

# Prognostic significance of hormone receptor (ER/PR) status in endometrial carcinoma in black women: implications with lymph node metastasis

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**Objective:** Integrating ER/PR receptors into clinical risk stratification is still under investigation and is proving to be an important component in endometrial cancer management. This study aimed to investigate the prognostic value of ER/PR receptors specifically its correlation with lymph node metastasis in black women which form a vulnerable group associated with poor outcomes. **Methods:** We reviewed black females (n = 70) diagnosed with endometrial cancer at our institution from 2015–2018 including endometrioid/non-endometrioid histology, FIGO stage I–IVA, grade 1–3 for ER/PR receptors and presence or absence of pelvic lymph nodes based on pre-operative endometrial curettage and post-surgical pathology specimens. **Results:** Majority of our patients were postmenopausal (59 out of 70) 84%. FIGO stage 1 and 2 constituted 72% (50 out of 70). Endometrioid histology constituted 39 out of 70 (55%) cases and non-endometrioid histology which includes serous, clear cell and carcinosarcomas constituted 45% of the cases. Loss of estrogen receptor (ER-) was observed in 19 of 70 patients (27%) and loss of progesterone receptor (PR-) was seen in 22 patients (31%) which was significantly associated with lymph node metastasis ( $p < 0.05$ ). Subgroup analyses showed a significant association between PR+ and absence of lymph node metastasis in cases of endometrioid cancer ( $p < 0.05$ ). Nevertheless, there was no statistically significant association ( $p = 0.10$ ) between ER receptors and lymph node metastasis in patients with endometrioid cancer. In non-endometrioid histology both ER- and PR- were found to be statistically significantly associated with lymph node involvement. **Conclusion:** Loss of ER and PR receptors independently predicts lymph node metastasis in endometrial cancers in black women.

## Keywords

Cancer; Receptors; Endometrium

## 1. Introduction

Endometrial cancer is the most common gynecological malignancy in the United States [1]. Endometrial cancers are further divided into endometrioid and non-endometrioid histology. Non-endometrioid histology includes serous, carcinosarcomas which are associated with poorer prognosis.

Risk factors for endometrial cancers mainly includes obesity, early menarche and late menopause, unopposed estrogen, and family history of endometrial cancer [2]. About 80% of the endometrial cancers are endometrioid and are diagnosed early with better prognosis [3]. There is a subset of the population that fail to reach 5 year overall survival even with endometrioid histology and early stage of the disease [4]. Various prognostic indicators including FIGO stage, grade and histology have been used for risk assessment and for treatment decisions. However, estrogen (ER) and progesterone (PR) receptor status are considered the most significant prognostic markers for endometrial cancer [5–7].

Racial disparity specially in the survival rates for endometrial cancer is evident and has been increasing over the last 10 years [8]. Black women have a 90% higher 5-year mortality than white females. Black women are diagnosed at an advanced stage and have a higher proportion of non-endometrioid histology associated with poor prognosis [9]. To address the gaps between black and white women comprehensive studies are required to assist us in better treatment decisions to improve survival in black women. Our study aimed to investigate if the correlation between hormone receptor status and lymph node metastasis holds true in black females which could aid in treatment protocols.

Gene expression of ER and PR receptors have been directly associated with prognosis of endometrial cancer in terms of survival. Loss of ER- and PR- receptors independently predict lymph node metastasis and shorter disease-free survival (DFS) [10]. Pre-operative endometrial curettage or biopsy is the first step in diagnosis and to identify receptor (ER/PR) status. Identifying the receptor status specially in surgical operable stages can help to individualize surgical therapy in endometrial cancer. Routine lymph node dissection has not been confirmed to improve survival and is associated with increased complications [11]. Hence, receptor status could aid us in moving forward with aggressive treatment with pelvic lymphadenectomy specially in our population of

black females. Our aim is to help in creating an algorithm for management of endometrial cancer for our population.

