion, low Ki-67, BMI>30 kg/m^2 and endometrioid type. Only positive ER was significantly correlated to stage I-II. Also, only positive PR was significantly correlated to age ≤57 and grade I-II **(Table 2)**.

High Ki-67 (≥10) was reported in 13 patient (24.5%) and significantly associated with higher

grade, stage, LVI, BMI≤30kg/m^2 and non-endometrioid type **(Table 3)**.

Twenty-nine patients (54.7%) in our study had BMI >30 kg/m^2, this was significantly associated with earlier stage and endometrioid type (**Table 4**).

The estimated mean disease-free survival was 40 months (**95% CI** 37.8:43.6) with 3- year DFS was 77.4%. Relation of disease-free survival to prognostic features was clarified in **figure (2)**.

Univariate analysis indicated that, less myometrial invasion, early disease stage, grade I-II tumor, low Ki-67 and positive ER expression were associated significantly with longer DFS **(Table 5)**.

Multivariate Cox regression analysis detected that myometrial invasion ≤1/2, grade I-II and positive ER expression remained statistically significant with DFS **(Table 6).**

Table (2) Correlation of patient characteristics and hormonal status

Population Characteristics **(N=53)**	**ER expression**		***P***	**PR expression**		***P***
	Positive n=29 (%)	**Negative n=24 (%)**		**Positive n=26 (%)**	**Negative n=27 %)**	
Age group						
≤57	14(48.3)	7 (29.2)		14(53.8)	7 (25.9)	0.038*
>57	15 (51.7)	17 (70.8)	0.157	12 (46.2)	20 (74.1)	
Myometrial invasion						
<1/2	21(72.4)	10 (41.7)		19 (73.1)	12 (44.4)	0.034*
>1/2	8 (27.6)	14 (58.3)	0.024*	7 (26.9)	15 (55.6)	
Cervical involvement						
No	20 (69)	17 (70.8)		17 (65.4)	20 (74.1)	0.491
Yes	9 (31)	7 (29.2)	0.883	9 (34.6)	7 (25.9)	
Stage						
I	13 (44.8)	3 (12.5)		10 (38.5)	6 (22.2)	0.219
II	11 (37.9)	8 (33.3)	0.007*	10 (38.5)	9 (33.3)	
III	5 (17.2)	13 (54.2)		6 (23.1)	12 (44.4)	
Tumor grade						
G1	6 (20.7)	0 (0)		5 (19.2)	1 (3.7)	0.038*
G2	15 (51.7)	14 (58.3)	0.054	16 (61.5)	13 (48.1)	
G3	8 (27.6)	10 (41.7)		5 (19.2)	13 (48.1)	
Lymphovascular invasion						
Absent	25 (86.2)	17 (70.8)		23 (88.5)	19 (70.4)	0.104
Present	4 (13.8)	7 (29.2)	0.170	3 (11.5)	8 (29.6)	
Ki 67						
<10%	27(93.1)	13 (54.2)		25 (96.2)	15 (55.6)	0.001*
≥10%	2 (6.9)	11 (45.8)	0.001*	1 (3.8)	12 (44.4)	
BMI						
≤30 kg/m^2	9 (31)	15 (62.5)		7 (26.9)	10 (37)	0.008*
> 30 kg/m^2	20 (69)	9 (37.5)	0.022*	19 (73.1)	17 (63)	
Histological type						
Endometrioid	26 (89.7)	15 (62.5)		24 (92.3)	17 (63)	0.011*
Non endometrioid	3 (10.3)	9 (37.5)	0.019*	2 (7.7)	10 (37)	

Table (3) Correlation of patient characteristics and Ki-67

Population Characteristics **(N=53)**	Ki-67 **<10 (%)**		**≥10 (%)**		***p***
Age group					
≤57	16	40	5	38.5	0.922
>57	24	60	8	61.5	
Myometrial invasion					
<1/2	15	37.5	7	53.8	0.299
>1/2	25	62.5	6	46.2	
Cervical involvement					
No	26	65	11	84.6	0.181
Yes	14	35	2	15.4	
Stage					
I	13	32.5	3	23.1	0.046*
II	17	42.5	2	15.4	
III	10	25	8	61.5	
Tumor grade					
G1	6	15	0	0	0.007*
G2	25	62.5	4	30.8	
G3	9	22.5	9	69.2	
Lymphovascular invasion					
Absent	35	87.5	7	53.8	0.009*
Present	5	12.5	6	46.2	
BMI					
≤ 30 kg/m^2	13	32.5	11	84.6	0.001*
>30 kg/m^2	27	67.5	2	15.4	
Histological type					
Endometrioid	38	95	3	23.1	0.001*
Non endometrioid	2	6	10	76.9	