Integrating biomarkers like ER/PR receptors with clinical and pathological parameters will improve risk stratification and will guide us in predicting the future course of treatment and possible long-term survival. Unlike some cancers like breast, where hormonal biomarkers have been incorporated for tailored therapy, targeted agents are still in its primitive stage in endometrial cancers [12].

Our study aimed at investigating (1) association of loss of ER and PR receptors with lymph node metastasis as detected in the post-operative specimens (2) role of ER and PR receptors in both endometrioid and non-endometrioid subtypes separately (3) to check if receptor hypothesis holds true for black females.

## 2. Methods and materials

### 2.1 Participants

We reviewed black females with endometrial cancer (n=70) at our institution diagnosed between 2015–2018. Patients included in our study underwent pre-operative endometrial curettage or biopsy followed by trans-abdominal or laparoscopic surgery with lymph node dissection/sampling or debulking surgery in advanced stage cancer. We included patients with FIGO stage I–IVA, grade 1–3, both endometrioid and non-endometrioid histology. Patients with distant metastasis were excluded from the study. Baseline characteristics including age, BMI, pre/post-menopausal status and were noted. Biomarkers specially ER and PR receptors status were noted for both endometrioid/non-endometrioid histology. Pelvic and para-aortic nodes involvement were identified from post-operative specimens.

### 2.2 Immunohistochemical staining and evaluation

ER, PR expression was assessed by IHC's using formalin-based paraffin embedded samples. The expression of ER, PR were evaluated by at least 2 pathologists. Staining of ER/PR was considered positive if the nuclei were stained in >1% of the cells.

### 2.3 Statistical analysis

Statistical analyses were performed with Python3.7 (SciPy, NumPy, Pandas, and Matplotlib libraries) using Fisher's Exact test exploring associations between categorical variables (ER/PR and Lymph nodes Metastasis). To corroborate the findings, estimated odds ratios (OR) for lymph node metastasis to ER/PR was calculated. The analysis was done for independent ER/PR positive and negative, for all subjects and for the two subtypes (endometrioid and non-endometrioid). All statistical tests were two-sided and considered significant if  $p < 0.05$ . Post-hoc power calculation was done using the software G\*Power 3.1 (HHU, Düsseldorf, Germany).

Descriptive statistics were used to characterize baseline parameters like age, BMI including molecular targets for non-endometrioid histology. Weighted percentages were

**Table 1. Characteristics of 70 endometrial cancer patients included in the study.**

Characteristics	N	%
Mean age (years)	61.45	
Range	33–94	
Menopausal status		
Premenopausal	59	84.28
Postmenopausal	11	15.71
FIGO stage		
I	45	64.28
II	5	7.14
III	10	14.28
IV	10	14.28
Histological subtype		
Endometrioid	39	55.71
Serous	19	27.14
Carcinosarcoma	12	17.14
Histological differentiation		
Grade 1	23	32.85
Grade 2	15	21.42
Grade 3	32	45.71
Estrogen receptor status		
Yes	51	72.85
No	19	27.14
Progesterone receptor status		
Positive	48	68.57
Negative	22	31.42
Pelvic lymph node metastasis		
Yes	20	28.57
No	50	71.42
Status at 1-year follow-up		
Alive	68	97.14
Dead	2	2.85
Status at time of follow-up		
Stable	42	60
Progressive	28	40

used to summarize the data. Our study was approved by the institutional review board (IRB).