Table (4) Correlation of patient characteristics and BMI

Population Characteristics **(N=53)**	BMI **>30 kg/m^2**		**≤30 kg/m^2**		***P***
Age group					
≤57	13	44.8	8	33.3	0.394
>57	16	55.2	16	66.7	
Myometrial invasion					
≤1/2	18	62.1	13	54.2	0.561
>1/2	11	37.9	11	45.8	
Cervical involvement					
No	19	65.5	18	75	0.454
Yes	10	34.5	6	25	
Stage					
I	9	31	7	29.2	0.047*
II	14	48.3	5	20.8	
III	6	20.7	12	50	
Tumor grade					
G1	5	17.2	1	4.2	0.253
G2	16	55.2	13	54.2	
G3	8	27.6	10	41.7	
Lymphovascular invasion					
Absent	25	86.2	17	70.8	0.170
Present	4	13.8	7	29.2	
Histological type					
Endometrioid	27	93.1	14	58.3	0.003*
Non endometrioid	2	6.9	10	41.7	

Table (5) Univariable analysis of clinicopathological factors affecting DFS

Population Characteristics	**3-year DFS (%)**	**95% CI**	***P***
Age group			
≤57	81	35.7:40.6	0.547
>57	75	35.4:43.6	
Myometrial invasion			
<1/2	87.1	31.1:40.7	0.045*
>1/2	63.6	40.1: 45.8	
Cervical involvement			
No	78.4	36.7: 43.9	0.862
Yes	75	33.6:39.7	
Stage			
I	93.8	42.1:47.1	0.014*
II	84.2	35.7:41.1	
III	55.6	27.2: 38.0	
Tumor grade			
G1	100		0.010*
G2	86		
G3	55.6	NR	
Lymphovascular invasion			
Absent	81	39.4:44.6	0.135
Present	63	25.5:40.2	
Ki 67			
<10	85	41:45.3	0.006*
≥10	53	23.5:36.9	
ER expression			
Positive	93.5	43.1:46.4	0.002*
Negative	58.3	28.7:37.7	
PR expression			
Positive	88.5	41.8:46.1	0.05
Negative	66.7	30.9: 39	
BMI			
≤ 30kg/m^2	66.7	33.5:43	0.105
> 30 kg/m^2	86.2	38.7:44.7	
Histological type			
Endometrioid	80.5	38.9:44.5	0.215
Non endometrioid	66.7	26.5:38.1	

Table (6) Multivariable analysis of clinicopathological factors affecting DFS

Characteristics	**HR**	**95% CI**	***P***
Myometrial invasion			
<1/2	0.14	0.031-0.707	0.017*
>1/2			
Stage			
I			
II	2.1	0.86-5.45	0.09
III			
Tumor grade			
G1			
G2	10.9	1.72-48.6	0.009*
G3			
Ki 67			
<10%	0.94	0.35-5.46	0.630
≥10%			
ER expression			
Positive	8.1	1.02-43.5	0.047*
Negative			

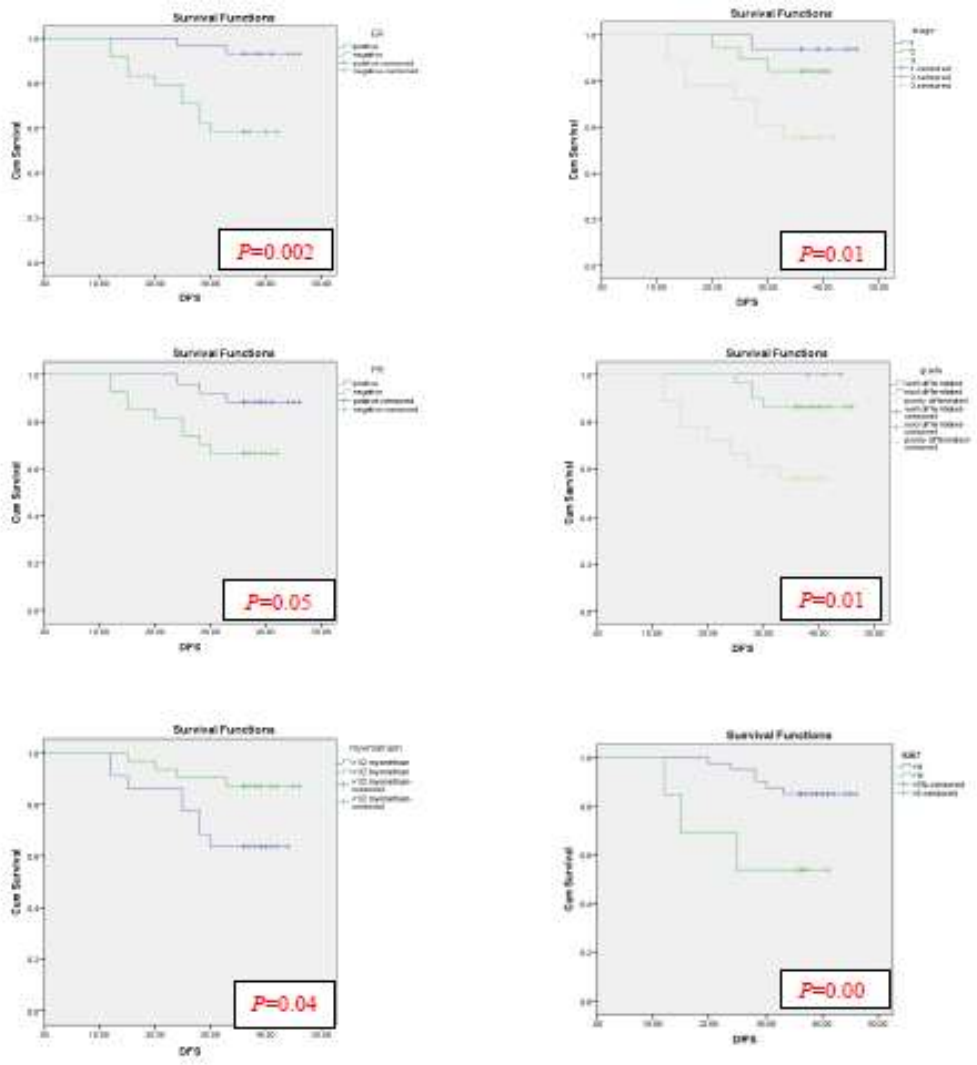

Figure (2) Disease free survival in relation to prognostic features.

4. Discussion:

Progesterone and estrogen receptors have long been appreciated as prognostic in EC and their positivity are associated with low grade, low-risk EC and to great extent more encouraging outcomes [(15)].

Obesity is considered great modifiable hazard agent for development of EC. Obesity shares in the cause of death in EC survivors with cardiovascular disease. After diagnosis, most of cancer survivors do not perform healthy style of life for weight reduction [(16)].

The aim of this study is to analyze the effect of estrogen and progesterone receptor status, Ki-67 expression and BMI on disease free survival in endometrial carcinoma patients and their association with other clinicopathological features.

In this work we confirmed the association of both hormone receptors status with outcomes, loss ER and PR correlated with higher incidence of disease recurrence[(17)].

Positive ER and PR were significantly associated with less myometrial invasion, low Ki-67, BMI>30kg/m^2 and endometrioid type. Only positive ER was significantly correlated to stage I-II. Also, only positive PR was significantly correlated to age ≤57 and grade I-II. This agree with other studies mention, that tumors with positive estrogen and progesterone expression have a significant association with the clinical and pathological parameters showing a better prognosis[(18, 19)].

So Immunohistochemical study of ER/PR should be put in application routinely as molecular markers

list for clinical requirement in patients with endometrial carcinoma.

Twenty-nine patients (54.7%) in our study had BMI **>30** kg/m^2, this was significantly associated with earlier stage and endometrioid type and usually associated with better clinical outcomes. Similar results were recorded by many series [20, 21, 22].