## 3. Results

### 3.1 General patient characteristics

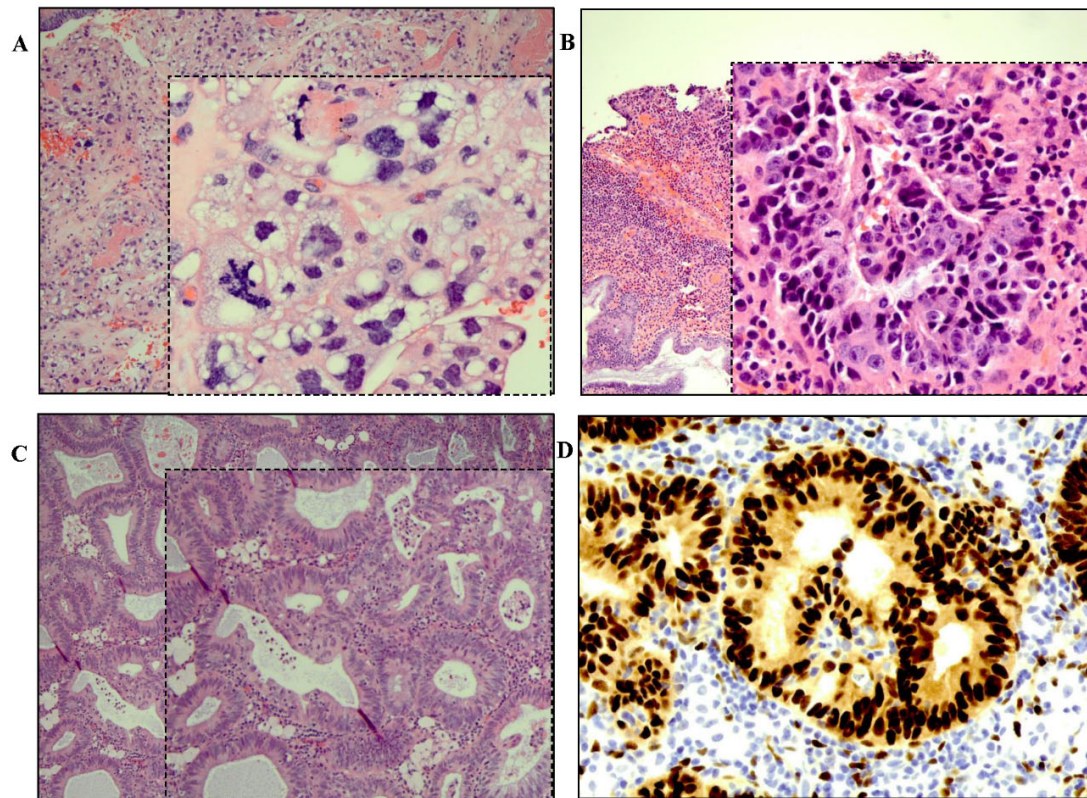
We included all black females only (n=70) that were diagnosed with endometrial cancer from 2015–2018 and who underwent laparoscopic or transabdominal surgery or debulking surgery (Table 1).

**Age**—The mean age of our population was 61 years with a range from 33–80 years.

**Body Mass Index**—The mean BMI of our patients were 36.94 kg/m<sup>2</sup>.

**Menstrual status**—Majority of our patients 59/70 (84%) were post-menopausal while remaining 16% were premenopausal.

**Stage**—Majority of our patients 50/70 (71%) were diagnosed with FIGO stage I and stage II disease while the remaining 28% were diagnosed with FIGO stage III and IVA. Pa-



**Fig. 1. Photomicrographs of endometrial samples.** (A) H&E of clear cell endometrial carcinoma (at magnification 20 $\times$ , inset: 40 $\times$ ). (B) H&E image of endometrioid carcinoma, FIGO grade II (at magnification 20 $\times$ , inset: 40 $\times$ ). (C) H&E image of endometrioid carcinoma, FIGO grade I (at magnification 20 $\times$ , inset: 40 $\times$ ). (D) ER positivity seen as strong nuclear staining in grade I endometrioid carcinoma.

tients with distant metastasis were excluded from the study.

**Grade**—Majority of our patients 32/70 (45%) had grade 3 disease followed by grade 1 in 32%.

**Histology**—Endometrioid cancers formed 39/70 (55%) of our sample followed by non-endometrioid which includes serous in 22% and carcinosarcoma in 16%.