Our study concluded that obesity do not impact EC recurrence which is similar to that reported by multiple studies whose confirmed that the increase in mortality is likely due to obesity-related diseases and not to EC recurrence or progression and encouraged for lifestyle management[23,24,25].

High Ki-67 (≥10) was reported in 13 patient (24.5%) and significantly associated with higher grade, stage, LVI, BMI≤ 30 and non-endometrioid type.

Masjeed et al, confirmed that Ki-67 expression and mean Ki-67 increased as the grade of EC increased[26].Although Ki-67 is associated with cell proliferation, as in most series in our study there was significant correlation between ki67 and recurrence in univariable analysis which was lost in multivariate evaluation,Ki-67 expression did not show prognostic significance on its own[27].

Conclusion:

Our study investigated that, different molecular factors such as ER, PR and Ki-67 in addition to obesity, significantly associated with tumor characteristics and survival that in turn could tailor patient therapy design.

Conflict of interest

The authors clarify that they don´t have interest conflict.

References:

1. Mao S, Ma J, Yu H. Sirtuin-7 knockdown inhibits the growth of endometrial cancer cells by inducing apoptosis via the NF-κB signaling pathway. OncolLett.2019;17(1):937-943.
2. Lee B, Suh DH, Kim K, No JH and Kim YB: Influence of positive peritoneal cytology on prognostic factors and survival in early-stage endometrial cancer: A systematic review and meta-analysis. Jpn J Clin Oncol. 2016 46: 711-717.
3. Wei J, Zhang W, Feng L, Gao W. Comparison of fertilitysparing treatments in patients with early endometrial cancer and atypical complex hyperplasia: a meta-analysis and systematic review. Medicine (Baltimore) 2017; 96(37):e8034.
4. Fujimoto T, Nanjyo H, Fukuda J, Nakamura A, Mizunuma H, Yaegashi N, et al. Endometrioid uterine cancer: histopathological risk factors of local and distant recurrence. GynecolOncol2009; 112:342-7.
5. Guan J, Xie L, Luo X, Yang B, Zhang H, Zhu Q, Chen X. The prognostic significance of estrogen and progesterone receptors in grade I and II endometrioid endometrial adenocarcinoma: hormone receptors in risk stratification. J GynecolOncol. 2019;30(1): e13.
6. Hertz DL, Henry NL, Kidwell KM, Thomas D, Goddard A, Azzouz F, et al. ESR1 and PGR polymorphisms are associated with estrogen and progesterone receptor expression in breast tumors. Physiol Genomics 2016; 48:688-98.
7. Gao Y, Dai X, Lee AC, Wise MR, Shen F, Chen Q.Body Mass Index is Negatively Associated with Endometrial Cancer Stage, Regardless of Subtype and Menopausal Status.J Cancer. 2018;9(24):4756-4761.
8. Masjeed NMA, Khandeparkar SGS, Joshi AR, Kulkarni MM, Pandya N. Immunohistochemical Study of ER, PR, Ki67 and p53 in Endometrial Hyperplasias and Endometrial Carcinomas. J ClinDiagn Res. 2017;11(8):EC31-EC34.
9. Speroff L, Fritz FA. Obesity. Clinical gynecologic endocrinology and infertility. Lippincott Williams & Wilkins Philadelphia. 2005.
10. Nagle CM, Crosbie EJ, Brand A, Obermair A, Oehler MK, Quinn M, Leung Y,Spurdle AB, Webb PM; Australian National Endometrial Cancer Study Group. Theassociation between diabetes, comorbidities, body mass index and all-cause andcause-specific mortality among women with endometrial cancer. GynecolOncol. 2018
11. Kabat GC, Xue X, Kamensky V, Lane D, Bea JW, Chen C, et al. Risk of breast, endometrial, colorectal, and renal cancers in postmenopausal women in association with a body shape index and other anthropometric measures. Cancer Causes Control 2015; 26:219–29.
12. . National Comprehensive Cancer Network, Clinical Practices Guidelines in Oncology V.1. 2008. Available at: http://www.nccn.org. Accessed on 15 August 2014.
13. Laskey RA, McCarrollML, von Gruenigen VE. Obesity-related endometrial cancer: an update on survivorship approaches to reducing cardiovascular death. BJOG. 2016;123(2):293-8.
14. Zhang Y, Liu Z, Yu X, Zhang X, Lu¨ S, Chen X, Lu¨ B. Theassociation between metabolic abnormality and endometrialcancer: a large case–control study in China. GynecolOncol2010; 117:41–46.
15. Shen F, Gao Y, Ding J, et al. Is the positivity of estrogen receptor or progesterone receptor different between type 1 and type 2 endometrial