### 3.2 Hormone receptors and lymph nodes

We observed presence of hormone receptors which involved ER and PR receptors in pre-operative endometrial specimens using biopsy or curettage samples. Presence or absence of lymph node involvement was detected in samples obtained through laparoscopic or transabdominal or debulking surgery. Presence or absence of hormone receptors and its correlation with lymph node metastasis was observed in the entire sample and a subgroup analysis was done separately for endometrioid and non-endometrioid histology. Estrogen receptors were positive (ER+) in 51/70 (72%) of our samples and PR receptors were positive (PR+) were positive in 48/70 (68%). On subgroup analysis in endometrioid cancers 35/39 (89%) were ER+ while 36/39(92%) were PR+. The non-endometrioid variant showed ER+ in 16/31 (51%) and PR+ 12/31(38%) of the samples (Fig. 1).

Loss of estrogen receptor (ER-) was observed in 19 of 70 patient samples (27%) and found to be significantly associated

with lymph node metastasis ( $p < 0.05$ ). Progesterone receptor loss was noted (PR-) in 22 (31%) and was associated with metastasis of lymph node (Table 2). On sub- group analysis the association between ER/PR with lymph node metastasis in patients with endometrioid and non- endometrioid (comprising of serous, carcinosarcoma and clear cell) endometrial cancer showed significant association between PR+ and absence of lymph node metastasis in endometrioid cancer type. There was no statistically significant association ( $p = 0.10$ ) between ER and lymph node metastasis in patients with endometrioid type cancer. In case of non-endometrioid cancers (comprising of serous, carcinosarcoma and clear cell) both ER- and PR- were found to be associated with metastasis to the lymph nodes ( $p < 0.05$ ) (Table 3).

All our patients were closely followed up as an outpatient. Patients eligible for adjuvant therapy post-surgery received necessary chemo-radiation according to the guidelines. At the end of one-year post-treatment 68/70 (97%) were alive. Nearly 40% of patients had progression in the form of metastasis to lung, vagina, or local spread. A noticeable observation made was majority of our patients with progression at one-year follow-up post treatment were from the non-endometrioid group.

**Table 2. Lymph node metastasis in 70 endometrial cancer patients and correlation with receptor biomarkers evaluated by Fisher's Exact test.**

Variables	Lymph node metastasis		p-value
	No	Yes	
	N (%)	N (%)	
ER positive	45 (88)	6 (12)	$1.35 \times 10^{-6}$
ER negative	5 (26)	14 (74)	$1.35 \times 10^{-6}$
PR positive	45 (94)	3 (6)	$2.86 \times 10^{-9}$
PR negative	5 (23)	17 (77)	$2.86 \times 10^{-9}$

**Table 3. Lymph node sampling in 31 non-endometrioid subtype patients and correlation with receptor biomarkers evaluated by Fisher's Exact test.**

Variables	Lymph node metastasis		p-value
	No	Yes	
	N (%)	N (%)	
ER positive	14 (88)	2 (12)	0.00024
ER negative	3 (20)	12 (80)	0.00024
PR positive	12 (100)	0 (0)	$8.83 \times 10^{-5}$
PR negative	5 (26)	14 (74)	$8.83 \times 10^{-5}$

#### 4. Discussion

We report for the first time the role of hormonal receptors and its significance with respect to lymph node metastasis in black women. Involvement of pelvic and para-aortic lymph nodes by itself is an indicator of poor outcomes in addition to race which is associated with poor survival. Our study aimed to observe if hormone receptor status and its association with lymph node metastasis holds true in black women which could help in creating proper algorithms for aggressive treatment in this vulnerable group [9]. This would also help us in identifying individuals who would benefit from pelvic lymph node dissection which has its own complications [11]. Black women have been seen to be diagnosed at a later stage and have higher proportion of non-endometrioid histology [13, 14].