cancer? Oncotarget 2017; 8: 506–511, Trovik J, Wik E, Werner HM, et al. Hormone receptor loss in endometrial carcinoma curettage predicts lymph node metastasis and poor outcome in prospective multicentre trial. Eur J Cancer 2013; 49: 3431–3441.

16. Laskey RA, McCarroll ML, von Gruenigen VE. Obesity-related endometrial cancer: an update on survivorship approaches to reducing cardiovascular death. BJOG. 2016; 123(2):293-8.
17. Karnezis AN, Leung S, Magrill J, McConechy MK, Yang W, Chow C, Kobel M, Lee CH, Huntsman DG, Talhouk A, Kommoss F, Gilks CB, McAlpine JN. Evaluation of endometrial carcinoma prognostic immunohistochemistry markers in the context of molecular classification. J PatholClin Res. 2017; 3(4):279-293.
18. Yu CG, Jiang XY, Li B, Gan L, Huang JF. Expression of ER, PR, C-erbB-2 and Ki-67 in endometrial carcinoma and their relationships with the clinicopathological features. Asian Pac J Cancer Prev, 2015; 16(15):6789–6794.
19. Kumari PR, Renuka IV, Apuroopa M, Chaganti PD. A study of expression of estrogen and progesterone receptor, in atrophic, hyperplastic and malignant endometrial lesions, with emphasis on relationship with prognostic parameters. Int J Res Med Sci, 2015; 3(11):3318–3325.
20. Basen-Engquist K, Scruggs S, Jhingran A, Bodurka DC, Lu K, Ramondetta L, Hughes D, Carmack Taylor C. Physical activity and obesity in endometrial cancer survivors: associations with pain, fatigue, and physical functioning. Am J Obstet Gynecol. 2009;200(3):288 e1-8.
21. Kerimoglu OS, Pekin A, Yilmaz SA, Yavas G, Beyhekim F, Demirtas AA, Dogan NU, Ilhan TT, Celik C. Effect of the percentage of body fat on surgical, clinical and pathological outcomes in women with endometrial cancer. JObstetGynaecol Res. 2015;41(3):449-55.
22. Gao Y, Dai X, Lee AC, Wise MR, Shen F, Chen Q. Body Mass Index is Negatively Associated with Endometrial Cancer Stage, Regardless of Subtype and Menopausal Status. J Cancer. 2018;9(24):4756-4761.
23. Ward KK, Shah NR, Saenz CC, McHale MT, Alvarez EA, Plaxe SC. Cardiovascular disease is the leading cause of death among endometrial cancer women. GynecolOncol 2012;126:176–9.
24. Martra F, Kunos C, Gibbons H, Zola P, Galletto L, DeBernardo R, et al. Adjuvant treatment and survival in obese women with endometrial cancer: an international collaborative study. Am J ObstetGynecol 2008;198:89 e1–8,
25. Laskey RA, McCarroll ML, von Gruenigen VE. Obesity-related endometrial cancer: an update on survivorship approaches to reducing cardiovascular death. BJOG. 2016;123(2):293-8.
26. Masjeed NMA, Khandeparkar SGS, Joshi AR, Kulkarni MM, Pandya N. Immunohistochemical Study of ER, PR, Ki67 and p53 in Endometrial Hyperplasias and Endometrial Carcinomas. J ClinDiagn Res. 2017; 11(8):EC31-EC34.
27. Ikeda Y, Oda K, Ishihara H, Wada-Hiraike O, Miyasaka A, Kashiyama T, Inaba K,Fukuda T, Sone K, Matsumoto Y, Arimoto T, Maeda D, Ikemura M, Fukayama M, KawanaK, Yano T, Aoki D, Osuga Y, Fujii T. Prognostic importance of CDK4/6-specific activity as a predictive marker for recurrence in patients with endometrial cancer, with or without adjuvant chemotherapy. Br J Cancer. 2015;113(10):1477-83.