Lymph node sampling is considered an important component in endometrial cancer management in particular for high grade and high-risk endometrial cancer [15]. Routine lymphadenectomy in every patient with endometrial cancer is not recommended, as it is associated with longer operative times and significant post-operative complications specially in obese women which form a significant proportion of black women diagnosed with endometrial cancer [16]. Our study reported a mean BMI of  $36.94 \text{ kg/m}^2$  keeping these patients at a higher risk of complications if subjected to extensive pelvic and para-aortic lymph node dissection. Improved tools to identify prognostic indicators like hormone receptors status (ER/PR) can guide us in identifying patients who will benefit from lymph node dissection. Pre-operative curettage or biopsy samples for receptor status identification should form the first step in the algorithm for management of endometrial cancers. Studies have also shown that non-endometrioid subtypes which are higher in black women and

associated with poor outcomes will benefit from these tools to a greater extent. Non-endometrioid cancers have been associated with deeper myometrial infiltration and have consistently demonstrated lymph node metastasis [17]. Larger and adequately powered randomized trials are required to study the effects of planned lymphadenectomy in black women who satisfy the pre-requisite based on hormone receptors which is beyond the scope of this study.

Various studies identifying the prognostic value of ER and PR receptors were evaluated across various histological subtypes [18, 19]. These studies have independently predicted prognostic value of ER and PR receptors in early stage and low-grade endometrial cancer. A study conducted by Trovik *et al.* [18] significantly predicted loss of ER (-) and PR (-) and its association with lymph node involvement thereby adding predictive and prognostic value specially in the low-risk group. This study also predicted poor disease-free survival (DFS) in patients with a negative receptor status. In our study, which is probably the first study to test this hypothesis in black women, who generally have a higher mortality rate and late stage of presentation in comparison to their white counterparts. We reported a statistically significant association of loss of ER (-) and PR (-) with positive lymph node involvement. On subgroup analysis with endometrioid and non-endometrioid subtypes we observed significant predictive value of both ER and PR receptors independently specially in serous and carcinosarcomas. This information can be utilized while addressing treatment strategies for black women with endometrial cancer. We strongly recommend conducting larger multicentric trials on black women for better understanding of the disease pattern and course of disease in black females. Creating a treatment algorithm that could be acceptable universally for this group could help in improving survival outcomes.

Studies have reported unfavorable subtypes like serous and carcinosarcomas in higher proportions in black women [20]. Our study revealed ER+ in 41% and PR+ in 33% with carcinosarcomas and 43% and 31% with serous variants respectively [21]. Incorporating molecular testing in the treatment algorithm specially in black women with non-endometrioid subtype is our recommendation.

Biomarkers like ER/PR receptors have been incorporated in the treatment algorithm for breast cancers. Despite sufficient studies in endometrial cancers, these biomarkers are not routinely used to tailor endometrium cancer management. Our study can add to the database and form the basis of a multicentric prospective trial in black women. We recommend using these biomarkers in patient risk stratification in a metastatic setting.

We acknowledge the limitation of our study being the sample size of our population (n=70) which is smaller than other studies assessing the role of endometrial receptors and its correlation. However, our study is exclusively limited to black females and is among the few studies assessing the correlation in this vulnerable group. Our study is based on a single institutional database and we are working in acquiring data and involving multiple centers in our study in the future. We expect better statistical correlation with an increase in our sample size.

Our study was not designated to test the role of lymphadenectomy in endometrial cancer but to incorporate molecular and targeted staging in the treatment algorithm specially in black women. As reported in our data we recommend that hormone status should be incorporated in randomized trials for surgical and systemic treatment. Pre-operative differentiation of patients can also decrease the burden of tertiary centers, as those with local and low-grade disease can be managed at a local center while advanced disease can be referred to specialized centers [22]. This stratification can only be possible if we have well established guidelines and algorithms.

## 5. Conclusions

Our results suggest that loss of ER and PR receptors independently predicts lymph node metastasis and has the potential of being used as a prognostic indicator in endometrial cancer in black females. However, further analysis and larger multicentric randomized trials are needed to ascertain their true prognostic significance. Molecular staging and targeted agents are the need of the hour in improving survival outcomes in endometrial cancers specially in black women.

## Author contributions

MS, GO, SS, SJ—original concept and writing of this manuscript. PS, SS—data extraction, review of literature and statistics. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

This project was approved by the Morehouse School of Medicine Institutional Review Board (IRB) under Title ID 1505964-2 and IRB ID 674.

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## Conflict of interest

The authors declare no conflict of interest.

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